Addressing Diagnosis and Treatment Gaps in Adults With Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) was originally defined in children but is now recognized to persist into adulthood for some patients. Despite this recognition, adult ADHD remains underdiagnosed. This narrative review describes the negative impact of ADHD across multiple functional domains, diagnostic guidelines for adult ADHD and its clinical features, the importance of screening tools and clinical interviews to help evaluate adults for ADHD, and adult ADHD treatment options. Diagnostic guidelines for ADHD now incorporate adult-specific symptoms and behavioral manifestations, which may aid in diagnosing adult ADHD. However, diagnosis of ADHD is complicated by symptom overlap between ADHD and psychiatric disorders that might be comorbid with ADHD. Screening tools, such as the Adult ADHD Self-Report Screening Scale for *DSM-5*, can identify adults requiring evaluation for ADHD. However, clinical interviews and longitudinal family histories provide critical information that diagnoses ADHD and differentiates ADHD from psychiatric comorbidities. Various pharmacologic and nonpharmacologic treatments are available for adults diagnosed with ADHD. First-line pharmacologic treatment of ADHD usually consists of treatment with a psychostimulant, and a variety of short-acting and long-acting formulations are available for use in adults. When developing a treatment plan for adults with ADHD, it is important to recognize that the demands of adult life, both at work and at home, necessitate symptom control throughout the entire day and into the evening and indicate that a long-acting medication formulation is often preferable. Furthermore, there are important safety concerns, including the potential for drug dependence and serious cardiovascular events, which must be considered before prescribing stimulants.

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Although it is now recognized that attention-deficit/hyperactivity disorder (ADHD) may persist into adulthood,[1,2] it often is underdiagnosed.[3] According to the World Health Organization World Mental Health (WHO WMH) report,[4] the conditional prevalence of ADHD in adults is 57% in individuals with a history of childhood ADHD, and evidence[5] suggests that nearly 66% of individuals diagnosed with ADHD in childhood report ≥ 1 ADHD symptom that causes clinically significant impairment during adulthood. A study[6] using a nationally representative sample of adults (aged 18–44 years old) in the United States estimated that the prevalence of ADHD in adults was 4.4%. More recently, the WHO WMH report[4] stated a 5.2% prevalence of ADHD in adults in the United States. This same study[4] reported a 2.8% prevalence of ADHD in adults across the 18 countries surveyed, which highlights that adult ADHD is a global health issue. Taken together, adult ADHD prevalence data support the notion that there is a need for clinicians to focus on understanding the impact of ADHD in their adult patients.

When ADHD persists into adulthood, it is associated with impairment across multiple domains, including home, social, school, and work, resulting in functional impairment throughout the day (Figure 1).[7] Importantly, symptom presentation changes over a lifetime in individuals with ADHD and can be associated with different profiles of functional impairment (Figure 2).[7–10] Symptoms of hyperactivity, impulsivity, and inattention during childhood often result in disruptive behavior at home and in academic impairment at school.[7] In addition to academic and behavioral difficulties, adolescents with ADHD often experience self-esteem issues, poor peer relationships, parental conflict, delinquency, and an increased risk of smoking and substance abuse.[10] In adulthood, symptoms further evolve such that hyperactivity decreases or morphs into more purposeful activity or inner restlessness, whereas inattention, disorganization, and impulsivity remain, which can lead to functional difficulties in home, social, and work settings.[7,9]

24-HOUR IMPACT OF ADHD-RELATED IMPAIRMENTS IN ADULTS

The impact of ADHD in adults is substantial across an array of domains and can be associated with impairment throughout the waking hours of the day (Figure 1). After waking, an individual's symptoms of ADHD can interfere with the ability to get ready for work and get children ready

Clinical Points

- Attention-deficit/hyperactivity disorder (ADHD) in adults often goes untreated, leading to impairment throughout the day and into the evening across multiple domains.
- Although the updated ADHD diagnostic criteria described in the *DSM-5* incorporate adult-specific ADHD symptoms to aid in diagnosis, screening instruments, comprehensive clinical interviews, and assessment of family histories also help clinicians better diagnose ADHD in adults, particularly in the presence of psychiatric comorbidities.
- An array of nonpharmacologic and pharmacologic treatment options is available for adults with ADHD; important issues to consider when prescribing pharmacotherapy include individual treatment response, tolerability and safety, and whether an individual's situation necessitates a treatment that provides coverage beyond the workday and into the evening; there are also data to support the effectiveness of nonpharmacologic treatment strategies.

Figure 1. Attention-Deficit/Hyperactivity Disorder Symptoms in Adults Require Treatment Throughout the Day

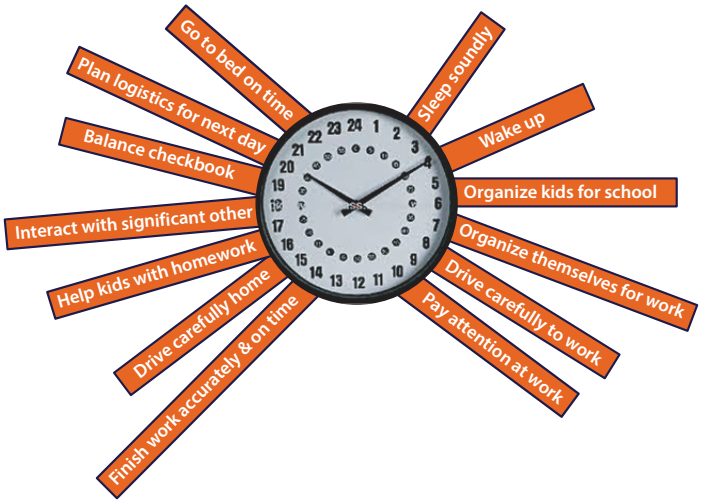
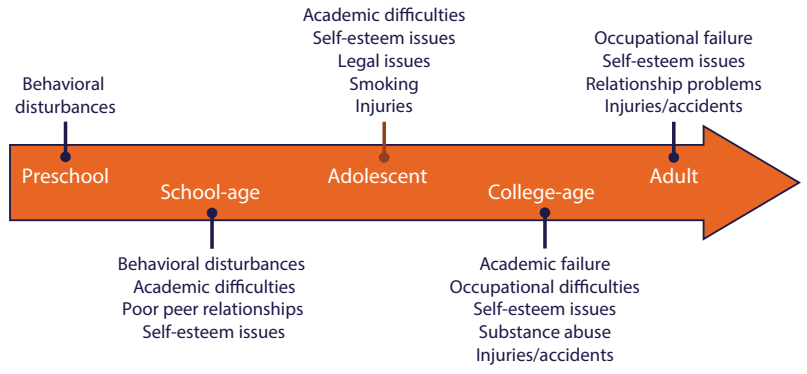


Figure 2. Symptom and Functional Impairment in Attention-Deficit/Hyperactivity Disorder Across the Lifespan

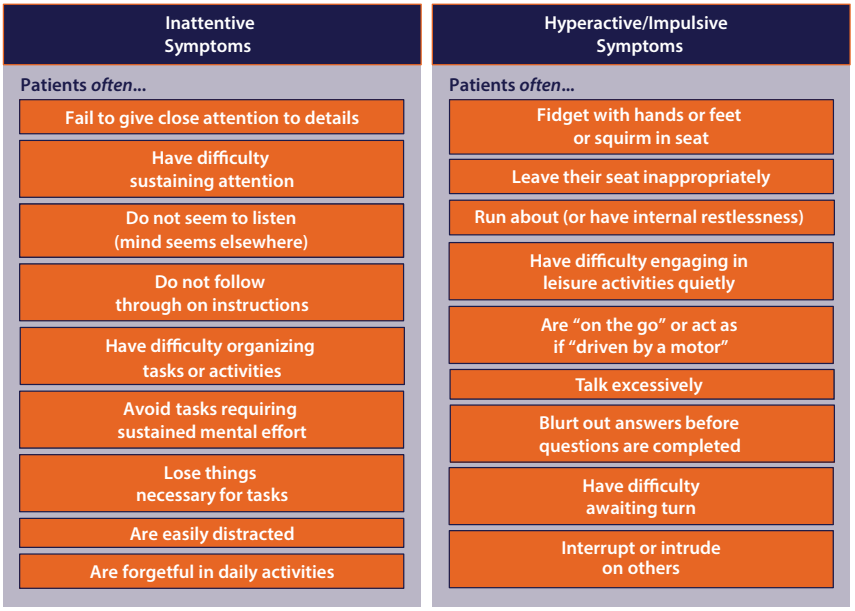


for school. In the workplace, individuals with ADHD must focus their attention, adhere to deadlines, multitask, and set priorities. After returning home from work, adults with ADHD often need to accomplish multiple home-related tasks (eg, helping children with homework, attending to household finances) before planning for the upcoming workday. Furthermore, an individual's symptoms of ADHD (eg, a forgotten event or work activity) can negatively affect relationships both at home and at work. It should also be noted that driving to and from work can be affected by ADHD symptoms. ADHD-related symptoms are common reasons for accidents, as noted by the significantly higher rates of traffic accidents in adults with ADHD (men: 6.5%, women: 3.9%) than adults without ADHD (men: 2.6%, women: 1.8%).[11]

Studies have shown that ADHD affects interpersonal relationships involving coworkers, spouses, children, or other family members. For example, it has been reported that parental ADHD is associated with reductions in family cohesion and with increases in familial conflict compared with households without a parent with ADHD, an association that remains even after controlling for other parental psychopathologies, socioeconomic status, and ADHD in the child.[12] ADHD is known to predispose an individual to risk-taking behaviors, such as committing violent crimes that result in incarceration and sexual activity that leads to the contraction of sexually transmitted diseases.[13] In 1 study,[8] adults who screened positive for ADHD (but who were never formally diagnosed) had greater levels of functional impairment and lower quality of life than individuals who did not screen positive for ADHD. Adults with undiagnosed ADHD were significantly less likely to have a postcollege degree, more likely to be unemployed, more likely to have >1 traffic citation in the past 5 years, and more likely to screen positive for problem drinking than adults without ADHD who were administered an alcohol abuse screener.[8]

Adults with ADHD also find that ADHD affects their sleep. There is substantial evidence that shows impairment across multiple domains of sleep in adults with ADHD, although there is some controversy over the role that comorbidities play.[14] In adults with ADHD who are free of comorbidities, compared with controls, sleep impairments include decreases in sleep efficiency, alterations in rapid eye movement sleep, and increased nocturnal awakenings as measured objectively using polysomnography.[15] In a study published in 2016,[16] more severe ADHD symptoms in adults with ADHD and comorbid lifetime

Figure 3. Characteristic (*DSM-5* described) Symptoms of Attention-Deficit/Hyperactivity Disorder



anxiety or depression were reported to be associated with increased risk of sleep disturbances (eg, reduced sleep duration, late circadian chronotype) compared to adults with lifetime anxiety or depression but without ADHD.

The overall impact of ADHD on emotional well-being is complex and is mediated by direct effects of ADHD on well-being, as well as by indirect effects of ADHD on maladaptive coping styles and perceived stress.[17] When treating adults with ADHD, it is imperative that the clinician address not only the hyperactive, impulsive, and inattentive symptoms of ADHD but also the affected sleep behaviors, perceived stress, and maladaptive coping styles[14,17] to maximize the potential for overall increases in well-being.

DIAGNOSTIC GUIDELINES AND CLINICAL FEATURES OF ADHD

As shown in Figure 3, the symptoms of ADHD in adults can be divided into the following 2 domains: inattention (A1) and hyperactivity/impulsivity (A2).[18] A formal *DSM-5*[18] diagnosis of ADHD is specified by the following 3 presentation types: predominantly inattentive (patient meets criterion A1 only), predominantly hyperactive/impulsive (patient meets criterion A2 only), and combined (patient meets both criterion A1 and criterion A2). The predominantly inattentive and combined presentation types are most common in adults.[19] Notably, for a *DSM-5* diagnosis of ADHD, the inattentive or hyperactive/impulsive symptoms must be (1) present in 2 or more settings (eg, home, school, work) (2) for at least 6 months, and (3) there must be clear evidence that the symptoms interfere with, have a direct negative impact on, or reduce the quality of social, academic, or occupational functioning.[19]

The *DSM-5* guidelines for the diagnosis of ADHD published in 2013 represent an update from the previous guidelines described in the *DSM-IV-TR*.[20] These updates, as outlined here, incorporated ADHD symptoms specific to affected adults, which may aid clinicians in diagnosing ADHD in this population.[21] Specifically, the *DSM-5* (1) requires fewer symptoms to establish a diagnosis of ADHD in individuals older than 17 years, such that individuals need to meet 5 of the 9 criteria in either the inattention or the hyperactivity/impulsivity criterion domains[18] instead of the previously specified 6 of 9 criteria in the *DSM-IV-TR*[20]; (2) has increased the age at onset to 12 years[18] versus the previously established age at onset of 7 years[20]; (3) includes further guidance to clinicians by providing examples of behavioral manifestations of ADHD that are more relevant to adults[18]; and (4) includes modifiers to indicate severity of disease (eg, mild, moderate, severe) and current disease state (eg, partial remission).[18]

A key clinical feature observed in individuals with ADHD is a high degree of medical and psychiatric comorbidity.[6] In a study[6] that analyzed data from the National Comorbidity Survey Replication, ADHD in adults was significantly associated with the following psychiatric disorders: any mood disorder (odds ratio [OR] = 5.0), any anxiety disorder (OR = 3.7), and any substance abuse disorder (OR = 3.0). The higher prevalence of substance abuse disorders in those with ADHD appears to not be differentiated by ADHD presentation type, substance, or sex. Regardless of ADHD presentation type, ADHD symptoms were significantly associated with increased odds for all substance abuse disorders in a Swedish study[22] involving adult twins. In a study[23] of first-year college students, individuals with ADHD had significantly higher rates of comorbid psychiatric

disorders compared with those without ADHD, with 55.0% versus 11.2% exhibiting ≥1 comorbidity and 31.8% versus 4.0% exhibiting ≥2 comorbidities. The differences in comorbidity rates were largely attributable to significantly increased rates of major depressive disorder (OR = 10.5), generalized anxiety disorder (OR = 10.0), trauma- and stressor-related disorders (OR = 8.7), and learning disorders (OR = 24.7) in those with ADHD.[23]

Adults with ADHD are also at increased risk of having a comorbid medical disorder, such as obesity, sleep disorders, asthma, and migraines.[24] The impact of ADHD symptoms on the management and outcomes of serious medical illnesses that require careful lifestyle and medication management (eg, hypertension, diabetes[25]) may be profound. When the high overall comorbidity rate of ADHD with other psychiatric disorders is considered in light of the low rate of ADHD diagnosis in adults, it could be speculated that the underdiagnosis and therefore lack of treatment in many adults with ADHD may be partially the result of misdiagnosis of ADHD as a different and often comorbid disorder.

SCREENING TOOLS

In light of the prevalence of ADHD in adults and its overall burden, screening for ADHD in adults is critical. However, the diagnosis of ADHD can be complicated by symptom overlap between ADHD and other potentially comorbid psychiatric disorders.[26,27] For example, distractibility, a key feature of ADHD, is observed across multiple psychiatric conditions, including depressive disorders, bipolar disorders, anxiety disorders, psychotic disorders, and substance abuse disorders.[26,27]

An array of tools exists for screening and diagnosing ADHD in adults, and there are multiple advantages to using assessment scales and screeners. First, these instruments are brief and time efficient; therefore, they can aid the clinician in instances when large numbers of individuals must be evaluated. Second, these instruments help avoid the possibility of missing important pieces of information, thereby minimizing the potential for making an incorrect diagnosis or missing the presence of a comorbid condition, which can help avoid potential catastrophic results (eg, missed diagnosis, hospitalization, suicidality/suicide, incarceration). Overall, the use of ADHD assessment scales and screeners allows physicians to identify potential cases of ADHD for further diagnosis (and subsequent treatment) more accurately and efficiently. As a result, it may be possible to mitigate negative outcomes.

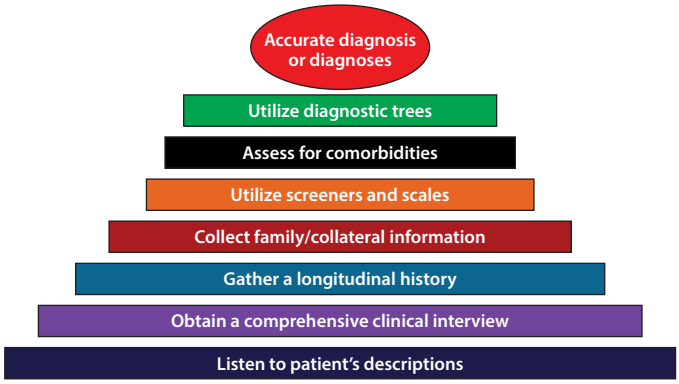
However, it is important to note that screening tools are designed to help demonstrate the probability of having (or not having) a specific disorder and not to discriminate among disorders. As such, screening tools alone do not have the ability to distinguish between ADHD and other psychiatric disorders because symptom overlap between comorbid disorders renders it difficult to make an accurate differential diagnosis. This overlap emphasizes the importance of using a variety of screeners and scales—which allow for the assessment of ADHD, mood disorders, or anxiety disorders—to aid in directing clinical interviews and obtaining patient histories. In this manner, screeners can help assist in making appropriate differential diagnoses and offer an additional layer of protection to guard against missing a comorbid condition.

Many primary care physicians are likely to have limited experience in screening for ADHD in adults, as evidenced by both the low rate of ADHD treatment and the lower percentage of ADHD diagnoses in adults compared with children.[6,28] One possible reason for this limited experience could be that many assessment tools are time consuming and therefore less likely to be used in a primary care setting. The self-administered 6-question Adult ADHD Self-Report Scale version 1.1 (ASRS-v1.1)[29,30] has been shown to be a good screener for ADHD in adults because it is easy to use, moderately sensitive (68.7%), and highly specific (99.5%). The ASRS-v1.1, which is structured to reflect adult criteria from the *DSM-IV*, includes 4 questions evaluating *DSM-IV* symptoms of inattention and 2 evaluating *DSM-IV* symptoms of hyperactivity/impulsivity.[30] The individual being screened for ADHD checks 1 of 5 boxes ("never," "rarely," "sometimes," "often," or "very often") in response to each question.[31] Individuals are considered to screen positive for ADHD if they respond "sometimes" through "very often" (for items 1–3) or "often" through "very often" (for items 4–6) to ≥4 questions, which indicates that the individual has symptoms that are highly consistent with ADHD.[31]

There is now an updated version of the ASRS-v1.1 (Adult ADHD Self-Report Screening Scale for *DSM-5*),[32] which has been clinically validated to the *DSM-5* diagnostic criteria for ADHD in adults. Unlike the ASRS-v1.1, which includes only *DSM-IV* symptom questions, the 6-question ADHD Self-Report Screening Scale for *DSM-5* includes 1 question related to *DSM-5* symptoms of inattention, 3 questions related to *DSM-5* symptoms of hyperactivity/impulsivity, and 2 questions related to non–*DSM-5* symptoms of executive dysfunction.[32] The ADHD Self-Report Screening Scale for *DSM-5* questions were selected using a machine-learning algorithm to optimize the operating characteristics of the screener. As a result, the ADHD Self-Report Screening Scale for *DSM-5* exhibits ease of use, high specificity (96%), and high sensitivity (91.4%). Each question includes 4 response options: "never," "sometimes," "often," or "very often." Scoring for the 6 questions is weighted based on the output from the machine-learning algorithm used in the development of the screener. The total score ranges from 0 to 24.[32] Scores ≥14 indicate the need for further assessment.[32]

The ADHD Rating Scale version IV (ADHD-RS-IV)[33] is a tool that was designed for the assessment of ADHD severity in children and adolescents; it consists of 18 items designed to reflect *DSM-IV* ADHD diagnostic criteria, 9 of which assess hyperactivity/impulsivity and 9 of which assess inattention. Although originally designed to rate ADHD symptoms in pediatric populations, the ADHD-RS-IV has been modified to include prompts specific to the adult presentation of ADHD.[34] For example, for the item related to talking excessively, the

Figure 4. Habits of Clinicians Who Successfully Diagnose and Treat Attention-Deficit/Hyperactivity Disorder



prompts for adults include the following: "Do you talk a lot? All the time? More than other people? Do people complain about your talking? Is it a problem?"[34] As such, the experience of ADHD in an adult can be assessed more specifically.[34]

Although assessment scales and screening instruments are efficient means to guide clinicians in identifying individuals with potential ADHD, they should not be used exclusively to diagnose ADHD.[35] As shown in Figure 4, other steps are important for successfully diagnosing and treating ADHD, including collecting a longitudinal history and family and collateral information via a comprehensive clinical interview. For example, in a study[35] assessing the differentiation of ADHD from bipolar disorder, it was found that interview measures, along with a developmental account of disease course, provided discriminative value, with the distinction between sustained traits and episodic symptoms being highly discriminative.

Screening and diagnosing ADHD are simply a first step; to provide comprehensive patient care, it is imperative that clinicians encourage and support the treatment of ADHD in adult patients. Notably, a study[6] using a nationally representative sample of adults (18–44 years old) in the United States found that only 10.9% of adults with ADHD had received treatment for their ADHD in the previous 12 months.

NONPHARMACOLOGIC TREATMENT OPTIONS FOR ADHD

As has been described in detail,[36] multiple nonpharmacologic options have been used in the treatment of ADHD in adults. One such psychosocial therapy approach is cognitive-behavioral therapy (CBT)—a model that combines higher-level organization and planning, behavioral skills training, and cognitive restructuring. CBT has been used extensively as a stand-alone therapy and in combination with pharmacotherapy in the treatment of ADHD in adults.[21,36] In a randomized, placebo-controlled, parallel-group study[37] of CBT alone or combined with dextroamphetamine in adults with ADHD, improvements in ADHD symptoms and functioning were observed with CBT alone and CBT combined with dextroamphetamine, with no significant differences in efficacy between treatment groups. When considering the overall published literature, it was reported that CBT can have large treatment effects on ADHD symptoms, mood, and overall functioning.[36]

Another psychosocial therapy approach, dialectical behavior therapy (DBT), has been used in the treatment of borderline personality disorder and includes skills aimed at improving emotion regulation, interpersonal effectiveness, distress tolerance, and mindfulness.[38] When modified to suit the needs and deficits specific to adults with ADHD, DBT has been shown effective in reducing ADHD symptoms.[39] In a pilot study[40] with 18 participants, the use of a combination of CBT and DBT produced significant reductions in ADHD symptoms, depressive symptoms, perceived psychological stress, and everyday disability in adults with ADHD. As 22% (n = 4) of participants in this study[40] had comorbid bipolar II disorder and 28% (n = 5) had comorbid depression, these findings may suggest that combined CBT and DBT would be useful in treating individuals with ADHD and comorbid depression. However, further studies in larger study populations are needed to confirm this possibility.

Physical exercise, which has been postulated to increase dopamine and norepinephrine activity in the brain in a manner similar to psychostimulant medications, has also been examined for its utility in treating ADHD in adults.[41] A study[42] in adult men who were not currently taking any stimulant medication showed that 20 minutes of moderately intense exercise transiently enhanced the motivation to complete cognitive tasks, increased feelings of energy, and reduced feelings of confusion, fatigue, and depression. However, behavioral measures of attention (continuous performance task and Bakan vigilance task) and hyperactivity (leg movement during performance of a cognitive task) were not significantly changed,[42] suggesting that exercise would be best suited for use as an augmentation therapy.[41]

Another type of nonpharmacologic therapy, mindful awareness practice, involves meditation exercises aimed at improving attention, executive functioning, and emotion regulation in adults with ADHD.[43] In 1 study,[44] adults with ADHD who underwent 8 weekly mindful awareness practice sessions exhibited improvement in the hyperactivity/impulsivity and inattention domains of ADHD and had improved mood and quality of life compared with pretherapy baseline and compared with individuals who did not undergo mindful awareness practice therapy. In a study[45] of adults with ADHD who were poor responders to medication, combined CBT and DBT that included a mindfulness component was shown to reduce residual symptoms of ADHD.

OVERVIEW OF THE NEUROBIOLOGY OF ADHD

Pharmacotherapy is a mainstay of treatment in adults with ADHD.[1,2,21] To better understand the rationale

Table 1. FDA-Approved Pharmacotherapy Options for Adults With ADHD

Agent	Formulation	Estimated Duration, h
Amphetamine-based psychostimulants		
Adderall XR[57]	Mixed salts (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate) of a single-entity amphetamine product capsule	8–12
Adzenys XR-ODT[58,59]	Amphetamine extended-release orally disintegrating tablets	10–12
Mixed amphetamine salts[60,a]	Mixed salts (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate) of a single-entity amphetamine product capsule	4–6
Vyvanse[61]	Lisdexamfetamine dimesylate (*d*-amphetamine prodrug) capsule and chewable tablet	8–14
Evekeo[62]	Amphetamine sulfate tablet	4–6
Methylphenidate-based psychostimulants		
Aptensio XR[63]	Methylphenidate HCl extended-release capsule	Up to 16 hours postdose
Concerta[64]	Methylphenidate HCl extended-release tablet	8–12
Focalin[65]	Dexmethylphenidate HCl tablet	3–6
Focalin XR[66]	Dexmethylphenidate HCl extended-release capsule	8–12
Ritalin[67]	Methylphenidate HCl tablet	3–4
Ritalin SR[68]	Methylphenidate HCl sustained-release tablet	6–8
Nonstimulants		
Strattera[69]	Atomoxetine (selective norepinephrine reuptake inhibitor) capsule	Up to 24

[a]Now available only as generic formulations (Adderall no longer marketed).
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, FDA = US Food and Drug Administration, HCl = hydrochloride.

for the pharmacologic treatment of ADHD, a brief overview of the neurobiology of ADHD is warranted. Dysfunction of the prefrontal cortex (PFC) is often implicated in the symptomatology of ADHD, specifically through the PFC's function in regulating attention and other higher-order cognitive abilities.[46] Alterations in monoamine function in the PFC, including the dopamine and norepinephrine systems that modulate PFC function, may partially account for ADHD symptoms and the significant association of other psychiatric comorbidities with ADHD.[47] Both dopamine and norepinephrine mediate PFC function and play a role in the regulation of executive function, including attention and inhibitory control.[47] During nonstressful conditions, the PFC coordinates the brain's activity in a "top-down" fashion to properly regulate behavior, thought, and emotion through its extensive connections with other cortical and subcortical brain regions.[48] However, under conditions of psychological stress, the activation of hypothalamic and brain stem pathways leads to the release of dopamine and norepinephrine and a switch to a "bottom-up" control of behavioral processes.[48] The "bottom-up" control of attentional processes by salient environmental stimuli is likely to play a role in the altered reward processing and impulsivity observed in individuals with ADHD, with a meta-analysis[49] reporting a medium effect size (0.48) for hyporesponsiveness of the ventral striatum (ie, decreased activity during reward anticipation and delivery) in functional MRI studies. Evidence[50] suggests not only that individuals with ADHD are impaired in tasks mediated by the PFC, but also that there is reduced dopaminergic function in the PFC of individuals with ADHD.

Structural changes in the dorsolateral PFC and the anterior cingulate cortex have also been implicated in the neuroanatomy of ADHD, with MRI data showing that there is significantly less overall cortical gray matter and smaller dorsolateral PFC and anterior cingulate cortex volumes in adults with ADHD compared with age-matched controls.[51] Deficiencies in cortical thickness are associated with ADHD in adults,[52,53] as evidenced by (1) significant delays in the age at which peak cortical thickness is attained in individuals with ADHD compared with those without ADHD[53] and (2) the higher rates and greater amount of cortical thinning observed in individuals diagnosed with ADHD as children who continue to meet ADHD diagnostic criteria as adults (compared with individuals diagnosed with ADHD as children who no longer meet ADHD diagnostic criteria as adults).[52]

There are also differences in functional connectivity in individuals whose symptoms of ADHD persist into adulthood compared with individuals whose symptoms remit in adulthood and compared with those without ADHD, as measured by functional MRI studies.[54,55] Individuals with ADHD exhibit less connectivity across multiple regions of the brain compared with individuals without ADHD, a difference that is not correlated with symptom severity,[54] and individuals with ADHD that persists into adulthood exhibit the lowest levels of connectivity relative to those without ADHD and to individuals whose ADHD remitted in adulthood.[55] Consistent with the neuropathology of ADHD, adults with ADHD exhibit impairments in executive function, divided attention, and sustained attention compared with adults without ADHD.[56]

PHARMACOLOGIC TREATMENT OPTIONS

Multiple agents are approved by the US Food and Drug Administration (FDA) for the treatment of ADHD in adults (Table 1[57–69]). These agents can be classified as psychostimulants (amphetamine-based or methylphenidate-based) or nonstimulants (ie, atomoxetine). From the perspective of efficacy, meta-analyses[70,71] have assessed the relative efficacy of psychostimulants and nonstimulants in

the treatment of ADHD in adults. In a meta-analysis of 13 medications published in 2010, Faraone and Glatt[70] reported that effect sizes favored active treatment over placebo for both psychostimulants (short-acting formulations and long-acting stimulants) and nonstimulants (included ABT-418, atomoxetine, bupropion SR, modafinil, bupropion XL, and paroxetine). The effect size for psychostimulants was significantly larger than the effect size for nonstimulants (long-acting stimulants: 0.73; short-acting stimulants: 0.86; nonstimulants: 0.39), and there were no significant differences in effect size between long-acting and short-acting psychostimulants or between amphetamine-based and methylphenidate-based psychostimulants.[70] Greater heterogeneity in effect sizes was reported for short-acting psychostimulants, but not for long-acting psychostimulants or nonstimulants.[70] A more recent meta-analysis[71] of 9,952 individuals published in 2016 confirmed the findings of Faraone and Glatt.[70] Cunill and colleagues[71] reported that pharmacologic treatment for ADHD was more effective than placebo in reducing ADHD symptoms (standardized mean difference: 0.45), with psychostimulants exhibiting larger effect sizes than nonstimulants (standardized mean difference: 0.18).

Several psychostimulant formulations have recently been approved for the treatment of ADHD (Aptensio XR[63] [methylphenidate extended-release capsule; approved for the treatment of ADHD in individuals ≥ 6 years old in April 2015], Evekeo[62] [amphetamine sulfate tablet approved for the treatment of ADHD in children ≥ 3 years old in September 2014], and Adzenys XR-ODT[58] [amphetamine extended-release orally disintegrating tablet approved for the treatment of ADHD in individuals ≥ 6 years old in January 2016]). There are currently no published phase 3 studies describing the efficacy of these agents in adults with ADHD.

Two other agents for the treatment of ADHD in adults are multilayer-release methylphenidate hydrochloride (MLR-MPH; in development) and SHP465 mixed amphetamine salts (MAS; approved June 2017 [Mydayis]). The duration of effect of MLR-MPH (also known as PRC-063; a prolonged-release formulation of MPH) was assessed in a double-blind, phase 3 study[72] using an adult workplace environment. In this study,[72] dose-optimized MLR-MPH (25–100 mg/d) produced significantly greater improvement than placebo on the primary efficacy endpoint of Permanent Product Measure of Performance total score (an objective measure of the ability to initiate a task and to self-monitor/stay on task) for up to 16 hours postdose. Participants treated with MLR-MPH also exhibited significantly fewer symptoms of ADHD on the ADHD Self-Report Screening Scale for *DSM-5* than did participants treated with placebo.[72] SHP465 MAS is a once-daily, extended-release, single-entity MAS product for oral administration. In 2 phase 3 placebo-controlled studies (1 dose-optimization study[73] and 1 forced-dose study[74]) in adults with ADHD, SHP465 MAS was found to be superior to placebo in reducing the core symptoms of ADHD, as measured by total score reductions on the ADHD-RS-IV. In a long-term safety and tolerability study,[75] SHP465 MAS exhibited a long-term safety profile comparable with observations from the short-term efficacy studies[73,74] and showed evidence of continued symptom control for up to 12 months. Another phase 3 placebo-controlled study of SHP465 MAS in adults with ADHD has been completed, but the data have not yet been published. Treatment options that are not approved by the FDA for the treatment of ADHD in adults include the nonstimulants guanfacine and clonidine (approved for use in pediatric populations only[1]) and antidepressants, such as bupropion and tricyclic antidepressants, which could be considered as alternatives if substance abuse is a concern or if the patient is refractory to first- and second-line treatment options.[1,21]

TREATMENT CONSIDERATIONS

When developing a treatment plan for adults with ADHD, it is important to recognize that the demands of adult life at home and work necessitate symptom control throughout the day (Figure 1). To address this consideration, some physicians may supplement their patients' long-acting psychostimulant with another ADHD medication later in the day, ostensibly to extend the duration of coverage so these individuals are able to better attend to their responsibilities into the evening. Consequently, the utility of immediate-release versus extended-release formulations should be considered to allow treatment to be tailored to an individual's needs. It is also important to consider that swallowing difficulties affect patients of all ages; thus, long-acting formulations that address this barrier will be critical for improving adherence and patient outcomes.[2]

Although psychostimulants are considered a first-line treatment for ADHD,[21] it is important to recognize the tolerability and safety considerations associated with their use in adults with ADHD. Psychostimulants are schedule II controlled substances with prescribing information that has black box warnings that include drug dependence, sudden death, and serious cardiovascular events,[76] as well as warnings and precautions that include psychiatric events, increased blood pressure and heart rate, and peripheral vasculopathy.[58,60,63–68] The potential for serious cardiovascular events warrants routine monitoring in individuals using psychostimulant medication; however, Habel and colleagues[77] found that current or new use of ADHD medications (both psychostimulants and atomoxetine) was not associated with an increased risk of serious cardiovascular events compared with no use or remote use (> 364 days since end of last supply) in a large cohort of > 150,000 young and middle-aged adults. The most frequently reported adverse events associated with psychostimulant treatment include insomnia, decreased weight and appetite, nausea, headache, and increased blood pressure and pulse.[58,63–68] In adults with a history of cardiac disease or in those with borderline hypertension, it has been suggested that increases in blood pressure and pulse could be clinically relevant.[64–68]

SUMMARY

In adults, ADHD often goes untreated[6] and leads to impairments in multiple domains, including home, social, school, and work.[7,9] The updated ADHD diagnostic criteria of the *DSM-5* incorporate ADHD symptoms specific to affected adults[18] and may aid clinicians in better diagnosing ADHD in the adult population. Despite the important updates that have been made to the *DSM-5* regarding ADHD, the presence of psychiatric comorbidities may complicate the differential diagnosis of ADHD. As such, it is important for clinicians to know the conditions that are often comorbid with ADHD and how the symptoms of these disorders may overlap with those of ADHD.[26,27] The use of screening and assessment instruments, such as the ADHD Self-Report Screening Scale for *DSM-5*[32] and ADHD-RS-IV with adult prompts,[34] can aid clinicians in identifying adults with probable ADHD. However, it is important to note that a comprehensive clinical interview that includes longitudinal and family histories is imperative to the accurate diagnosis of ADHD.

An array of nonpharmacologic[36] and pharmacologic[1,2,21] treatments is available for the treatment of ADHD in adults. Nonpharmacologic therapies, such as CBT,[36] DBT,[39] physical exercise,[42] and mindfulness awareness practice,[44] have all been shown to confer benefits in adults with ADHD. Pharmacologic options include psychostimulants, which have demonstrated the greatest levels of efficacy for treating the core symptoms of ADHD in adults,[70,71] and nonstimulants, which can be considered when there are concerns related to response, tolerability, or safety with psychostimulants.[1,21] A further consideration regarding pharmacologic treatment concerns the demands of adult life, which often extend well beyond the typical 8-hour workday, and whether an individual's situation necessitates a treatment option that provides coverage beyond the workday and into the evening.

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