COURSE #66213 — 5 CE CREDITS RELEASE DATE: 10/01/21 EXPIRATION DATE: 09/30/24

# Attention Deficit Hyperactivity Disorder

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### *Faculty*

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### *Faculty Disclosure*

Contributing faculty, John J. Whyte, MD, MPH, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Contributing faculty, Paul Ballas, DO, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

### *Audience*

This intermediate course is designed for psychologists involved in the care of patients with attention deficit hyperactivity disorder.

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American Psychological Association

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### *Course Objective*

Attention deficit hyperactivity disorder (ADHD) has a significant effect on day-to-day functioning and quality of life; however, it often goes unrecognized. The purpose of this course is to educate psychologists about the epidemiology, diagnosis, and management of ADHD.

### *Learning Objectives*

*Upon completion of this course, you should be able to:*

1. Review the epidemiology of attention deficit hyperactivity disorder (ADHD).
2. Outline the diagnostic criteria for ADHD for children and adults.
3. Identify ways in which ADHD symptoms change as patients approach adulthood.
4. Discuss what is known about the pathophysiology of ADHD.
5. Describe evidence-based recommendations and the use of pharmacotherapy in the treatment of ADHD.
6. Describe the use of behavioral therapy in the treatment of ADHD.
7. Discuss the treatment of children, adolescents, and adults with ADHD and medical and psychiatric comorbidities, including the importance of patient and family education and the unique needs of non-English-proficient patients.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

## INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a debilitating psychiatric illness affecting approximately 4% to 12% of the population [1]. Characterized by persistent problems with distractibility, impulsivity, and/or hyperactivity, ADHD has a significant effect on day-to-day functioning and on quality of life.

Unfortunately, ADHD often goes unrecognized. Patients may hesitate to disclose their symptoms, and physicians unfamiliar with this disorder may confuse its manifestations with other psychiatric illnesses. Common comorbidities can further cloud the diagnosis.

This course will cover the epidemiology, diagnostic criteria, pathophysiology, and differential diagnosis of ADHD. It will review the first-line pharmacologic treatments, recommended duration of therapy, and options for patients who do not respond to initial therapy. Finally, it will address the roles of other therapeutic options, such as behavioral therapy.

## EPIDEMIOLOGY

The exact prevalence of ADHD is unknown. The 2016 National Survey of Children's Health (NSCH) found that 6.1 million children in the United States have ever been diagnosed with ADHD. This includes 388,000 children 2 to 5 years of age, 2.4 million children 6 to 11 years of age, and 3.3 million adolescents 12 to 17 years of age [2]. The percent of children 4 to 17 years of age ever diagnosed with ADHD increased from 7.8% in 2003 to 11.0% in 2011–2012 [2]. Note: Because the 2016 NSCH survey used different methods, estimates are not directly comparable with estimates based on previous NSCH data. Also, due to the increased focus on ADHD in younger children, the age ranges surveyed were expanded to include children 2 to 17 years of age [2].

In children, ADHD is more than twice as common in boys (11.7%) as in girls (5.7%) [3]. In 2016–2018, 13.8% of children 3 to 17 years of age had ever been diagnosed with either ADHD or a learning disability. Non-Hispanic Black children (16.9%) were more likely than non-Hispanic White (14.7%) or Hispanic (11.9%) children to be diagnosed with either condition, although the reason is not clear [3; 4]. The prevalence of ADHD among children with family incomes less than 100% of the poverty level was 10% from 1998 to 2009 and 11% for those with family income from 100% to 199% of the poverty level [5].

Although often thought of as a disorder of children, ADHD is seen in adults as well. Data from the National Comorbidity Survey Replication show a prevalence of 4.4% among adults 18 to 44 years of age [6; 7]. A random telephone survey of adults also found that 4.4% of the 966 respondents reported a previous ADHD diagnosis [8]. Looked at more closely, 2.9% of respondents met "narrow" criteria for ADHD (symptoms often) and 16.4% met "broad" criteria (symptoms sometimes or often). Among adults, the diagnosis of ADHD is associated with being male, being White/non-Hispanic, being divorced, and being in the "other" employment category, primarily unemployed or disabled [6].

In children, ADHD can lead to educational difficulties, social difficulties, injuries and accidents, and family problems. Adults with a childhood history of ADHD are more likely to exhibit antisocial and criminal behavior, are more prone to injuries and accidents, and have more health problems than the general population [9]. They also have more employment and marital difficulties and are more likely to have children out of wedlock.

In a community sample of 500 adults with self-reported ADHD and 501 community-based controls, the adults with ADHD were significantly less likely to have graduated from high school (83% vs. 93%), less likely to have obtained a college degree (19% vs. 26%), and less likely to be currently employed (52% vs. 72%). They were more likely to have had job changes (5.4 vs. 3.4 jobs over 10 years), to have been arrested (37% vs. 18% of controls), and to have been divorced (28% vs. 15%). They were also less likely to be satisfied with their professional, family, and social lives [10].

## DIAGNOSTIC CRITERIA

The first step in correctly diagnosing and treating ADHD is understanding the definition. ADHD is classified within the Neurodevelopmental Disorders in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [11]. Depending on the subtype, the diagnosis of ADHD involves a persistent pattern of inattention, hyperactivity, and/or impulsivity, more than would be expected for a typical person at the same level of development. Typically, several symptoms must be present before the age of 12 years. Also, there must also be clear evidence that the symptoms cause distress or interfere with functioning. These criteria are currently used for both children and adults, although the number of criteria varies.

According to the DSM-5 criteria for ADHD, one of the following groups of symptoms must be present [11]:

- Inattention: At least six (or five for persons 17 years of age and older) of the following symptoms of inattention have persisted for at least six months to a degree that is inconsistent with developmental level and that negatively impacts social and academic/occupational activities:
  - Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
  - Often has difficulty sustaining attention in tasks or play activities
  - Often does not seem to listen when spoken to directly
  - Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
  - Often has difficulty organizing tasks and activities
  - Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork, homework)
  - Often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, tools)
  - Is often easily distracted by extraneous stimuli
  - Is often forgetful in daily activities
- Hyperactivity/Impulsivity: At least six (or five for persons 17 years of age and older) of the following symptoms of hyperactivity/impulsivity have persisted for at least six months to a degree that is inconsistent with developmental level and that negatively impacts social and academic/occupational activities:
  - Often fidgets with hands or feet or squirms in seat
  - Often leaves seat in classroom or in other situations in which remaining seated is expected

- Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
- Often unable to play or engage in leisure activities quietly
- Is often "on the go" or often acts as if "driven by a motor"
- Often talks excessively
- Often blurts out an answer before question has been completed
- Often has difficulty awaiting turn
- Often interrupts or intrudes on others (e.g., butts into conversations or games)

Impairment from the symptoms must be present in two or more settings (e.g., at school [or work] and at home). There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning. For a diagnosis of ADHD, the symptoms may not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder or be better accounted for by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, or personality disorder). For individuals (especially adolescents and adults) who have symptoms that no longer meet full criteria, "in partial remission" should be specified. The category unspecified ADHD is for disorders with prominent symptoms of inattention or hyperactivity-impulsivity that do not meet the full criteria for ADHD [11].

Patients with ADHD often have features that are not part of the diagnosis but are consequences of functional impairment. Examples include low frustration tolerance, temper outbursts, stubbornness, poor self-esteem, and devaluation of academic achievement. People may have the impression that children with ADHD are lazy, irresponsible, oppositional, or willful.

## MAKING THE DIAGNOSIS

The diagnostic evaluation of a child or teenager suspected to have ADHD requires a thorough evaluation, including information from parents and teachers. Laboratory, radiologic, and other studies are not usually needed. However, in 2013, a device based on electroencephalogram (EEG) technology was approved to help assess ADHD in children and adolescents 6 to 17 years of age [12]. The Neuropsychiatric EEG-Based Assessment Aid System calculates the ratio of theta and beta waves, which are shown to be higher in children with ADHD. The role of this device has not yet been established, and it should not be used alone to diagnose ADHD.

Both the American Academy of Pediatrics (AAP) and the American Academy of Child and Adolescent Psychiatry (AACAP) have developed recommendations for the assessment of ADHD. The AAP guideline for the diagnosis of ADHD was revised in 2019, and this updated guideline is in line with DSM-5 criteria and provides a general guide for identifying the disorder in children 4 to 18 years of age [13]. The AACAP guideline, published in 2007, addresses ADHD in children and adolescents between 3 and 17 years of age [9].

Mental health assessment should include screening for ADHD [9]. The AACAP guideline assumes a psychiatric primary complaint, but any child may be screened for ADHD using questions about impulsivity, hyperactivity, and inattention. If ADHD is suspected, additional evaluation can be pursued.


According to the American Academy of Pediatrics, the clinician should initiate an evaluation for ADHD for any child or adolescent 4 to 17 years of age who presents with academic or behavioral problems and symptoms of inattention, hyperactivity, or impulsivity

(https://pediatrics.aappublications.org/content/144/4/e20192528. Last accessed September 28, 2021.)

**Level of Evidence**: B (Randomized controlled trials or diagnostic studies with minor limitations; overwhelmingly consistent evidence from observational studies)

Full evaluation should include information from both the parent and child and should incorporate information about functioning at school or day care [9; 13]. Each symptom in the diagnostic criteria should be assessed and duration, frequency, and severity determined. The possibility of comorbid disorders, including learning disability and depression, should be explored. In addition to parent and patient interviews, family history and developmental history may increase the likelihood of ADHD diagnosis or shed light on comorbid disorders or other underlying causes of symptoms. A standardized behavior rating scale should be completed by a parent and, if possible, a teacher. Report cards and homework papers may also be helpful.

Unless medical history indicates, laboratory tests and neurologic testing are not needed [9]. Some medical conditions can cause behavior similar to ADHD, but other indications of an underlying cause will usually be present. Children who are likely to have had lead exposure, such as those in inner cities or older housing, may benefit from lead testing because this exposure has been associated with ADHD. Hyperthyroidism, on the other hand, does not usually present as purely ADHD with no other symptoms. Imaging, such as magnetic resonance imaging and electroencephalography, are not part of the routine evaluation of ADHD [9]. They should be reserved for cases when a specific indication is present.

Psychologic and neuropsychologic testing are also not generally needed. However, patients who appear to have low cognitive ability and those whose math or language performance does not seem to match their ability may require this type of evaluation. Testing can help differentiate learning disorders from learning problems that are secondary to ADHD.

Special attention should be paid to the possibility of a comorbid psychiatric disorder [9]. Comorbidities are common in patients with ADHD and may require additional treatment. In addition, symptoms resembling ADHD may be due to another psychiatric problem. ADHD itself may lead to some of the symptoms of depression or mania. When patients meet full criteria for ADHD plus another disorder, both diagnoses should be made.

As in children, diagnosis in adult patients should involve a careful history and diagnostic interview. The interview should cover childhood symptoms and developmental history, as well as current symptoms and impact on the patient's life [14]. Input from a close friend, parent, or spouse may be helpful, and alternative psychiatric diagnoses and comorbidities should be considered. A physical exam should be performed; testing should be pursued as needed to evaluate for potential physical causes for symptoms, such as hearing and vision problems, anemia, and hyperthyroidism. Current medications should be discussed to help rule out the possibility that symptoms are due to medication side effects.

**Behavior Rating Scales**

There are several established rating scales for evaluating ADHD symptoms, some of which are available on the Internet. Some scales focus on children, teens, or adults. Many are brief and can be completed quickly either before or during an appointment. It is worth noting whether the scale is based primarily on DSM-5 criteria or on other aspects of functioning or symptoms.

Rating scales can provide a way to determine the severity of symptoms compared to developmental norms, and they can also alert clinicians to the possibility of comorbid psychiatric disorders. Additionally, they may be useful for monitoring treatment. However, rating scales should not be used to diagnose ADHD. It is also important to ensure that the scale is appropriately standardized in order to avoid gathering inaccurate information that can adversely affect treatment.

## AGE AND CHANGING SYMPTOMS

ADHD often continues into adolescence. Some children do seem to outgrow their symptoms, but many either continue to have residual symptoms or will meet DSM-5 criteria for ADHD as adults. Symptoms tend to shift as patients age, but do not necessarily resolve.

The actual number of children with ADHD who continue to have the disorder in adulthood is unknown for several reasons. Attrition in cohort studies tends to be high, and different studies use different inclusion and exclusion criteria. The diagnostic criteria used in studies may differ from DSM-5 criteria for ADHD. DSM-5 criteria were tested on and geared toward children, and although these criteria are used for adults, they may not accurately capture all people with the disorder.

There have been several estimates of the prevalence of ADHD in adults who were diagnosed as children. Biederman and colleagues conducted a 10-year prospective case-control study with White boys 6 to 18 years of age at the study entry point [15]. At the 10-year follow-up, the mean age of participants was 22 years. Fifty-eight percent of subjects had current full or sub-threshold ADHD at follow-up, compared to only 6% of controls. "Sub-threshold" was defined as meeting fewer criteria than required for diagnosis. Biederman and colleagues subsequently published results of a controlled 10-year follow-up study conducted to examine the age-dependent persistence of ADHD in boys transitioning from adolescence to early adulthood [16]. The study included 110 boys with ADHD and 105 non-ADHD controls who were 6 to 17 years of age at the study entry point. ADHD was defined as persistent if the youth met full or sub-threshold DSM-IV diagnostic criteria, failed to attain functional remission, or were receiving treatment for ADHD. At the 10-year follow-up point, 65% of the ADHD group no longer met the full DSM-IV criteria; 78% met at least one criterion for the definition of persistence. The authors also found that persistent ADHD was associated with more psychiatric comorbidity, more familiality with mood disorders, and higher levels of educational and interpersonal impairments than controls [16].

Barkley and colleagues conducted a prospective case-control study of children diagnosed with hyperactivity [17]. These children were diagnosed between 4 and 12 years of age, then reassessed at 19 years of age or older. At follow-up, they were evaluated for ADHD using criteria from the third edition of the DSM (DSM-III-R). Based on self-report, the prevalence of DSM-III-R defined ADHD in young adulthood was 5%, not significantly different from those in the control group. Based on parent report, the prevalence of ADHD was 46% compared to 1% in controls. Using a developmental definition, prevalence by self-report was similar to controls. Control subjects in this study were slightly younger and had more education.

Manuzza and colleagues published a report on hyperactive boys followed from a mean age of 7 years to a mean age of 24 years [18]. Adult ADHD, based on DSM-III-R criteria, was present in only 4% of this population. Antisocial personality disorder and non-alcohol substance abuse were significantly higher in the hyperactive group. These results may be limited by the fact that children with high levels of aggression or conduct problems were excluded from the study.

### SYMPTOMS OF ADHD IN ADULTHOOD

There are several changes in symptoms as patients approach adulthood. There appear to be fewer overt symptoms of hyperactivity (e.g., running and climbing, inability to remain seated), but these may be replaced with or confined to fidgetiness, jitteriness, or restlessness. Restlessness may lead to difficulty participating in sedentary activities and even avoiding sedentary occupations. Impulsivity may manifest as a tendency to make decisions without thinking them through [19]. Patients may start on projects without reading or listening to instructions. An adult with ADHD may also have a tendency to speed when driving.

Other typical adult ADHD symptoms include having trouble getting organized, planning ahead, or preparing for events [19]. These patients may appear inefficient, failing to do tasks in the order that makes the most sense. Inattention may manifest as failure to persist in uninteresting tasks or daydreaming instead of concentrating.

Several screening tools have been developed for adults. The World Health Organization (WHO) created a short and long version of the Adult ADHD Self-Report Scale (ASRS) [20]. The ASRS has good specificity (98.3% long version and 99.5% short version) but limited sensitivity (56.3% and 68.7%). Because this version of the ASRS was calibrated to DSM-IV criteria, which are narrower than DSM-5 criteria, researchers sought to update the ASRS for DSM-5 criteria [21]. A semistructured diagnostic interview for DSM-5 adult ADHD was administered to two general population surveys: 119 from a household survey and 218 from a managed care subscriber survey. A novel algorithm was applied to the pooled data to create a DSM-5 version of the ASRS. The accuracy of the new scale was then confirmed in independent clinical samples of patients seeking evaluation at the New York University Langone Medical Center Adult ADHD Program (NYU Langone) from 2011–2012 and in 300 primary care controls from 2015–2016. Data analysis was conducted from April to September 2016. Of the 637 total participants, 44 household survey respondents, 51 managed care respondents, and 173 NYU Langone respondents met DSM-5 criteria for adult ADHD. Of these, 123 were male, with a mean age of 33.1 years. A six-question screening scale was found to be optimal in distinguishing ADHD from non-ADHD individuals in the first two samples. The DSM-5 ASRS screening scale detected the vast majority of general population cases of ADHD with a high specificity and positive predictive value [21].

The Utah criteria are a set of diagnostic criteria developed specifically to identify adults with ADHD [22]. Although they do not match the DSM-5 definition, they may be useful in assessing adult patients. The Utah criteria include [22]:

- History of ADHD diagnosis or symptoms consistent with ADHD during childhood
- Hyperactivity and poor concentration as an adult
- At least two additional symptoms: labile mood, hot temper, stress intolerance, impulsivity, or disorganization and inability to complete tasks

These criteria have a number of limitations. Patients with the inattentive subtype of ADHD may be missed. When hyperactivity is present in childhood ADHD, it tends to decline over time or manifest in more subtle ways. The listed symptoms, particularly lability and outbursts of temper, may indicate other psychiatric disorders. Although early research suggested that "hot temper" and irritability were aspects of ADHD, it has been found that such symptoms are associated more with the social environment and that they predict different developmental outcomes [23]. Problems with temper may be associated with ADHD but are no longer considered part of the diagnostic criteria.

Barkley and colleagues have suggested diagnostic criteria based largely on patients in an adult ADHD study based at the University of Massachusetts (UMASS) Medical School [19]. This study involved comparing adults with ADHD to adults with other disorders and to a community sample (control). Patients were recruited through an adult ADHD clinic, and community controls were recruited through flyers and advertisements. When characteristics of the adults with ADHD were compared to those of the other two groups, there were clear differ-

ences. Being easily distracted by extraneous stimuli was a clear dissimilarity between adults with ADHD and community controls; in fact, this one symptom clearly divided the two groups. However, it did not necessarily separate adults with ADHD from those with other disorders. An additional set of symptoms was found to be useful in distinguishing ADHD from other psychiatric problems. Patients more likely to have ADHD were those who often [19]:

- Made decisions impulsively
- Had difficulty stopping activities or behavior when one should do so
- Started projects or tasks without reading or listening to directions carefully
- Failed to follow through on promises or commitments made to others
- Had trouble doing things in the proper order or sequence
- Tended to speed while driving (or, in patients who do not drive, difficulty engaging in leisure/fun activities quietly)

Two additional symptoms, having difficulty sustaining attention in tasks or play activities and having difficulty organizing tasks and activities, added a small increase in classification accuracy between patients with ADHD and community controls. The proposed diagnostic criteria suggest that adults who have six of these nine symptoms, in addition to meeting certain other criteria (including onset of symptoms prior to the age of 16 years), may be considered to have ADHD. Interestingly, in this study the diagnostic criterion of having trouble staying seated when expected to do so was more likely to identify a patient with some other psychiatric disorder than an adult with ADHD.

## PATHOPHYSIOLOGY

Although the exact etiology of ADHD is unknown, certain genetic and neurologic factors have been implicated in the development of this disorder. ADHD often occurs in multiple members of the same family. Fifteen to 25% of first-degree relatives of children with ADHD are also affected [24]. Twenty-five to 50% of cases occur in families, and close to 50% of children who have parents with ADHD also have the disorder [24].

There have been several genes associated with ADHD, including the dopamine-beta-hydroxylase gene, the dopamine transporter gene, and the dopamine receptor gene [5; 24]. However, no gene has been found that reliably predicts ADHD.

Current theory focuses on dopaminergic function as the basis of ADHD. Animal models of ADHD have shown an imbalance between dopamine and norepinephrine, with increased dopaminergic activity and decreased noradrenergic activity [5; 25]. In addition, the stimulant medications used to treat ADHD influence the availability of dopamine.

Neuroimaging studies suggest that multiple areas of the brain may be involved in ADHD. The frontal striatal regions are implicated in several studies [5; 26]. There may also be changes in the corpus callosum and in the cerebellum [5; 27]. Functional imaging studies support the possibility that fronto-subcortical-cerebellar circuits are involved [5; 26].

## TREATMENT

### EVIDENCE-BASED RECOMMENDATIONS

Stimulant medications, including amphetamine and methylphenidate, are considered first-line therapy in the treatment of ADHD [5; 28]. However, other medications, such as atomoxetine, may be considered [5]. Behavior modification has a role in the overall treatment plan of ADHD, and cognitive-behavioral therapy (CBT) may be helpful for adults, although the evidence for stimulant medications is stronger.

Both the AACAP and AAP guidelines regarding ADHD include recommendations for the treatment of children and adolescents. There are no current guidelines for adult treatment from national organizations in the United States, but a Canadian group and the United Kingdom's National Institute for Health and Care Excellence (NICE) have published recommendations that may be helpful [29; 30; 31]. The NICE guideline contains recommendations for the diagnosis and management of ADHD in children, adolescents, and adults [31].

The AAP guideline emphasizes the need to view ADHD as a chronic disease and treatment as an ongoing process [13]. It recommends collaboration among the child, parents, and teachers to set goals and evaluate progress. Systematic follow-up is needed to assess the effects of treatment, whether medication, behavior therapy, or both, and to determine whether adjustments are needed. A child who fails to respond to one stimulant may respond to another. If treatment is not having a positive effect, evaluation should include adherence, the possibility of comorbid conditions, and confirmation that ADHD is the correct diagnosis.

Guidance from the 2007 AACAP guideline includes the recommendation that the treatment plan should be comprehensive but flexible and should be reviewed regularly [9]. It should include education for both the patient and his or her parents and take advantage of school and community resources and supports. Education should focus on information about ADHD, prepare parents for developmental challenges common in affected children, and provide general advice about managing behavior and academic functioning. The NICE guideline recommends that healthcare providers have regular discussions with patients with ADHD and their families or caregivers regarding their desired level of involvement in treatment planning and decisions. Ensuring continuity of care is stressed [31]. The NICE guideline also recommends that prior to starting any treatment, healthcare providers should discuss with patients and their families: the benefits/harms of treatment, both pharmacologic and nonpharmacologic; potential adverse effects and nonresponse rates; benefits of a healthy lifestyle, including exercise; their preferences and concerns; the impact of other mental health or neurodevelopmental conditions on treatment choices; and the importance of adherence to treatment [31].

First-line medical therapy with agents that are approved by the U.S. Food and Drug Administration (FDA) for ADHD is also recommended [9]. If treatment with these agents fails, the diagnosis should be reconsidered and either changed or confirmed. Off-label medications should be used for ADHD only if all the approved agents have proven unsatisfactory [9]. Treatment with behavior therapy alone may be helpful in these cases. For children younger than 5 years of age, the NICE recommends parent or caregiver participation in an ADHD-focused group training program as first-line treatment [31]. Medication for ADHD for any child younger than 5 years of age is not recommended without a second specialist opinion [31].

EVIDENCE-BASED PRACTICE RECOMMENDATION

For elementary and middle school-aged children (6 to 11 years of age), the American Academy of Pediatrics recommends prescription of an FDA-approved medications for ADHD, along with parent training in behavior management and/or behavioral classroom intervention (preferably both).

(https://pediatrics.aappublications.org/content/144/4/e20192528. Last accessed September 28, 2021.)

**Level of Evidence:** A (Well-designed randomized controlled trials or diagnostic studies on relevant populations)

Healthcare professionals should be alert for side effects of medications used in the treatment of ADHD and manage them as needed. Dose reduction or a change to a different medication may be necessary. In some cases, the medication that helps the most with ADHD will also have a bothersome side effect. If this medication must be continued, certain adjunctive medications to treat the side effect may be helpful.

If medication achieves a satisfactory response, then additional treatment such as behavioral therapy is not essential, although it may be offered. Parental preference should be considered in this case [9]. Psychosocial treatment may be helpful when the response to medication is sub-optimal, when family stressors are present, or when there is a comorbid disorder.

Periodic assessments should be conducted at least several times each year for children taking medication for ADHD. If symptoms are no longer present and this continues for at least one year, consideration may be given to stopping treatment. Treatment can be restarted if ADHD signs or symptoms return.

In general, the approach for adults is similar, with many experts agreeing that pharmacotherapy is an appropriate first-line option. Some also feel that many adults will benefit from psychosocial therapy to assist them in learning important coping skills or overcoming a demoralizing self-image.

The 2018 guideline from the Canadian ADHD Resource Alliance (CADDRA), a not-for-profit alliance of professionals working in the area of ADHD, includes a section on ADHD in adults [29]. CADDRA recommends the use of mixed amphetamine salts (extended-release), long-acting methylphenidate, or atomoxetine as first-line agents. Short- or intermediate-acting stimulants are recommended as second-line or adjunctive agents, for example if a patient requires additional medication in the evening, when a long-acting preparation wears off. The guideline also recommends psychologic interventions, such as ongoing education about ADHD and coping strategies. Patients' goals should be discussed and treatment structured accordingly.

The 2018 NICE guideline asserts that treatment for adults should be comprehensive and should address psychologic, behavioral, and occupational or educational needs [31]. The recommended first-line medication is lisdexamfetamine or methylphenidate, with atomoxetine or dexamphetamine as options if lisdexamfetamine or methylphenidate cannot be tolerated or does not produce an optimal response. Six weeks of lisdexamfetamine or methylphenidate is suggested as adequate trial [31].

## PHARMACOTHERAPY

### Stimulant Medications

Stimulant medications appear to be effective in treating ADHD, and most children with ADHD will respond to at least one of them [13]. In a review of studies in which subjects underwent a trial of both amphetamine and methylphenidate, about 85% of children responded to one or both of these medications [32]. Forty-one percent responded equally to both classes, and 44% responded preferentially to one or the other. Stimulants are also effective in adults. One systematic review and meta-analysis sought to estimate the comparative efficacy and tolerability of amphetamines (including lisdexamfetamine), methylphenidate, modafinil, atomoxetine, bupropion, clonidine, and guanfacine with each other or placebo for ADHD in children, adolescents, and adults [33]. Efficacy was defined as the change in

severity of ADHD core symptoms based on teachers' and clinicians' ratings. For ADHD core symptoms rated by clinicians in children/adolescents closest to 12 weeks, all drugs included in the review were superior to placebo, whereas only methylphenidate was superior to placebo based on teachers' ratings [33]. In adults, amphetamines, methylphenidate, bupropion, and atomoxetine were superior to placebo according to clinicians' ratings. With respect to tolerability, amphetamines were inferior to placebo in all three age groups; guanfacine was inferior to placebo only in children and adolescents; and atomoxetine, methylphenidate, and modafinil were less well tolerated than placebo only in adults. In head-to-head comparisons of the drugs, differences in efficacy, not tolerability, were found (according to clinicians' ratings). Amphetamines were favored over modafinil, atomoxetine, and methylphenidate in all three age groups at 12 weeks [33].

Stimulant medications have been shown to improve the core symptoms of ADHD, those of attention, hyperactivity, and impulsivity [13]. For children, classroom and social behavior have also been shown to improve with stimulant medication use, and these treatments may also reduce emotional over-reactivity and increase the ability to follow rules [9; 13].

### *Characteristics of Stimulant Medications*

The effect of stimulants is thought to be mediated primarily though their actions on dopamine and norepinephrine transmission. Stimulants have been shown to increase the concentration of these neurotransmitters in the frontal cortex, midbrain, and brain stem, which may explain their effect of increasing attention span and the ability to concentrate [9]. Amphetamines and methylphenidate may differ in specific actions regarding dopamine release [34]. Methylphenidate is to a large extent a norepinephrine and dopamine reuptake inhibitor, while amphetamines promote dopamine and norepinephrine efflux from neurons [35].

There is an extensive list of amphetamine and methylphenidate preparations available in the United States. Available amphetamines include dextroamphetamine, amphetamine mixed salts, and lisdexamfetamine dimesylate (prodrug of dextroamphetamine). Dexmethylphenidate and D,L-methylphenidate are methylphenidate preparations.

Stimulant medications are widely used in adults as well as children. Clinicians should review the prescribing information to determine which preparations have specifically been tested and approved for adults.

### *Dosing Options*

Amphetamine and methylphenidate preparations are available in a variety of short- and long-acting formulations that can be taken orally. A transdermal methylphenidate patch is available as well. There is no one "best" dose for these medications. In general, stimulants should be started at a low dosage then titrated up about once a week to the desired effect [5].

The AACAP guideline supports a schedule of increasing the dose every one to three weeks until symptoms remit, side effects prevent further increase, or the maximum dose is reached [9]. If a long-acting formulation is preferred, there is no need to start with a short-acting formulation. It is often helpful to have reports from a parent or teacher after a week on each dose and to have an office visit after the first month of treatment. Titration should continue even if some improvement is seen at a lower dose. Higher doses may lead to better effect, but if side effects become problematic or improvement levels off, the dose can be reduced.

Patients and their families often report immediate improvement with stimulant medication [36]. In children, worsening behavior is sometimes seen in the evenings, when the drug begins to wear off [9].

This is sometimes interpreted as a "rebound" effect. However, based on studies showing this phenomenon even in children taking placebo, it is unlikely that this is an effect of the medication. If behavior is worse in late afternoon and evening, a small dose of immediate-release stimulant in the evening may help alleviate symptoms during this time.

Close follow-up multiple times a year is essential in order to evaluate progress, side effects, and adherence to medications. If medication is to be stopped, careful attention should be paid for a return of ADHD signs or symptoms. AACAP recommends not attempting to stop medication during demanding times, such as the beginning of a school year. Of note, there is an FDA-issued black box warning for severe depression during withdrawal of methylphenidate [9; 35].

### *Side Effects*

Many side effects associated with stimulant use are likely to resolve with time. Side effects that are reported commonly include insomnia, reduced appetite, headaches, stomachaches, and emotional lability [36]. Anorexia often resolves after a few weeks. In children, some height delay has been observed when treatment is initiated, but research shows this growth delay levels off by the end of adolescence [37; 38; 39].

Some medications may cause side effects that require adjustment of the dose, schedule, or choice of drug. Some side effects, particularly insomnia, can be improved with long-acting formulations. Occasional reactions (e.g., mood disturbances, hallucinations, psychosis) occur if the dose is too high.

In some cases, if side effects persist despite improvement in the symptoms of ADHD and changing medications is not effective or not an option, side effects may be treated with an additional medication [9]. Clonidine has been used for tics. Insomnia may be treated with an antihistamine, clonidine, or trazodone. However, the risk of priapism often discourages the use of trazodone to treat insomnia in males [35; 40].

### *Precautions*

Stimulant medications are considered safe for use in most children and adults. However, there are areas of concern that should be considered prior to initiating treatment. Although the actual cardiac risk is not known, stimulant medications carry a warning against use in persons with certain cardiac abnormalities, due to sympathomimetic effects [41]. The AAP and the American Heart Association recommend that prior to starting a patient on ADHD medications, patient and family health histories should be obtained and a physical exam should be performed with a focus on cardiovascular disease risk factors [41]. This was a Class I recommendation with level of evidence C, meaning that the recommendation was strong although based primarily on expert consensus, case studies, and/or standard of care. Acquiring an electrocardiogram (ECG) prior to starting treatment was considered reasonable but not mandatory. It was also recommended that the blood pressure and heart rate of the patient be monitored, within 1 to 3 months of starting medication and every 6 to 12 months thereafter (also a IC recommendation) [41]. Later the same year, AAP released a statement supporting the use of careful history and physical exam to assess for cardiac abnormalities [42]. However, this statement noted a lack of evidence to support routine ECGs before prescribing stimulant medications. Cardiac risk should also be considered when prescribing stimulant medications for adults. This risk will be discussed in detail later in this course.

Methylphenidate has been reported to lower seizure threshold in certain children; however, stimulants may be used safely in children who have epilepsy that is well-controlled [43; 44; 45]. Studies suggest that low doses of methylphenidate may also be safely used in children with difficult-to-treat epilepsy; in these instances, its use positively impacts the patient's quality of life [46; 47].

Stimulants carry several black box warnings. Methylphenidate may exacerbate or induce psychosis [35; 48; 49]. Caution is advised for patients who are emotionally unstable. Patients with histories of alcoholism or drug dependence may become tolerant and psychologically dependent on methylphenidate. During withdrawal, severe depression may occur or be unmasked [35].

Amphetamines also carry several black box warnings. They have high abuse potential and may lead to drug dependence. There is a potential for nontherapeutic use or distribution to others. Also, there is a black box warning for serious cardiovascular adverse events and sudden death reported with misuse of this medication [35].

**Non-Stimulant Medications**

***Atomoxetine***

Atomoxetine has been approved by the FDA for the treatment of ADHD in both children and adults; however, it may be less effective than stimulant medications. Atomoxetine is a noradrenergic reuptake inhibitor, and it has several important differences in comparison to stimulants [9; 35]. Atomoxetine has different side effects than stimulant medication and is more likely to cause sedation and nausea. The treatment effect may be smaller than that observed with stimulant medications, and its effect may take longer to appear.

Atomoxetine should be discontinued if symptoms of hepatic disease appear. This medication also carries cardiac warnings similar to stimulants. Lastly, atomoxetine carries a black box warning for suicidal ideation in children with ADHD, especially in the first month of treatment [35].

***Clonidine***

Clonidine has been evaluated for the treatment for ADHD in children with co-existing conditions, especially sleep disturbance. In a double-blind, randomized, placebo-controlled study of 122 children given clonidine, methylphenidate, or both, the authors concluded that methylphenidate offered a better combination of efficacy and tolerability compared to clonidine [50]. Clonidine was efficacious but was also associated with increased sedation.

In 2010, extended-release clonidine was FDA approved for use alone or in conjunction with stimulant therapy for pediatric ADHD [51]. The recommended initial dose is 0.1 mg at bedtime for children 6 years of age or older [35]. The dose is then increased by 0.1 mg every week until the desired response is achieved, to a maximum of 0.4 mg per day. It should also be tapered down slowly upon discontinuation [35].

***Guanfacine***

After being used for many years off label, extended-release guanfacine was approved for the treatment of ADHD in children and adolescents in 2009, either as monotherapy or an adjunct to stimulants [35]. Guanfacine is an alpha-2A adrenergic agonist and acts by enhancing prefrontal cortical regulation of attention and impulse control [35; 52]. In a multicenter, double-blind, placebo-controlled, fixed-dosage escalation study involving 345 patients 6 to 17 years of age, three dosages of guanfacine (2 mg, 3 mg, or 4 mg per day) were associated with significant improvements on hyperactivity/impulsivity and inattentiveness subscales compared to placebo [53]. Additional studies have indicated that it may be particularly useful in children with ADHD and oppositional symptoms [54; 55].

The recommended dose of guanfacine is 1 mg once daily; the dose may be adjusted by increments no larger than 1 mg/week, as tolerated, to a maximum dose of 4 mg/day [35]. The most common adverse effects are somnolence, xerostomia, headache, fatigue, and sedation, but they are generally mild to moderate and/or transient [35; 56].

Other non-stimulant drugs, including bupropion and tricyclic antidepressants, have been used to treat ADHD. However, there is limited evidence to support their use, and they have not received indications from the FDA for ADHD [35; 57]. The AACAP recommends clinicians consider using behavior therapy before using these agents because the level of effect may be similar [9].

### *Bupropion*

Although bupropion does not have FDA approval for ADHD, it is considered by many to be a second-line agent for ADHD and possibly a first-line agent for patients who have both ADHD and either a mood disorder or a substance abuse disorder [9; 35; 58; 59]. Studies suggest that bupropion is effective and well tolerated in children and adolescents with ADHD and may have some efficacy in treating children with ADHD and conduct disorder (CD) [60; 61; 62; 63]. Small trials and one systematic review have also supported the use of bupropion for ADHD in adults, but more research is needed to determine its benefit and long-term outcomes in this population [64; 65; 66; 67]. However, more research is needed to establish the most appropriate role for this medication in the adult population.

### *Tricyclic Antidepressants*

Certain tricyclic antidepressants, in particular desipramine, appear to have some efficacy in treating ADHD in children and adults [68; 69]. However, there were reports of four children who had sudden death while being treated with desipramine, which led to a contraindication of its use in children younger than 12 years of age [5; 70; 71]. If tricyclic antidepressants are to be tried, a baseline ECG and ongoing monitoring are needed [9]. These medications also carry warnings, including a boxed warning about suicide risk in children, adolescents, and young adults with depression. Use of desipramine for ADHD is off-label and should be reserved for cases where other medications have not been effective or were not tolerated [35].

### *Modafinil*

Modafinil is a non-stimulant alertness agent initially approved for the treatment of narcolepsy and is currently not FDA approved in children or for ADHD [35]. Concerns about serious skin rash and preliminary safety data have limited its use in children with ADHD [72].

## BEHAVIORAL THERAPY

Behavioral therapy is a term commonly used to describe a type of psychosocial approach to treating childhood ADHD. One aspect of this therapy is parent training; a typical program of behavioral therapy involves 10 to 20 sessions for parents, including information about ADHD and advice on managing behavior, anticipating misconduct, using a token economy, and using a daily school report card [9]. Therapies for children may include teaching skills and adaptive behaviors, such as how to organize school materials or how to improve relationships with peers [73]. Parent training in behavior therapy (also known as behavior management training for parents, parent behavior therapy, and behavioral parent training) has been shown to strengthen the relationship between the parent and child and to decrease children's negative or problem behaviors [74].

The Multimodal Treatment Study of Children with ADHD was a 14-month trial of specific medication management, intensive behavioral therapy (group and individual sessions, teacher consults, a classroom behavioral aide for 12 weeks, and a summer program), both medication and behavioral therapy, or ordinary community care [75]. This study revealed that combination treatment did not significantly differ from medication management alone on direct comparisons.

Combined treatment was found to be superior to intensive behavioral therapy and/or community care for oppositional and/or aggressive symptoms, internalizing symptoms, teacher-rated social skills, parent-child relations, and reading achievement. At follow-up three and eight years after intensive study treatments had concluded, all treatment groups were similar on measures of ADHD symptoms [76; 77].

A two-year trial compared the efficacy of methylphenidate alone; methylphenidate with psychosocial treatment (including parent training and counseling, social skills training, psychotherapy, and academic assistance); and methylphenidate plus a psychosocial control treatment [78]. Significant improvement was seen with all treatments; combination treatment did not provide an advantage.

A randomized clinical trial compared combined treatment (brief intensive multimodal behavior therapy and methylphenidate) to treatment with methylphenidate alone. The 45 children who participated were reassessed at adolescence in a naturalistic follow-up 4.5 to 7.5 years after treatment. A matched non-ADHD control group included 23 children. Of the adolescents who participated in the follow-up study, 50% still met the diagnostic criteria for ADHD [79]. Adolescents in the combined treatment group used significantly less medication than those in the methylphenidate-alone group. Overall, the adolescents showed a significant decline in hyperactivity/impulsivity and oppositional and CD symptoms from post-test to follow-up. Adolescents originally diagnosed with ADHD fared significantly worse than the matched controls on all outcomes except CD and substance abuse symptoms [79].

As stated, for children younger than 5 years of age, the NICE recommends parent or caregiver participation in an ADHD-focused group training program as first-line treatment [31]. The NICE guideline also recommends training for parents and caregivers of school-aged children with ADHD [31]. Parent training and group-based ADHD-focused support is recommended for parents of school-aged children who display symptoms of oppositional defiant disorder (ODD) or CD [31]. This guideline also recommends that CBT be considered in children who have benefited from medication but whose symptoms continue to cause significant impairment in social skills with peers, problem-solving, self-control, active listening skills, and dealing with and expressing feelings [31].

Evidence regarding psychosocial treatments in adults is very limited. However, there may be a role for CBT [80; 81]. A few small studies support the use of CBT programs, and CBT is often used in practice. The NICE guideline recommends either elements of or a full program of CBT for adults with ADHD in whom nonpharmacologic treatment is indicated [31].

The focus of CBT for ADHD in adults includes both the patient's thought process and his or her coping behaviors. Cognitive therapy addresses beliefs that reinforce problematic behaviors, such as feelings of failure; the goal is to diminish the power of such beliefs and to help the patient cope efficiently with the symptoms that led to them. In addition, there are many specific skills and behaviors that patients can learn, such as ways to improve organization or reduce the chance of making an impulsive decision. These skills can be individualized, depending on what works best for each patient.

Other areas of patients' lives may also be affected by ADHD. For adults, couples counseling, family therapy, and education about parenting may all be of use. Some patients will also benefit from therapy to improve their interpersonal skills.

## TRIGEMINAL NERVE STIMULATION

In 2019, the FDA permitted marketing of the first medical device for the treatment of ADHD [82]. The Monarch external Trigeminal Nerve Stimulation (eTNS) System is indicated for patients 7 to 12 years of age who are not currently taking prescription ADHD medication. The device consists of a cell-phone-sized device that generates a low-level electrical pulse and connects via a wire to a small

patch that adheres to a patient's forehead, just above the eyebrows [82]. TNS is done at home during sleep and may take up to four weeks to produce a noticeable response. In studies, children who used TNS showed considerable improvements in severity and frequency of ADHD symptoms [82]. The most common side effects are drowsiness, increased appetite, sleep difficulties, teeth clenching, headache, and fatigue.

## COMORBIDITIES IN CHILDREN

Comorbidities are common in patients with ADHD, and many psychiatric diagnoses may be confused with ADHD in children. Often, individuals with ADHD and a comorbid psychiatric disorder require additional treatment for the comorbid illness in order to achieve optimal functioning.

Multiple studies have shown that among children who have ADHD, 54% to 84% have ODD, 15% to 19% smoke or have other substance abuse disorders, and 25% to 35% have a learning or language problem [9]. Up to one-third of children with ADHD also have an anxiety disorder or depression, and approximately 16% meet the criteria for mania [9].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Academy of Pediatrics recommends that the primary care clinician, if trained or experienced in diagnosing comorbid conditions, may initiate treatment of such conditions or make a referral to an appropriate subspecialist for treatment. After detecting possible comorbid conditions, the patient should be referred to an appropriate subspecialist to make the diagnosis and initiate treatment.

(https://pediatrics.aappublications.org/content/144/4/e20192528. Last accessed September 28, 2021.)

**Level of Evidence**: C (Single or few observational studies or multiple studies with inconsistent findings or major limitations)

Rarely, certain medical conditions may present with symptoms of ADHD, including head trauma, encephalopathies, and thyroid disorders, in particular hyperthyroidism [9]. Patients who have ADHD and medical or psychiatric comorbidities require consideration of the effects of different medications and interactions between symptoms.

### LEARNING DISABILITY

Often, ADHD is confused with learning disability, but they are distinct entities. Learning disorders are classified as specific learning disorders in the DSM-5, with divisions that specify disability in reading, writing, and mathematics [11]. Specific learning disorders are listed under neurodevelopmental disorders alongside ADHD, autism spectrum disorder, communication disorders, coordination disorders, and intellectual disability [83]. An estimated 31% to 45% of children have ADHD with specific learning disorders and 5% have ADHD without specific learning disorders [84; 85].

For patients with ADHD and specific learning disorders, it is important to assess whether low performance may be secondary to ADHD and/or whether inattentiveness may be due to the specific learning disorders. It is appropriate to consider treating ADHD first, as this may allow better assessment of learning problems after symptoms of ADHD improve.

In addition to deficits in learning abilities, youth with ADHD, particularly those with a family history of substance use disorder, also exhibit deficits in reward processing. One study investigated reward-based learning as a function of the severity of substance abuse risk in drug-naïve youth with ADHD [86]. The youth were asked to perform a novel anticipation, conflict, and reward task. The authors measured reaction time, accuracy, and learning rates and assessed the influence of learned predictions of reward probability and stimulus congruency on reaction times. The most significant deficits in accuracy, in learning rates, and in adjusting to task difficulty were observed in high-risk youth (i.e., those with ADHD and parental substance use disorder) [86].

## DEPRESSION

In patients who have ADHD and depression, clinicians must decide whether to treat depression or ADHD first or whether to begin treatment for both at once. If the patient is experiencing a mild depression, there is a possibility that the depressive symptoms are related to demoralization resulting from the multiple functional difficulties that ADHD can cause [9; 87].

There is limited evidence for the use of antidepressants in combination with ADHD medications. In a double-blind trial, children with ADHD and depression or anxiety were treated with fluoxetine or placebo for eight weeks, and then atomoxetine was added for the final five weeks of the study [88]. ADHD, depressive, and anxiety symptoms were significantly reduced in both groups. Although this may seem to suggest that both fluoxetine and atomoxetine can treat depression, lack of a placebo-only arm precludes conclusions about such an effect. The combination was well-tolerated, however.

In a small trial of sustained-release bupropion in 24 children 11 to 16 years of age with comorbid depression, clinician-rated improvement was observed in 58% of participants for both depression and ADHD, 29% for depression only, and 4% for ADHD only. Both parents' and children's ratings of depression and ADHD improved, as did parents' ratings of ADHD. Teachers' ratings for ADHD did not improve in this study [89].

## CONDUCT DISORDER AND OPPOSITIONAL DEFIANT DISORDER

Children with CD or ODD are often included in trials of ADHD treatment. Fewer studies exist that specifically assess the treatment of comorbid CD/ODD and ADHD. In a four-week randomized, double-blind study of 308 children 6 to 17 years of age with ODD, 79% of whom had comorbid ADHD, treatment with mixed amphetamine salts improved ODD symptoms as measured by parent rating scales [90]. A meta-analysis of three controlled trials concluded that atomoxetine was effective for ADHD symptoms whether or not ODD was present, and that reduction in ODD symptoms was highly related to the magnitude of ADHD response [91]. In 84 children 6 to 15 years of age with and without ADHD in a five-week randomized trial, methylphenidate improved CD symptoms [92]. A prospective study of 37 children 6 to 14 years of age with ODD and ADHD found methylphenidate and atomoxetine to be effective in the treatment of ODD comorbid with ADHD of short duration [93].

Stimulant treatment for ADHD may also help with both overt and covert aggression-related behaviors, whether or not CD or ODD is present. Overt aggression involves confrontations such as assault, threats, and tantrums. Covert aggression includes lying, cheating, and stealing. A meta-analysis involving 28 studies examined the effect of stimulants on such behaviors [94]. This analysis showed statistically significant reductions in parents' and teachers' ratings of overt aggression and in overall ratings of covert aggression as well. A retrospective review was conducted for 97 children 4 to 7 years of age, diagnosed with disruptive behavior disorders, and enrolled in an intensive outpatient behavioral intervention program [95]. Child Behavior Checklist (CBCL) scores both pre- and post-intervention were compared between children who received stimulants and those who did not. While there were significant improvements in behavior outcomes pre- and post-intervention among both groups, the authors found no benefit with the use of stimulants for long-term treatment of disruptive behavior in children younger than seven years of age [95].

Clonidine may also help with aggressive behaviors, although this is not an FDA-approved indication [35]. In a randomized trial involving 67 children with ADHD and comorbid ODD or CD, clonidine added to stimulant treatment produced significantly more responders on the conduct scale of the Connors Behavior Checklist (but not on the hyperactive index) compared to placebo and a stimulant medication [96]. Clonidine was associated with transient sedation and dizziness in this study.

Additional medications have been studied in the treatment of CD or ODD in children with ADHD. In a small, three-week study involving 24 children 12 to 16 years of age, quetiapine added to a long-acting methylphenidate reduced symptoms of ADHD in children with severe aggression who did not respond to methylphenidate alone [97]. However, a Cochrane review found no evidence to support the use of quetiapine for disruptive behavior disorders in children and adolescents, but it did find limited evidence of efficacy of risperidone in reducing aggression and conduct problems in the short term in this population [98].

## SUBSTANCE ABUSE

A common concern clinicians and parents have when considering stimulant medications for the treatment of ADHD is the risk of substance abuse. In patients with a history of substance use disorder, amphetamines are generally contraindicated and caution is advised with methylphenidate.

Evidence is mixed regarding whether stimulant treatment increases the risk of substance abuse, and while predictors of risk remain understudied, the presence of CD appears to predict future substance abuse [99; 100; 101; 102; 103]. Of the core ADHD symptoms, hyperactivity/impulsivity is more consistently associated with substance abuse than inattention, which is associated only with alcohol use [102]. Studies have suggested that the use of stimulant medication may protect against future substance abuse. In a 10-year follow-up study involving 140 White male children (112 reassessed at the 10-year point) who were 6 to 17 years of age at entry, there were no statistically significant associations between treatment with stimulants and drug, alcohol, or nicotine use disorders at a mean age of 22 years [100]. These results were adjusted for CD. In a five-year follow-up study comparing 94 adolescents who had been treated with stimulants to 20 who had not, no increase in the risk of substance use disorders or cigarette smoking was seen [104]. Stimulant treatment had a protective effect on development of substance use disorders and cigarette smoking, an effect that remained after controlling for CD. However, independent of treatment with stimulants, ADHD is a significant risk factor for the development of substance use disorder and cigarette smoking in both men/boys and women/girls. A 10-year follow-up study of 268 children and adolescents with and without ADHD were followed prospectively and blindly into their young adult years. Over the follow-up period, ADHD was found to be a significant predictor of any substance use disorder and cigarette smoking. Comorbid CD and ODD at baseline were also significant predictors of substance use disorder in both sexes [103].

Increasing age at initiation of treatment with stimulant medication was positively associated with the incidence of non-alcohol substance abuse disorder in one study [105]. Post hoc analysis showed that controlling for the development of antisocial personality disorder eliminated this association. A long-term follow-up study also found an association between older age at initiation of stimulant treatment and increased risk of later substance use disorder and alcohol abuse [106]. The study of 208 boys and girls with ADHD found the relative risk for substance use disorder and alcohol abuse in adulthood was 7.7 and 5.2, respectively, compared to age-matched population controls. Female sex and childhood CD were also positively associated with an increased risk of later substance and alcohol abuse [106].

Meta-analysis was conducted on six long-term studies, with a total of 674 medicated subjects and 360 unmedicated subjects [107]. Two studies had follow-up in adolescence and four in young adulthood. Subjects were followed for a minimum of four years. Compared to subjects who were not using pharmacotherapy, those who did receive medication had a 1.9-fold lower risk for substance abuse disorders. The protective effect was larger in studies that stopped at adolescence than in studies that went into adulthood. Since this review, results from multiple longitudinal studies have not found protective effects of stimulant treatment on substance use outcomes [100; 105; 108]. A meta-analysis of 15 longitudinal studies examined whether treatment with stimulants for ADHD predicted later substance outcomes. A

total of 2,565 individuals were analyzed across five types of substance (i.e., alcohol, cocaine, marijuana, nicotine, and nonspecific drugs) for lifetime use and abuse or dependence [109]. The results indicated that substance use/abuse outcomes for children with ADHD who were treated with stimulant medication were comparable to outcomes for children with ADHD who were not treated with stimulant medication [109].

The possibility of diversion of ADHD medication, including patients sharing stimulants with friends or selling their medication, is also a concern. Experts often suggest choosing certain preparations, including the longer-acting stimulants, to help reduce the risk of both diversion and abuse.

## ANXIETY

Anxiety is comorbid with ADHD in 33% of cases, an association that aggravates inattention and concentration problems [87]. Stimulant medication has been investigated in the treatment of children with ADHD and symptoms of anxiety. One study involving 45 children 8 to 14 years of age with ADHD investigated changes in depression, anxiety, obsessive-compulsive symptoms, and health-related quality of life during treatment with methylphenidate [110]. Based on self, parent, and teacher report at baseline and at the end of the first and third months of treatment, the children were evaluated for changes in inattention, hyperactivity, impulsivity, depression, anxiety, obsessive-compulsive symptoms, and quality of life. Over three months of treatment with methylphenidate, symptoms of depression, anxiety, and checking compulsion decreased while quality of life and symptoms of inattention, hyperactivity, and impulsivity improved [110]. In a double-blind placebo-controlled study involving 176 children 8 to 17 years of age, atomoxetine was found to reduce ADHD symptoms in children with comorbid anxiety [111]. Atomoxetine was also found to reduce anxiety, on both clinician- and self-rated measures.

One small study assessed the use of fluvoxamine for anxiety in combination with methylphenidate. Twenty-six children whose ADHD symptoms had responded to methylphenidate but who still had anxiety were randomized to receive fluvoxamine or placebo in addition to the stimulant [112]. While the combination was well-tolerated, fluvoxamine was not found to have a statistically significant effect on anxiety in this group.

The role of behavior therapy in the treatment of anxiety in children also diagnosed with ADHD was examined through analysis of data from the Multimodal Treatment Study [113]. Children with ADHD plus anxiety disorders (but not ODD/CD) were likely to respond equally well to behavioral and medication treatments. Children with ADHD and no comorbidities or ADHD with ODD/CD (but without anxiety disorders) responded best to medication with or without behavioral treatments. Children with ADHD, anxiety, and ODD/CD had optimal response when treatments were combined.

The application of CBT in children with ADHD and co-occurring anxiety disorder varies depending on the type of disorder (i.e., generalized, social, or separation anxiety disorder) and should emphasize cognitive restructuring processes. Children with ADHD and anxiety disorder generally benefit less from CBT than children who are solely anxious. The distractibility and hyperactivity of the child with ADHD may interfere with and decrease the effectiveness of CBT [114].

## OTHER DISORDERS

One concern with using stimulant medications is the risk of triggering mania in a patient with bipolar disorder. Evidence is limited and based on small trials but supports stimulant use after mood is stabilized [115; 116; 117]. Also, the development of tics is a potential side effect of stimulant medications [87]. In general, however, treatment of ADHD with stimulants does not appear to increase existing tics and may even provide improvement [9; 118; 119; 120; 121].

## COMORBIDITIES IN ADULTS

Comorbidities are also common in adults with ADHD. Based on the National Comorbidity Survey Replication, the odds ratio of an adult with ADHD having any mood disorder is 5.0, any anxiety disorder is 3.7, any substance use disorders is 3.0, and intermittent explosive disorder is 3.7 [6].

### SUBSTANCE ABUSE

Studies in teens and young adults show that diversion and misuse of stimulants are common [122; 123]. One study, examining more than 100 four-year colleges in the United States, found that non-medical stimulant use was as high as 25% at some schools [124]. Data from the 2019 National Survey on Drug Use and Health indicate that the highest rates of past-year prescription stimulant misuse occurred among young adults 18 to 25 years of age (5.8%) and adolescents 12 to 17 years of age (1.7%) [125]. First use of stimulants in adolescence and adulthood may be associated with higher risk of stimulant misuse/abuse [126].

As with children, it is recommended that stimulants be used with caution if a patient has a history of substance abuse. In fact, amphetamine-based drugs are generally contraindicated in this population. If a patient has a current substance abuse problem, it is important to treat this appropriately while addressing symptoms of ADHD. When both disorders are diagnosed at once, it is often recommended that the substance use be addressed first, in part because behaviors related to substance abuse can mimic ADHD symptoms [29; 127]. After the patient has stopped the substance misuse and is in recovery, he or she can be reassessed for ADHD and treated, as necessary. Evidence suggests stimulant medications may not exacerbate addiction. In a 12-week, double-blind, placebo-controlled trial involving 48 cocaine-dependent adults with ADHD, the use of methylphenidate did not lead to group differences in self-reported cocaine use or cocaine craving or in urinalysis results [128].

A double-blind, 12-week trial involving 98 methadone-maintained patients (53% of whom also had cocaine dependence/abuse) did not find evidence of medication misuse or worsening of cocaine use in a group receiving methylphenidate [129]. In this study, the reduction in ADHD symptoms was similar with methylphenidate, bupropion, and placebo, and neither treatment nor placebo appeared to offer an advantage for reducing cocaine use. In a later study with cocaine abusers, analysis of urine toxicology data suggested that methylphenidate users had less cocaine use than a placebo group during the trial [130]. A Cochrane review found that psychostimulants, including methylphenidate, appeared to increase the proportion of patients achieving sustained cocaine and heroin abstinence among methadone-maintained, dual heroin-cocaine addicts. However, retention to treatment was low [131].

There may be an advantage to using long-acting or controlled-release formulations of stimulant medications. Spencer and colleagues studied plasma d-methylphenidate levels, responses to detection/likeability questionnaires, and dopamine transporter receptor occupancies in 12 healthy adults randomly assigned to single doses of immediate-release or osmotic-release methylphenidate [132]. Subjects receiving osmotic-release methylphenidate had a longer time to maximum concentration and to maximum central nervous system dopamine transporter occupancy, and they had no detection or likeability on questionnaires. Kollins and colleagues found stimulant-like drug effects (such as increased ratings of "good effects") with immediate-release methylphenidate, while a sustained-release formulation had smaller and more transient effects [133].

There may also be an advantage in using the prodrug lisdexamfetamine dimesylate, which was designed to limit abuse potential. Jasinski and colleagues studied "liking effects" in single IV doses of lisdexamfetamine dimesylate (25 or 50 mg) and immediate-release d-amphetamine sulfate (10 or 20 mg) compared to placebo [134]. Data was gathered in a randomized, double-blind, crossover study including 12 total subjects, all adult substance abusers.

Abuse-related liking scores were higher with 20 mg of d-amphetamine than with placebo. For 50 mg lisdexamfetamine dimesylate, there was no significant difference from placebo.

## DEPRESSION

Evidence is lacking to guide treatment of depression in adults who have ADHD, although selective serotonin reuptake inhibitors (SSRIs) and bupropion are common choices. Monoamine oxidase inhibitors (MAOIs) are contraindicated in patients taking stimulants or atomoxetine. With atomoxetine, caution with SSRIs that are strong cytochrome P450 2D6 (CYP2D6) inhibitors is advised as they may increase atomoxetine levels; bupropion also inhibits this enzyme [135]. With methylphenidate, caution is advised with SSRIs and tricyclic antidepressants due to the possibility of decreased metabolism of these drugs [35]. Amphetamines may enhance the activity of tricyclic antidepressants, and cardiovascular risks may be increased with this combination [136]. Caution is also advised with amphetamines in patients taking bupropion, as this is associated with an increased risk of seizures. It is also recommended that amphetamines be avoided in patients taking venlafaxine, as this combination is associated with increased weight loss [35].

## MEDICAL COMORBIDITIES

Caution is advised in prescribing stimulants or atomoxetine in adults with cardiovascular concerns. A full medical history, physical exam, and additional evaluation may be needed. Sudden death, stroke, and myocardial infarction have been reported at usual doses for ADHD, but the role of the medications in these events is not known [35]. In general, it is recommended that stimulants be avoided in adults with serious cardiac structural abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, and other serious cardiac problems. Regular monitoring for changes in blood pressure and heart rate is suggested, and stimulants and atomoxetine should be used with caution if a patient has conditions that could be worsened by such changes [35]. Clinicians must be vigilant regarding cardiac symptoms that develop during treatment.

Stimulants may increase blood pressure and heart rate, but there have been few studies on the effects on this phenomenon. In an open-label trial, 13 adults with ADHD and controlled essential hypertension took extended-release mixed amphetamine salts for six weeks and then discontinued medication for two weeks [137]. The stimulant did not cause sustained blood pressure elevations, did not increase the number of single episodes of hypertension, and did not lead to a group mean increase in blood pressure or pulse.

Weisler and colleagues found that with extended-release mixed amphetamine salts used for up to 24 months, doses of 20–60 mg/day were associated with small but statistically significant changes in blood pressure and pulse [138]. At 24 months, there was a clinically insignificant increase in QT, although no subject had a QT interval greater than 480 msec. Seven subjects stopped treatment due to a cardiovascular adverse event (two for palpitations/tachycardia and five for hypertension), although none were considered serious.

Data were reanalyzed from placebo-controlled studies of five different ADHD medications (methylphenidate, amphetamine compounds, pemoline, bupropion, and desipramine) in order to evaluate the effects of these medications on blood pressure and pulse [139]. Statistically significant increases in systolic blood pressure were observed with bupropion (5.9 mm Hg) and amphetamine (5.4 mm Hg). Significant increases in diastolic blood pressure were observed with desipramine (7.1 mm Hg). Statistically significant increases in heart rate were observed for bupropion, amphetamine, and methylphenidate. The authors concluded that, in general, adults being treated for ADHD should have blood pressure and heart rate monitored during treatment.

## EDUCATING PATIENTS AND PARENTS

Communication with patient and family is essential to ADHD care. This includes explaining risks and benefits of medications. Ongoing education, communication, and follow-up are recommended. It is often helpful if clinicians encourage questions and have patients repeat back information in their own words.

Alerting patients and/or parents to potential side effects may help with adherence by letting them know that such responses are not unexpected. It can also be helpful to let patients and/or caregivers know that some side effects resolve on their own, and if necessary, a lower dose or adjunctive medication can reduce discomfort.

Patients and their families should also know that medication is not a cure for ADHD. Signs and symptoms will return as the medication's effect tapers. In addition, while medication can be expected to reduce core manifestations, such as hyperactivity and inattention, and may also help with children's behavior, it will not necessarily address all the problems associated with ADHD. Even if formal behavior therapy is not part of treatment, advice about managing children's behavior may be helpful.

The AACAP guideline includes education and communication as essential parts of ADHD treatment [9]. Patients, and parents when the patients are children, can benefit from information about ADHD tailored to developmental age and health literacy. Healthcare professionals should have information available about school and community supports, including special accommodations for any comorbid learning disability. In some cases, ADHD itself may be considered a disability and services may be available through the public schools.

### CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

As a result of the evolving racial and immigration demographics in the United States, interaction with patients for whom English is not a native language is inevitable. Because patient education is such an important aspect of the care of patients with ADHD, it is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for patient or caregiver understanding. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. (In many cases, the terms "interpreting" and "translating" are used interchangeably, but interpreting is specifically associated with oral communication while translating refers to written text.) Frequently, this may be easier said than done, as there may be institutional and/or patient barriers.

Depending upon the patient's language, an interpreter may be difficult to locate. Or, an organization may not have the funds to bring in an interpreter. Also, bringing in an interpreter creates a triangular relationship with a host of communication dynamics that must be negotiated [140]. Many view interpreters merely as neutral individuals who communicate information back and forth. However, another perspective is that the interpreter is an active agent, negotiating between two cultures and assisting in promoting culturally competent communication and practice [141; 142]. In this more active role, the interpreter's behavior is also influenced by a host of cultural variables such as gender, class, religion, educational differences, and power/authority perceptions of the patient [141; 142]. Consequently, an intricate, triangular relationship develops between all three parties. Another factor affecting the communication process is the fact that many interpreters are not adequately trained in the art of interpretation in mental health and general health settings, as there are many technical and unfamiliar terms. An

ideal interpreter goes beyond being merely proficient in the needed language/dialect [143]. Interpreters who are professionally trained have covered aspects of ethics, impartiality, accuracy, and completeness [144]. They are also well-versed in interpreting both the overt and latent content of information without changing any meanings and without interjecting their own biases and opinions [144]. Furthermore, knowledge about cross-cultural communication and all the subtle nuances of the dynamics of communicating in a mental health or general health setting is vital [142; 143].

On the patients' side, they may be wary about utilizing interpreters for a host of reasons. They may find it difficult to express themselves through an interpreter [145]. If an interpreter is from the same community as the patient, the client/patient may have concerns about sharing private information with an individual who is known in the community and the extent to which the information disclosed would remain confidential. In some cases, raising the issue of obtaining an interpreter causes the client/patient to feel insulted that their language proficiency has been questioned. Finally, if an interpreter is from a conflicting ethnic group, the patient may refuse having interpreter services [140]. The ideal situation is to have a well-trained interpreter who is familiar with health and mental health concepts.

If an interpreter is required, the practitioner must acknowledge that an interpreter is more than a body serving as a vehicle to transmit information verbatim from one party to another [145]. Instead, the interpreter should be regarded as part of a collaborative team, bringing to the table a specific set of skills and expertise [145]. Several important guidelines should be adhered to in order to foster a beneficial working relationship and a positive atmosphere.

A briefing time between the practitioner and interpreter held prior to the meeting with the client/patient is crucial. The interpreter should understand the goal of the session, issues that will be discussed, specific terminology that may be used to allow for advance preparation, preferred translation formats, and sensitive topics that might arise [143; 145; 146]. It is important for the client/patient, interpreter, and practitioner to be seated in such a way that the practitioner can see both the interpreter and client/patient. Some experts recommend that the interpreter sit next to the client/patient, both parties facing the practitioner [144].

The practitioner should always address the client/patient directly. For example, the practitioner should query the client/patient, "How do you feel?" versus asking the interpreter, "How does she feel?" [144]. The practitioner should also always refer to the client/patient as "Mr./Mrs. D" rather than "he" or "she" [145]. This avoids objectifying the client/patient.

At the start of the session, the practitioner should clearly identify his/her role and the interpreter's role [145]. This will prevent the client/patient from developing a primary relationship or alliance with the interpreter, turning to the interpreter as the one who sets the intervention [143]. The practitioner should also be attuned to the age, gender, class, and/or ethnic differences between the client/patient and the interpreter [145]. For example, if the client/patient is an older Asian male immigrant and the interpreter is a young, Asian female, the practitioner must be sensitive to whether the client/patient is uncomfortable given the fact he may be more accustomed to patriarchal authority structures. At the conclusion of the session, it is advisable to have a debriefing time between the practitioner and the interpreter to review the session [143; 145; 146].

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter. In any case in which information regarding diagnostic procedures, treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered.

## RESOURCES

Some patients and families will appreciate web-based or written information. Several reliable sources are available.

**American Academy of Pediatrics**
https://www.aap.org

**ADHD: Parents Medication Guide, from the American Psychiatric Association and the American Academy of Child and Adolescent Psychiatry**
http://www.parentsmedguide.org/parentguide_english.pdf

**National Institute of Mental Health ADHD Booklet**
https://www.nimh.nih.gov/health/publications/attention-deficit-hyperactivity-disorder-adhd-the-basics/index.shtml

**National Resource Center on ADHD, a program of Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD)**
https://chadd.org/about/about-nrc

## CONCLUSION

ADHD has a significant effect on the health of millions of Americans. Accurate and timely diagnosis, referral, and treatment are necessary in order to effectively manage the disease and to maintain patients' quality of life. However, ADHD can be difficult to recognize, particularly in adults and patients with comorbid psychiatric conditions. The continued stigma of the disease further complicates diagnosis and treatment.

For clinicians, a clear understanding of the epidemiology, diagnostic criteria, pathophysiology, differential diagnosis, and treatment of ADHD is necessary in order to ensure patient-centered care. The information provided in this course should assist healthcare professionals in providing the best possible care to patients with ADHD.

## FACULTY BIOGRAPHIES

**John J. Whyte, MD, MPH**, is currently the Chief Medical Officer at WebMD. In this role, he leads efforts to develop and expand strategic partnerships that create meaningful change around important and timely public health issues. Previously, Dr. Whyte was the Director of Professional Affairs and Stakeholder Engagement at the FDA's Center for Drug Evaluation and Research and the Chief Medical Expert and Vice President, Health and Medical Education at Discovery Channel, part of the media conglomerate Discovery Communications.

Prior to this, Dr. Whyte was in the Immediate Office of the Director at the Agency for Healthcare Research Quality. He served as Medical Advisor/Director of the Council on Private Sector Initiatives to Improve the Safety, Security, and Quality of Healthcare. Prior to this assignment, Dr. Whyte was the Acting Director, Division of Medical Items and Devices in the Coverage and Analysis Group in the Centers for Medicare & Medicaid Services (CMS). CMS is the federal agency responsible for administering the Medicare and Medicaid programs. In his role at CMS, Dr.Whyte made recommendations as to whether or not the Medicare program should pay for certain procedures, equipment, or services. His division was responsible for durable medical equipment, orthotics/prosthetics, drugs/biologics/therapeutics, medical items, laboratory tests, and non-implantable devices. As Division Director as well as Medical Officer/Senior Advisor, Dr. Whyte was responsible for more national coverage decisions than any other CMS staff.

Dr. Whyte is a board-certified internist. He completed an internal medicine residency at Duke University Medical Center as well as earned a Master's of Public Health (MPH) in Health Policy and Management at Harvard University School of Public Health. Prior to arriving in Washington, Dr. Whyte was a health services research fellow at Stanford and attending physician in the Department of Medicine. He has written extensively in the medical and lay press on health policy issues.

**Paul Ballas, DO**, is a child psychiatrist and formerly chief medical officer at the Green Tree School, an approved private school for children with autism spectrum disorder, developmental delays, or emotional disturbances. He has authored peer reviewed articles on ADHD, sleep disorders, and psychopharmacology and has recently co-authored a book chapter on sleep disorders.

## Works Cited


1. National Institute of Mental Health. Attention-Deficit/Hyperactivity Disorder. Available at https://www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd. Last accessed September 22, 2021.
2. Centers for Disease Control and Prevention. Attention-Deficit/Hyperactivity Disorder. Data and Statistics About ADHD. Available at https://www.cdc.gov/ncbddd/adhd/data.html. Last accessed September 22, 2021.
3. *QuickStats*: Percentage of children aged 3–17 years who ever received a diagnosis of attention-deficit/hyperactivity disorder, by sex and age group—National Health Interview Survey, United States, 2019. *MMWR*. 2021;70:1024.
4. Zablotsky B, Alford JM. Racial and Ethnic Differences in the Prevalence of Attention-Deficit/Hyperactivity Disorder and Learning Disabilities Among U.S. children Aged 3–17 Years. Available at https://www.cdc.gov/nchs/products/databriefs/db358.htm. Last accessed September 22, 2021.
5. Soreff S. Attention Deficit Hyperactivity Disorder (ADHD): Pathophysiology. Available at https://emedicine.medscape.com/article/289350-overview. Last accessed September 22, 2021.
6. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry*. 2006;163(4):716-723.
7. Anxiety and Depression Association of America. Adult ADHD. Available at https://adaa.org/understanding-anxiety/related-illnesses/other-related-conditions/adult-adhd. Last accessed September 22, 2021.
8. Faraone SV, Biederman J. What is the prevalence of adult ADHD? Results of a population screen of 966 adults. *J Atten Disord*. 2005;9(2):384-391.
9. American Academy of Child and Adolescent Psychiatry. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894-921.
10. Biederman J, Faraone SV, Spencer TJ, Mick E, Monuteaux MC, Aleardi M. Functional impairments in adults with self-reports of diagnosed ADHD: a controlled study of 1001 adults in the community. *J Clin Psychiatry*. 2006;67(4):524-540.
11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Publishing, Inc.; 2013.
12. U.S. Food and Drug Administration. Press Release. FDA Permits Marketing of First Brain Wave Test to Help Assess Children and Teens for ADHD. Available at https://wayback.archive-it.org/7993/20170112223021/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm360811.htm. Last accessed September 22, 2021.
13. Wolraich ML, Hagan JF Jr, Allan C, et al. Clinical practice guideline for the diagnosis, evaluation and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2019;144(4):1-27.
14. Ramsay JR. Psychological assessment of adults with ADHD. In: Barkley RA (ed). *Attention-Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment*. 4th ed. New York, NY: The Guilford Press; 2015.
15. Biederman J, Monuteaux MC, Mick E, et al. Young adult outcome of attention deficit hyperactivity disorder: a controlled 10-year follow-up study. *Psychol Med*. 2006;36(2):167-179.
16. Biederman J, Petty CR, Evans M, Small J, Faraone SV. How persistent is ADHD? A controlled 10-year follow-up study of boys with ADHD. *Psychiatry Res*. 2010;177(3):299-304.
17. Barkley RA, Fischer M, Smallish L, Fletcher K. The persistence of attention-deficit/hyperactivity disorder into young adulthood as a function of reporting source and definition of disorder. *J Abnorm Psychol*. 2002;111(2):279-289.
18. Mannuzza S, Klein RG, Bessler A, Malloy P, LaPadula M. Adult psychiatric status of hyperactive boys grown up. *Am J Psychiatry*. 1998;155(4):493-498.
19. Barkley RA, Murphy KR, Fischer M. *ADHD in Adults: What the Science Says*. New York, NY: The Guildford Press; 2008.
20. Kessler RC, Adler LA, Gruber MJ, Sarawate CA, Spencer T, Van Brunt DL. Validity of the World Health Organization Adult ADHD Self-Report Scale (ASRS) Screener in a representative sample of health plan members. *Int J Methods Psychiatr Res*. 2007;16(2):52-65.
21. Ustun B, Adler LA, Rudin C, et al. The World Health Organization Adult Attention-Deficit/Hyperactivity Disorder Self-Report Screening Scale for DSM-5. *JAMA Psychiatry*. 2017;74(5):520-526.
22. Wender PH. *Attention-Deficit Hyperactivity Disorder in Adults*. 1st ed. New York, NY: Oxford University Press; 1998.
23. McGough JJ, Barkley RA. Diagnostic controversies in adult attention deficit hyperactivity disorder. *Am J Psychiatry*. 2004;161(11):1948-1956.
24. Wilens TE, Dodson W. A clinical perspective of attention-deficit/hyperactivity disorder into adulthood. *J Clin Psychiatry*. 2004;65(10):1301-1313.
25. Van der Kooij MA, Glennon JC. Animal models concerning the role of dopamine in attention-deficit hyperactivity disorder. *Neurosco Biobehav Rev*. 2007;31(4):597-618.
26. Biederman J, Faraone S. Attention-deficit hyperactivity disorder. *Lancet*. 2005;366(9481):237-248.
27. Nass R, Sidhu R, Ross G. Autism and other developmental disabilities. In: Daroff RB, Jankovic J, Mazziotta J, Pomeroy SL (eds). *Bradley's Neurology in Clinical Practice*. 7th ed. Philadelphia, PA: Elsevier Saunders; 2016: 1301-1323.

28. Tcheremissine OV, Salazar JO. Pharmacotherapy of adult attention deficit/hyperactivity disorder: review of evidence-based practices and future directions. *Expert Opin Pharmacother*. 2008;9(8):1299-1310.
29. Canadian Attention Deficit Hyperactivity Resource Alliance. *Canadian ADHD Practice Guidelines*. 4th ed. Toronto: CADDRA; 2020.
30. National Collaborating Centre for Mental Health. Attention Deficit Hyperactivity Disorder: The NICE Guideline on Diagnosis and Management of ADHD in Children, Young People, and Adults. Leicester: The British Psychological Society and the Royal College of Psychiatrists; 2008.
31. National Institute for Health and Care Excellence. *Attention Deficit Hyperactivity Disorder: Diagnosis and Management*. Available at https://www.nice.org.uk/guidance/ng87. Last accessed September 22, 2021.
32. Arnold LE. Methylphenidate vs. amphetamine: comparative review. *J Atten Disord*. 2000;3(4):200-211.
33. Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2018;S2215-S0366(18):30269-30274.
34. Kollins SH. A qualitative review of issues arising in the use of psycho-stimulant medications in patients with ADHD and co-morbid substance use disorders. *Curr Med Res Opin*. 2008;24(5):1345-1357.
35. LexiComp Online. Available at https://online.lexi.com/lco/action/login. Last accessed September 22, 2021.
36. Washington N. Treating ADHD: What Are My Options?. Available at https://psychcentral.com/disorders/adhd/treatment-for-attention-deficit-hyperactivity-disorder-adhd. Last accessed September 22, 2021.
37. Swanson J, Greenhill L, Wigal T, et al. Stimulant-related reductions of growth rates in the PATS. *J Am Acad Child Adolesc Psychiatry*. 2006;45(11):1304-1313.
38. Kim HW, Kim SO, Shon S, Lee JS, Lee HJ, Choi JH. Effect of methylphenidate on height and weight in Korean children and adolescents with attention-deficit/hyperactivity disorder: a retrospective chart review. *J Child Adolesc Psychopharmacol*. 2014;24(8):448-453.
39. Moungnoi P, Maipang P. Long-term effects of short-acting methylphenidate on growth rates of children with attention deficit hyperactivity disorder at Queen Sirikit National Institute of Child Health. *J Med Assoc Thai*. 2011;94(Suppl 3):S158-S163.
40. Carson CC 3rd, Mino RD. Priapism associated with trazodone therapy. *J Urology*. 1988;139(2):369-370.
41. Vetter VL, Elia J, Erickson C, et al. Cardiovascular monitoring of children and adolescents with heart disease receiving medications for attention deficit/hyperactivity disorder: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. *Circulation*. 2008;117(18):2407-2423.
42. Perrin JM, Friedman RA, Knilans TK, the Black Box Working Group, the Section on Cardiology and Cardiac Surgery. Cardiovascular monitoring and stimulant drugs for attention-deficit/hyperactivity disorder. *Pediatrics*. 2008;122(2):451-453.
43. Feldman H, Crumrine P, Handen BL, Alvin R, Teodori J. Methylphenidate in children with seizures and attention-deficit disorder. *Am J Dis Child*. 1989;143(9):1081-1086.
44. Hemmer SA, Pasternak JF, Zecker SG, Trommer BL. Stimulant therapy and seizure risk in children with ADHD. *Pediatr Neurol*. 2001;24(2):99-102.
45. Aldenkamp AP, Arzimanoglou A, Reijs R, Van Mil S. Optimizing therapy of seizures in children and adolescents with ADHD. *Neurology*. 2006;67:S49-S51.
46. Santos K, Palmini A, Radziuk AL, et al. The impact of methylphenidate on seizure frequency and severity in children with attention-deficit-hyperactivity disorder and difficult-to-treat epilepsies. *Dev Med Child Neurol*. 2013;55(7):654-660.
47. Radziuk AL, Kieling RR, Santos K, Rotert R, Bastos F, Palmini AL. Methylphenidate improves the quality of life of children and adolescents with ADHD and difficult-to-treat epilepsies. *Epilepsy Behav*. 2015;46:215-220.
48. Hesapcioglu ST, Goker Z, Bilginer C, Kandil S. Methylphenidate-induced psychotic symptoms: two case reports. *J Med Cases*. 2013;4(2):106-108.
49. Bloom AS, Russell LJ, Weisskopf B, Blackerby JL. Methylphenidate-induced delusional disorder in a child with attention deficit disorder with hyperactivity. *J Am Acad Child Adolesc Psychiatry*. 1988;27(1):88-89.
50. Palumbo DR, Sallee FR, Pelham WE Jr, Bukstein OG, Daviss WB, McDermott MP. Clonidine for attention-deficit/hyperactivity disorder: I. Efficacy and tolerability outcomes. *J Am Acad Child Adolesc Psychiatry*. 2008;47(2):180-188.
51. Waknine Y. FDA Approves Extended-Release Clonidine for Pediatric ADHD. Available at https://www.medscape.com/viewarticle/730140#. Last accessed September 22, 2021.
52. Strange BC. Once-daily treatment of ADHD with guanfacine: patient implications. *Neuropsychiatr Dis Treat*. 2008;4(3):499-506.
53. Biederman J, Melmed RD, Patel A, et al. A randomized, double-blind, placebo-controlled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. *Pediatrics*. 2008;121(1):e73-e84.
54. Connor DF, Findling RL, Kollins SH, et al. Effects of guanfacine extended release on oppositional symptoms in children aged 6–12 years with attention-deficit hyperactivity disorder and oppositional symptoms: a randomized, double-blind, placebo-controlled trial. *CNS Drugs*. 2010;24(9):755-768.

55. Findling RL, McBurnett K, White C, Youcha S. Guanfacine extended release adjunctive to a psychostimulant in the treatment of comorbid oppositional symptoms in children and adolescents with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2014;24(5):245-252.
56. Biederman J, Melmed RD, Patel A, McBurnett K, Donahue J, Lyne A. Long-term, open-label extension study of guanfacine extended release in children and adolescents with ADHD. *CNS Spectr*. 2008;13(12):1047-1055.
57. Wolraich ML, Hagan JF, Allan C, et al. AAP Subcommittee on Children and Adolescents with Attention-Deficit/Hyperactivity Disorder. Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2019;144(4):e20192528.
58. Wilens TE, Spencer TJ, Biederman J, et al. A controlled clinical trial of bupropion for attention deficit hyperactivity disorder in adults. *Am J Psychiatry*. 2001;158(2):282-288.
59. Pliszka S, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894-921.
60. Casat CD, Pleasants DZ, Schroeder DH, Parler DW. Bupropion in children with attention deficit disorder. *Psychopharmacol Bull*. 1989;25(2):198-201.
61. Clay TH, Gualtieri CT, Evans RW, Gullion CM. Clinical and neuropsychological effects of the novel antidepressant bupropion. *Psychopharmacol Bull*. 1988;24(1):143-148.
62. Riggs PD, Leon SL, Mikulich SK, Pottle LC. An open trial of bupropion for ADHD in adolescents with substance use disorders and conduct disorders. *J Am Acad Child Adolesc Psychiatry*. 1998;37(12):1271-1278.
63. Barrickman LL, Perry PJ, Allen AJ, et al. Bupropion versus methylphenidate in the treatment of attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 1995;34(5):649-657.
64. Wilens TE, Spencer TJ, Biederman J, et al. A controlled clinical trial of bupropion for attention deficit hyperactivity disorder in adults. *Am J Psychiatry*. 2001;158(2):282-288.
65. Wilens TE, Haight BR, Horrigan JP, et al. Bupropion XL in adults with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled study. *Biol Psychiatry*. 2005;57(7):793-801.
66. Reimherr FW, Hedges DW, Strong RE, Marchant BK, Williams ED. Bupropion SR in adults with ADHD: a short-term, placebo-controlled trial. *Neuropsychiatr Dis Treat*. 2005;1(3):245-251.
67. Verbeeck W, Bekkering GE, Van den Noortgate W, Kramers C. Bupropion for attention deficit hyperactivity disorder (ADHD) in adults. *Cochrane Database Syst Rev*. 2017;10(10):CD009504.
68. Biederman J, Baldessarini RJ, Wright V, Knee D, Harmatz JS. A double-blind placebo-controlled study of desipramine in the treatment of ADD. I: efficacy. *J Am Acad Child Adolesc Psychiatry*. 1989;28(5):777-784.
69. Wilens TE, Biederman J, Prince J, et al. Six week, double-blind, placebo-controlled study of desipramine for adult attention deficit hyperactivity disorder. *Am J Psychiatry*. 1996;153(9):1147-1153.
70. Riddle MA, Nelson JC, Kleinman CS, et al. Sudden death in children receiving Norpramin: a review of three reported cases and commentary. *J Am Acad Child Adolesc Psychiatry*. 1991;30(1):104-108.
71. Riddle MA, Geller B, Ryan N. Another sudden death in a child treated with desipramine. *J Am Acad Child Adolesc Psychiatry*. 1993;32(4):792-797.
72. Waknine Y. Provigil Linked to Risk for Serious Skin Rash, Psychiatric Symptoms. Available at https://www.medscape.com/viewarticle/564854. Last accessed September 22, 2021.
73. Pfiffner LJ, Barkley RA, DuPaul GJ. Treatment of ADHD in school settings. In: Barkley RA (ed). *Attention-Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment*. 3rd ed. New York, NY: The Guilford Press; 2006.
74. Centers for Disease Control and Prevention. Attention-Deficit/Hyperactivity Disorder (ADHD): Treatment of ADHD. Available at https://www.cdc.gov/ncbddd/adhd/treatment.html. Last accessed September 22, 2021.
75. The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention deficit hyperactivity disorder. *Arch Gen Psychiatry*. 1999;56(12):1073-1086.
76. Molina BSG, Hinshaw SP, Swanson JM, et al. The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. *J Am Acad Child Adolesc Psychiatry*. 2009;48(5):484-500.
77. Jensen PS, Arnold LE, Swanson JM, et al. 3-year follow-up of the NIMH MTA study. *J Am Acad Child Adolesc Psychiatry*. 2007;46(8):989-1002.
78. Abikoff H, Hechtman L, Klein RG, et al. Symptomatic improvement in children with ADHD treated with long-term methylphenidate and multimodal psychosocial treatment. *J Am Acad Child Adolesc Psychiatry*. 2004;43(7):802-811.
79. van der Oord S, Prins PJ, Oosterlaan J, Emmelkamp PM. The adolescent outcome of children with attention deficit hyperactivity disorder treated with methylphenidate or methylphenidate combined with multimodal behavior therapy: results of a naturalistic follow-up study. *Clin Psychol Psychother*. 2012;19(3):270-278.
80. Safren SA, Otto MW, Sprich S, Winett CL, Wilens TE, Biederman J. Cognitive-behavioral therapy for ADHD in medication-treated adults with continued symptoms. *Behav Res Ther*. 2005;43(7):831-842.

81. Bramham J, Young S, Bickerdike A, Spain D, McCartan D, Xenitidis K. Evaluation of group cognitive behavioral therapy for adults with ADHD. *J Atten Disord*. 2009;12(5):434-441.
82. U.S. Food and Drug Administration. FDA Permits Marketing of First Medical Device for Treatment of ADHD. Available at https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-first-medical-device-treatment-adhd. Last accessed September 22, 2021.
83. Masi L, Gignac M. ADHD and comorbid disorders in childhood psychiatric problems, medical problems, learning disorders and developmental coordination disorder. *Clin Psychiatry*. 2015.
84. CHADD. ADHD and Co-Occurring Conditions. Available at https://chadd.org/about-adhd/co-occuring-conditions/. Last accessed September 22, 2021.
85. DuPaul GJ, Gormley MJ, Laracy SD. Comorbidity of LD and ADHD: implications of DSM-5 for assessment and treatment. *J Learn Disabil*. 2013;46(1):43-51.
86. Parvaz MA, Kim K, Froudist-Walsh S, Newcorn JH, Ivanov I. Reward-based learning as a function of severity of substance abuse risk in drug-naïve youth with ADHD. *J Child Adolesc Psychopharmacol*. 2018;28(8):547-553.
87. Masi G, Manfredi A, Nieri G, Muratori P, Pfanner C, Milone A. A naturalistic comparison of methylphenidate and risperidone monotherapy in drug-naïve youth with attention-deficit/hyperactivity disorder comorbid with oppositional defiant disorder and aggression. *J Clin Psychopharmacol*. 2017;37(5):590-594.
88. Kratochvil CJ, Newcorn JH, Arnold LE, et al. Atomoxetine alone or combined with fluoxetine for treating ADHD with co-morbid depressive or anxiety symptoms. *J Am Acad Child Adolesc Psychiatry*. 2005;44(9):915-924.
89. Daviss WB, Bentivoglio P, Racusin R, Brown KM, Bostic JQ, Wiley L. Bupropion sustained release in adolescents with co-morbid attention-deficit/hyperactivity disorder and depression. *J Am Acad Child Adolesc Psychiatry*. 2001;40(3):307-314.
90. Spencer TJ, Abikoff HB, Connor DF, et al. Efficacy and safety of mixed amphetamine salts extended release (Adderall XR) in the management of oppositional defiant disorder with or without co-morbid attention-deficit/hyperactivity disorder in school-aged children and adolescents: a 4-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, forced-dose-escalation study. *Clin Ther*. 2006;28(3):402-418.
91. Biederman J, Spencer TJ, Newcorn JH, et al. Effect of co-morbid symptoms of oppositional defiant disorder on responses to atomoxetine in children with ADHD: a meta-analysis of controlled clinical trial data. *Psychopharmacology (Berl)*. 2007;190(1):31-41.
92. Klein RG, Abikoff H, Klass E Ganeles D, Seese LM, Pollack S. Clinical efficacy of methylphenidate in conduct disorder with and without attention deficit hyperactivity disorder. *Arch Gen Psychiatry*. 1997;54(12):1073-1080.
93. Garg J, Arun P, Chavan BS. Comparative efficacy of methylphenidate and atomoxetine in oppositional defiant disorder comorbid with attention deficit hyperactivity disorder. *Int J Appl Basic Med Res*. 2015;5(2):114-118.
94. Connor DF, Glatt SJ, Lopez ID, Jackson D, Melloni RH Jr. Psychopharmacology and aggression. I: a meta-analysis of stimulant effects on overt/covert aggression-related behaviors in ADHD. *J Am Acad Child Adolesc Psychiatry*. 2002;41(3):253-261.
95. Parsley I, Zhang Z, Hausmann M, et al. Effectiveness of stimulant medications on disruptive behavior and mood problems in young children. *Clin Psychopharmacol Neurosci*. 2020;18(3):402-411.
96. Hazell PL, Stuart JE. A randomized controlled trial of clonidine added to psychostimulant medication for hyperactive and aggressive children. *J Am Acad Child Adolesc Psychiatry*. 2003;42(8):886-894.
97. Kronenberger WG, Giaugue AL, Lafata DE, Bohnstedt BN, Maxey LE, Dunn DW. Quetiapine addition in methylphenidate treatment-resistant adolescents with co-morbid ADHD, conduct/oppositional-defiant disorder, and aggression: a prospective, open-label study. *J Child Adolesc Psychopharmacol*. 2007;17(3):334-347.
98. Loy JH, Merry SN, Hetrick SE, Stasiak K. Atypical antipsychotics for disruptive behavior disorders in children and youths. *Cochrane Database Syst Rev*. 2017;8:CD008559.
99. Barkley RA, Fischer M, Smallish L, Fletcher K. Does the treatment of attention-deficit/hyperactivity disorder with stimulants contribute to drug use/abuse? A 13-year prospective study. *Pediatrics*. 2003;111(1):97-109.
100. Biederman J, Monuteaux MC, Spencer T, Wilens TE, Macpherson HA, Faraone SV. Stimulant therapy and risk for subsequent substance use disorders in male adults with ADHD: a naturalistic controlled 10-year follow-up study. *Am J Psychiatry*. 2008;165(5):597-603.
101. Kollins SH. ADHD, substance use disorders, and psychostimulant treatment current literature and treatment guideline. *J Atten Disord*. 2008;12(2):115-125.
102. Miranda A, Colomer C, Berenguer C, Roselio R, Roselio B. Substance use in young adults with ADHD: Comorbidity and symptoms of inattention and hyperactivity/impulsivity. *Int J Clin Health Psychol*. 2015;16(2):157-165.
103. Wilens TE, Martelon M, Joshi G, et al. Does ADHD predict substance-use disorders? A 10-year follow-up study of young adults with ADHD. *J Am Acad Child Adolesc Psychiatry*. 2011;50(6):543-553.
104. Wilens TE, Adamson J, Monuteaux MC, et al. Effect of prior stimulant treatment for attention-deficit/hyperactivity disorder on subsequent risk for cigarette smoking and alcohol and drug use disorders in adolescents. *Arch Pediatr Adolesc Med*. 2008;162(10):916-921.

105. Mannuzza S, Klein RG, Truong NL, et al. Age of methylphenidate treatment initiation in children with ADHD and later substance abuse: prospective follow-up into adulthood. *Am J Psychiatry*. 2008;165(5):604-609.

106. Dalsgaard S, Mortensen PB, Frydenberg M, Thomsen PH. ADHD, stimulant treatment in childhood and subsequent substance abuse in adulthood: a naturalistic long-term follow-up study. *Addict Behav*. 2014;39(1):325-328.

107. Wilens TE, Faraone SV, Biederman J, Gunawardene S. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. *Pediatrics*. 2003;111(1):179-185.

108. Molina BSG, Flory K, Hinshaw SP, et al. Delinquent behavior and emerging substance use in the MTA at 36 months: prevalence, course, and treatment effects. *J Am Acad Child Adolesc Psychiatry*. 2007;46(8):1028-140.

109. Humphreys KL, Eng T, Lee SS. Stimulant medication and substance use outcomes: a meta-analysis. *JAMA Psychiatry*. 2013;70(7):740-749.

110. Gürkan K, Bilgic A, Türkoglu S, Kilic BG, Aysev A, Uslu R. Depression, anxiety and obsessive-compulsive symptoms and quality of life in children with attention-deficit hyperactivity disorder (ADHD) during three-month methylphenidate treatment. *J Psychopharmacol*. 2010;24(12):1810-1818.

111. Geller D, Donnelly C, Lopez F, et al. Atomoxetine treatment for pediatric patients with attention-deficit/hyperactivity disorder with co-morbid anxiety disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(9):1119-1127.

112. Abikoff H, McGough J, Vitiello B, et al. Sequential pharmacotherapy for children with co-morbid attention-deficit/hyperactivity and anxiety disorders. *J Am Acad Child Adolesc Psychiatry*. 2005;44(5):418-427.

113. Jensen PS, Hinshaw SP, Kraemer HC, et al. ADHD comorbidity findings from the MTA study: comparing co-morbid subgroups. *J Am Acad Child Adolesc Psychiatry*. 2001;40(2):147-158.

114. Halldorsdottir T, Ollendick TH. Comorbid ADHD: implications for the treatment of anxiety disorders in children and adolescents. *Cog Behavior Pract*. 2014;21(3):310-322.

115. Findling RL, Short EJ, McNamara NK, et al. Methylphenidate in the treatment of children and adolescents with bipolar disorder and attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(11):1445-1453.

116. Scheffer RE, Kowatch RA, Carmody T, Rush AJ. Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of co-morbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. *Am J Psychiatry*. 2005;162(1):58-64.

117. Hah M, Chang K. Atomoxetine for the treatment of attention-deficit/hyperactivity disorder in children and adolescents with bipolar disorders. *J Child Adolesc Psychopharmacol*. 2005;15(6):996-1004.

118. Pringsheim T, Steeves T. Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders. *Cochrane Database Syst Rev*. 2011;4:CD007990.

119. Cohen SC, Mulqueen JM, Ferracioli-Oda E, et al. Meta-analysis: risk of tics associated with psychostimulant use in randomized, placebo-controlled trials. *J Am Acad Child Adolesc Psychiatry*. 2015;54(9):723-736.

120. Osland ST, Steeves TD, Pringsheim T. Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders. *Cochrane Database Syst Rev*. 2018;6:CD007990.

121. Gulisano M, Rizzo R, Cali PV, Curatolo B. Tourette Syndrome and comorbid ADHD: current pharmacological treatment options. *Eur J Paediatric Neurol*. 2013;17:421-428.

122. Bright GM. Abuse of medications employed for the treatment of ADHD: results from a large-scale community survey. *Medscape J Med*. 2008;10(5):111.

123. Wilens TE, Gignac M, Swezey A, et al. Characteristics of adolescents and young adults with ADHD who divert or misuse their prescription medications. *J Am Acad Child Adolesc Psychiatry*. 2006;45(4):408-414.

124. McCabe SE, Knight JR, Teter CJ, Wechsler H. Nonmedical use of prescription stimulants among U.S. college students: prevalence and correlates from a national survey. *Addiction*. 2005;100(1):96-106.

125. Substance Abuse and Mental Health Services Administration. *Key Substance Use and Mental Health Indicators in the United States: Results from the 2019 National Survey on Drug Use and Health*. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental health Services Administration; 2020.

126. McCabe SE, Teter CJ, Boyd CJ. Medical use, illicit use and diversion of prescription stimulant medication. *J Psychoactive Drugs*. 2006;38(1):43-56.

127. Wilens TE. ADHD with substance use disorders. In: Brown TE (ed). *ADHD Comorbidities: Handbook for ADHD Complications in Children and Adults*. Washington, DC: American Psychiatric Publishing; 2009.

128. Schubiner H, Saules KK, Arfken CL, et al. Double-blind placebo-controlled trial of methylphenidate in the treatment of adult ADHD patients with co-morbid cocaine dependence. *Exp Clin Psychopharmacol*. 2002;10(3):286-294.

129. Levin FR, Evans SM, Brooks DJ, Kalbag AS, Garawi F, Nunes EV. Treatment of methadone-maintained patients with adult ADHD: double-blind comparison of methylphenidate, bupropion and placebo. *Drug Alcohol Depend*. 2006;81(2):137-148.

130. Levin FR, Evans SM, Brooks DJ, Garawi F. Treatment of cocaine dependent treatment seekers with adult ADHD: double-blind comparison of methylphenidate and placebo. *Drug Alcohol Depend*. 2007;87(1):20-29.

131. Castells X, Cunill R, Péerez-Mañá C, Vidal X, Capella D. Psychostimulant drugs for cocaine dependence. *Cochrane Database Syst Rev*. 2016;9:CD007380.

132. Spencer TJ, Biederman J, Ciccone PE, et al. PET study examining pharmacokinetics, detection and likeability, and dopamine transporter receptor occupancy of short- and long-acting oral methylphenidate. *Am J Psychiatry*. 2006;163(3):387-395.

133. Kollins SH, Rush CR, Pazzaglia PJ, Ali JA. Comparison of acute behavioral effects of sustained-release and immediate-release methylphenidate. *Exp Clin Psychopharmacol*. 1998;6(4):367-374.

134. Jasinski DR, Krishnan S. Human pharmacology of intravenous lisdexamfetamine dimesylate: abuse liability in adult stimulant abusers. *J Psychopharmacol*. 2009;23(4):410-418.

135. Eli Lilly and Company. Strattera (Atomoxetine) Prescribing Information. Available at http://pi.lilly.com/us/strattera-pi.pdf. Last accessed September 22, 2021.

136. Shire US, Inc. Adderall XR (Mixed Salts of A Single-Entity Amphetamine Product) Prescribing Information. Available at http://pi.shirecontent.com/PI/PDFs/AdderallXR_USA_ENG.PDF. Last accessed September 22, 2021.

137. Wilens TE, Zusman RM, Hammerness PG, et al. An open-label study of the tolerability of mixed amphetamine salts in adults with attention-deficit/hyperactivity disorder and treated primary essential hypertension. *J Clin Psychiatry*. 2006;67(5):696-702.

138. Weisler RH, Biederman J, Spencer TJ, Wilens TE. Long-term cardiovascular effects of mixed amphetamine salts extended release in adults with ADHD. *CNS Spectr*. 2005;10(12 Suppl 20):35-43.

139. Wilens TE, Hammerness PG, Biederman J, et al. Blood pressure changes associated with medication treatment of adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2005;66(2):253-259.

140. Ayonrinde O. Importance of cultural sensitivity in therapeutic transactions: considerations for healthcare providers. *Dis Manage Health Outcomes*. 2003;11(4):233-248.

141. Hwa-Froelich DA, Westby CE. Considerations when working with interpreters. *Commun Disord Q*. 2003;24(2):78-85.

142. National Council on Interpreting in Health Care, Inc. National Standards for Healthcare Interpreter Training Programs. Available at https://www.ncihc.org/assets/documents/publications/National_Standards_5-09-11.pdf. Last accessed September 22, 2021.

143. Lynch EW. Developing cross-cultural competence. In: Lynch EW, Hanson MJ (eds). *A Guide for Working with Children and their Families: Developing Cross-Cultural Competence*. 4th ed. Baltimore, MD: Paul H. Brookes Publishing, Co.; 2011: 41-78.

144. Tribe R. Working with interpreters in mental health. *Int J Cult Ment Health*. 2009;2(2):92-101.

145. Dysart-Gale D. Clinicians and medical interpreters: negotiating culturally appropriate care for patients with limited English ability. *Fam Community Health*. 2007;30(3):237-246.

146. Raval H, Smith J. Therapists' experiences of working with language interpreters. *Int J Ment Health*. 2003;32(2):6-31.

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