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Novel and Emerging Treatments for Adult ADHD: The Path From Inception to Implementation

Based on a Medscape Education Online Activity

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CME / ABIM MOC / CE
Release Date: 11/14/22
Expiration Date: 11/14/23

CREDITS AVAILABLE

Physicians - maximum of 0.50 *AMA PRA Category 1 Credit(s)*™

TARGET AUDIENCE

This activity is intended for psychiatrists, primary care physicians, pediatricians, nurse practitioners, physician assistants and other clinicians who care for individuals with attention-deficit/hyperactivity disorder (ADHD).

GOAL STATEMENT

The goal of this activity is for learners to be better able to provide background on the clinical considerations for nonstimulant therapy in ADHD management and increase understanding of available evidence for nonstimulant medications for adult ADHD.

LEARNING OBJECTIVES

Upon completion of this activity, participants will:

Have increased knowledge regarding the
- Latest clinical data on novel and emerging pharmacotherapies for adult ADHD

Have greater competence related to
- Using stimulants vs nonstimulants in specific patient populations with ADHD

Demonstrate greater confidence in their ability to
- Use stimulants vs nonstimulants in specific populations with ADHD

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Faculty
Andrew Cutler, MD
Clinical Associate Professor of Psychiatry
SUNY Upstate Medical University
Rochester, New York

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Editor
Clinton W. Wright, PharmD, BCPP
Medical Education Director, Medscape, LLC

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Medical Writer
Megan Breuer, PhD

Medical Writer, Medscape, LLC

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Novel and Emerging Treatments for Adult ADHD: The Path From Inception to Implementation

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Andrew Cutler, MD

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What are the hallmarks of adult ADHD?

Attention-deficit/hyperactivity disorder (ADHD) is classically defined as a disturbance of both attention and of hyperactivity/impulsivity, leading to difficulty in functioning in at least 2 separate settings of daily life.[1-3] The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM-5*) classification contains a list of 18 diagnostic criteria, half of which are symptoms of inattention and half are symptoms of hyperactivity/impulsivity.[1] To qualify for the diagnosis, patients who are 17 or older should have at least 5 or more of the 9 potential symptoms of either or both of the 2 clusters of symptoms (**TABLE 1**).[1]

Depending on the pattern of symptoms, patients may show different manifestation of ADHD. For example, if a patient has symptoms that fulfill both the inattention and hyperactivity/impulsivity criteria, this is considered a combined presentation. Patients with symptoms that fulfill the inattention criteria, but not the hyperactivity/impulsivity criteria, have the predominantly inattentive presentation of ADHD, while patients fulfilling the hyperactivity/impulsivity criteria, but not the inattention criteria, will have the predominantly hyperactive/impulsive presentation of ADHD.[1]

Adults tend to display more of an inattentive presentation and a little less of the combined type. These symptoms need to be present in 2 or more settings in the person's life. As patients get older, they display less of the external hyperactivity and the hyperactivity tends to become more internalized.[2] As children grow into adulthood, cognitive demands increase. This creates a need for structured discipline and greater organization, which is where issues can arise specifically for adults with ADHD, who may have previously used adaptive strategies to disguise their ADHD symptoms in childhood.[2]

What are some common comorbid conditions associated with adult ADHD?

In childhood, the most common comorbidities have to do with behavior and conduct issues, such as oppositional defiant disorder, or conduct disorder.[4] Approximately 80% of adults with ADHD will have at least one coexisting psychiatric disorder.[5] In adulthood, anxiety, depression, and substance use disorder are the 3 most common comorbidities. Other comorbidities that can be seen in adults less frequently include bipolar disorder, tics, and Tourette syndrome.[6]

ADHD is associated with a spectrum of comorbidities, including autism spectrum disorder, communication and learning disorders, and motor developmental disorders. Other common psychiatric comorbidities include anxiety, depression, substance use disorders, bipolar disorder, social phobia, impulse control disorders, and eating disorders.[2,5]

Depression and anxiety occur in approximately 40% to 60% of adults with ADHD.[5] This is extremely important because they are often the primary complaint and can have a substantial impact on the way the patient with ADHD presents in the clinical setting.

What can cause delays in ADHD diagnosis?

ADHD may be a missed diagnosis in older adults because the condition was not identified in childhood, sometimes because the condition was not recognized as a distinct clinical entity. Furthermore, the symptoms may have been disguised by adaptive strategies throughout the patient's life.[2] The vast majority of the time, ADHD begins in childhood and is a highly genetic condition, with a mean heritability of approximately 75%.[7] Approximately 50% of offspring with one parent with ADHD will also have ADHD.[3]

TABLE 1. *DSM-5* Adult ADHD Diagnostic Criteria[1]

Symptom	Criteria
Inattention	Five or more symptoms in adolescents ages 17 years and older and in adults that are inappropriate for developmental level and have been present for at least 6 months: • Often fails to play close attention to details/makes careless mistakes at work or during other activities • Often has trouble sustaining attention during tasks • Often does not appear to listen when spoken to directly • Often does not follow through on instructions and fails to finish duties in the workplace • Often has trouble organizing tasks and activities • Often avoids, dislikes, or is reluctant to perform tasks that require mental effort over a long period of time • Often loses things necessary for tasks and activities (eg, keys, paperwork, eyeglasses, mobile phones) • Often easily distracted • Often forgetful during everyday activities
Hyperactivity and impulsivity	Five or more symptoms in adolescents ages 17 years and older and in adults that are inappropriate for developmental level and have been present for at least 6 months: • Often fidgets or taps hands/feet, or squirms in seat • Often leaves seat in situations where remaining seated is expected • Often feels restless • Often incapable of taking part in leisure-time activities quietly • Often "on the go" as if "driven by a motor" • Often talks excessively • Often blurts out an answer before a question has been completed • Often has trouble waiting their turn • Often interrupts or intrudes on others
Conditions	All of the following conditions must be met for an ADHD diagnosis: • Several inattentive or hyperactive/impulsive symptoms were present before age 12 • Several symptoms are present in 2 or more settings • There is clear evidence that symptoms interfere with or reduce the quality of social or work functioning • The symptoms are not better explained by some other psychiatric disorder (eg, mood disorder, anxiety disorder, dissociative disorder, personality disorder) • The symptoms are seen beyond the course of schizophrenia or another psychiatric disorder

Abbreviations: *DSM-5, Diagnostic and Statistical Manual of Mental Disorders.*

It is certainly possible to develop secondary ADHD due to trauma, a tumor, or an infection; something that causes damage to the brain.[7] Compensatory skills may delay or prevent an ADHD diagnosis; patients who are very intelligent, for example, may not show the classic *DSM-5* symptoms until later in adulthood when cognitive demands become greater and external social supports, such as parents, teachers, or friends, are not as present.[5]

New research is revealing that ADHD persists into adulthood in approximately 90% of children, far more than previous estimates of 50% to 60%. The results of the Multimodal Treatment Study of ADHD (MTA), which included 558 children with ADHD, demonstrated that 30% of children experienced full, but not necessarily sustained, remission from ADHD at some point during a period of 2 to 16 years. However, 60% of children experienced an ADHD recurrence after an initial remission period, and only 9.1% of the participants demonstrated recovery (sustained remission) by the end of the study. Most participants (63.8%) showed fluctuating periods of

remission and recurrence during the follow-up period, depending on environmental factors and stressors.[8] This highlights the importance of ongoing monitoring and psychoeducation for all patients who have been diagnosed with, or are showing symptoms of, ADHD. Patients are particularly vulnerable to showing symptoms and impairment during periods of stress or increased environmental cognitive demands.[5,8]

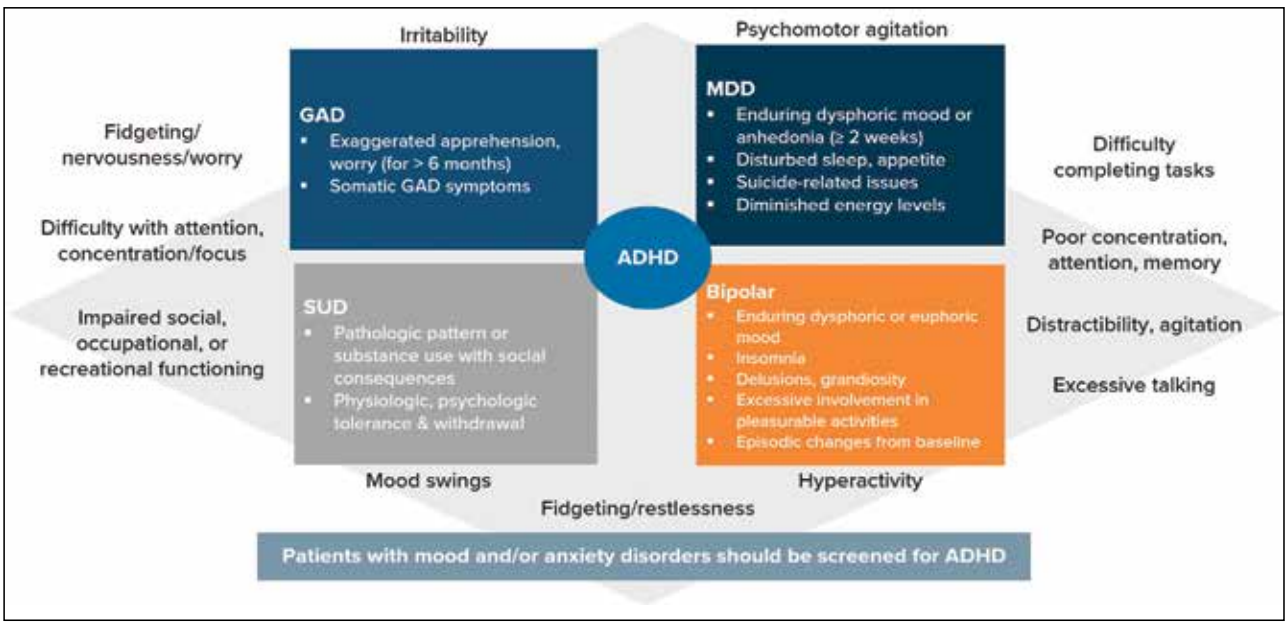
The presence of one or more comorbidities may also play a role in ADHD diagnostic delays. Adults often present with the comorbidity as the primary issue. A comorbidity, such as anxiety or depression, may be recognized, while the main condition of ADHD remains undiscovered and untreated. Unrecognized ADHD is also associated with poor treatment response and treatment noncompliance, or possible mismanagement when a medication is given that will only address a comorbidity, but not the underlying ADHD. For example, a patient with ADHD and comorbid depression who receives only a selective serotonin reuptake inhibitor (SSRI) for depression, but nothing to address the primary premorbid ADHD, may experience a worsening of their symptoms instead of an improvement.[5] So-called treatment-resistant depression or anxiety, therefore, is often unrecognized ADHD with comorbidity. Substance use disorders may similarly mask underlying ADHD and complicate treatment.

What is the role of comorbidities in developing adult ADHD treatment plans?

As previously noted, the overlapping characteristics of ADHD and mood, anxiety, and substance use disorders (**FIGURE**) often complicates ADHD diagnosis and treatment; physicians tend to be more familiar with these other disorders, which may also lead to misdiagnosis and treatment delays.[5] Psychiatric disorders occur in approximately 80% of adult patients with ADHD.[5] Substance use, particularly alcohol, and/or nicotine, cannabis, or cocaine use, is common among adults with ADHD. Substance use disorders are approximately twice as common in patients with ADHD, compared with those without ADHD.[5] Other psychiatric disorders, such as anxiety, depression, and bipolar disorder, occur in approximately 50% of adults with ADHD, with rates for depression ranging from 18.6% to 53.5% of patients, and bipolar disorder rates ranging from 5.1% to 47.1% of patients. [5]

Both the ADHD itself and its comorbidities should be taken into account when formulating a treatment plan for adult patients with ADHD. Treatment selection should also be based on the proposed medication's efficacy in terms of functional outcomes such as reduction in symptoms, improved daily functioning, and improved quality of life.[5] Treatment considerations should include safety and tolerability assessments. The currently available stimulant and nonstimulant medications have possible

FIGURE. Overlapping and Distinctive Features of ADHD and Common Psychiatric Comorbidities[5]



Abbreviations: GAD, generalized anxiety disorder; MDD, major depressive disorder; SUD, substance use disorder.

adverse effects and drug-drug interactions that should be discussed with the patient and caregivers prior to therapy initiation.[5] Common adverse effects associated with stimulant medications include headache, appetite suppression, nausea, dry mouth, mood fluctuations, agitation, irritability, sleep difficulties, and increased heart rate and blood pressure. Common adverse events associated with nonstimulant medications can include appetite suppression, dry mouth, insomnia, constipation, vomiting, fatigue, nausea, dyspepsia, and mood swings.[5]

Further, the nature of the comorbidity will also drive treatment decisions. For example, some patients with comorbid depression or anxiety may not benefit from treatment with stimulant monotherapy, as these may worsen the depressive or anxious symptoms. Patients who are prone to substance use may also not be prime candidates for treatment with a stimulant. However, some patients with comorbid depression may benefit from combined treatment with a stimulant and an SSRI, although these patients may benefit from nonstimulant medications.[6] For each adult patient with ADHD, a tailor-made treatment strategy should be formulated to achieve the best possible outcomes.[6]

It is important to recognize that ADHD not only impacts the patient's school or work performance, but also has significant implications for the patient's quality of daily life, affecting intimate and family relationships and financial management. When making treatment decisions, the clinician and patient should strive to choose the very best option to help the patient accomplish their goals. Treatment choices should also be made with the understanding that dose adjustments may need to be made over time, or that medications may need to be added or taken away from the current regimen, all of which requires careful monitoring.

What steps can clinicians take to properly screen and diagnose patients with ADHD?

The current estimated prevalence of adult ADHD is 4% in the United States. The actual prevalence, however, is more likely closer to 8%, based on the Sibley et al study that found over 90% persistence into adulthood vs the 50% to 60% cited in older studies. Only a fraction of these patients are recognized and receive treatment.[8] The use of proper screening and diagnostic tools would help identify adult patients with ADHD in a more timely manner, and allow for swift treatment initiation.[9]

The Adult Attention-Deficit/Hyperactivity Disorder Investigator Symptom Rating Scale (AISRS) is a survey consisting of 18 items that contains questions based on the symptoms from the *DSM-5*, and is meant to identify patients at risk for ADHD.[9] Each symptom is rated on a scale from 0 to 3, with 0 meaning that the symptom is not at all present, and a 3 meaning that the symptom is present very often and causing the patient difficulty. A patient with a score of approximately 23 to 26 would indicate a moderate level of ADHD that would require intervention.[10] A 6-item screening tool, called the Adult Self-Report Scale (ASRS), which can be completed by the patient, is also available.[9]

Several diagnostic tools are also currently available and can help clinicians establish the key diagnostic ADHD criteria.[9] Commonly used diagnostic tools include the Diagnostic Interview for ADHD in Adults (DIVA-5), Conner's Adult ADHD Diagnostic Interview for DSM-IV (CAADID), and the Adult ADHD Clinical Diagnostic Scale (ACDS v1.2). These tools can aid clinicians in gauging the history and persistence of symptoms and ensure a thorough review of the symptoms and their impact on the patient.[9]

What stimulants are currently approved for the treatment of adult ADHD?

The currently approved stimulants for adult ADHD (**TABLE 2**) include both methylphenidates and amphetamines, such as mixed amphetamine salts and the amphetamine prodrug lisdexamfetamine dimesilate.[11-21] Stimulant medications are available in a variety of delivery mechanisms, including immediate-release, intermediate-release, and extended-release formulas (only extended-release formulations are approved for adults), helping clinicians to develop and customize patient-specific treatment plans based on patient needs.[22]

The results from randomized clinical trials have shown that treatment with methylphenidate is beneficial for adult patients with ADHD, resulting in significant reductions in patient symptoms and clinician estimates of ADHD severity.[22] The results of a phase 3, double-blind, placebo-controlled, parallel study design using an osmotic-release oral system (OROS) of methylphenidate demonstrated that treatment was effective in reducing ADHD symptoms and generally well tolerated for more than 34 weeks.[22,23] Studies examining other methylphenidate formulations, including dexmethylphenidate extended-release,[24] extended-release multilayer methylphenidate,[25] delayed-release and extended-release methylphenidate (MPH DR/ER),[26] and serdexmethylphenidate/d-methylphenidate (serdexMPH/dMPH)[27] have also shown that these treatments are safe and efficacious in adult patients, although MPH DR/ER and serdexMPH/dMPH have not specifically been examined in adults.

Amphetamines are structurally similar to catecholamines, and while they block reuptake of norepinephrine and dopamine like methylphenidate, they also increase the release of norepinephrine and dopamine at higher doses.[28] They have also been shown to be effective in treating adult ADHD, and both the immediate- and slow-release formulas are effective. However, only extended-release formulations are approved by the US Food and Drug Administration (FDA) for the treatment of adult ADHD, and they are considered the standard of care to decrease risk of abuse, misuse, and diversion.[22] Lisdexamfetamine, an FDA-approved prodrug, undergoes gradual enzymatic breakdown to become the active ingredient d-amphetamine, resulting in a long-lasting effect. It is an effective therapy for adults with ADHD and is thought to have less potential for abuse and drug tampering, compared with other forms of amphetamines. In a randomized, 4-week, placebo-controlled trial, treatment with lisdexamfetamine resulted in significant improvements in adult ADHD-Rating Scale (ADHD-RS) and Clinical Global Impression (CGI) scores, compared with placebo, for all doses of lisdexamfetamine.[22,29]

Mixed amphetamine salts, in double-bead (an even mix of immediate and delayed release beads) and triple-bead (an even mix of immediate release and 2 types of delayed release beads) formulations, are also available for the treatment of adult ADHD.[30,31] The double-bead formulation has been shown to be effective in adult patients with ADHD, with significant improvements in ADHD-RS scores after 4 weeks of treatment in a randomized, double-blind, forced dose-escalation study.[30] The results of a phase 3, double-blind, randomized, forced-dose trial showed that treatment with triple-bead MAS in adult patients with ADHD resulted in significant improvements from baseline in the ADHD Rating Scale IV (ADHD-RS-IV) scores. The most frequently reported adverse events for both formulations were insomnia, decreased appetite, and dry mouth.[30,31] Amphetamine extended-release tablets are also approved for patients of 6 years of age and older, including adults. In a randomized, double blind, placebo controlled, fixed dose study in adults with ADHD, treatment with extended-release amphetamine resulted in significant improvements in the mean Permanent Product Measure of Performance scores, compared with placebo. Common adverse events included decreased appetite, insomnia, and dry mouth.[32]

What nonstimulants are currently approved for the treatment of adult ADHD?

The current FDA-approved nonstimulant therapies for adult ADHD management (**TABLE 2**) include atomoxetine and viloxazine XR.[20,21] Atomoxetine is a norepinephrine-specific reuptake inhibitor and binds to norepinephrine transporters to block the reuptake of norepinephrine and dopamine in the prefrontal cortex, thus helping to ameliorate the catecholaminergic deficits associated with ADHD. The results of randomized clinical trials have shown that atomoxetine is effective in long-term use, particularly when the patient is also experiencing comorbid anxiety, emotional dysregulation, or has the potential for substance addiction due to a comorbid substance use disorder.[22] Clinical trial results have shown that treat-

TABLE 2. Currently Approved Treatments for Adult ADHD Management[7]

Medication	Type
Osmotic release oral system methylphenidate hydrochloride (OROS-MPH)[11]	Stimulant
Dexmethylphenidate hydrochloride extended-release (d-MPH XR)[12]	Stimulant, extended-release formula
Methylphenidate hydrochloride extended-release (MPH DR/ER)[13]	Stimulant, extended-release formula
Methylphenidate hydrochloride (MPH XR MLR)[14]	Stimulant, extended-release formula
Serdexmethylphenidate and dexmethylphenidate (serdex MPH/d-MPH)[15]	Stimulant
Mixed amphetamine salts (MAS XR double bead)[16]	Stimulant, extended-release formula
Mixed amphetamine salts (MAS XR triple bead)[17]	Stimulant, extended-release formula
Lisdexamfetamine[18]	Stimulant, available in extended-release formula
Amphetamine XR liquid and tablets[19]	Stimulant, extended-release formula
Atomoxetine hydrochloride[20]	Nonstimulant
Viloxazine XR[21]	Nonstimulant, extended-release formula

ment with atomoxetine resulted in significantly greater mean reductions on the Connors' Adult ADHD Rating Scale-Investigator-Rated: Screening Version (CAARS-Inv:SV) after 10 to 16 weeks of treatment, and after 6 months of treatment, compared with placebo.[33] However, atomoxetine can require up to 2 to 3 weeks or more to achieve a maximal therapeutic effect, after a dose adjustment. Pooled data from 3 open-label studies showed that the median time to improvement was 3.7 weeks, and remission did not occur until a median of 14.3 weeks.[34,35]

Atomoxetine is associated with nausea, decreased appetite, insomnia, and dry mouth. Irritability, dizziness, dyspepsia, and erectile dysfunction have also been reported in clinical trials. Further, the patient's cardiac history should also be examined prior to initiating treatment. Treatment should be used with caution in patients with hypertension, tachycardia, or cardiovascular/cerebrovascular disease, as it can result in increases in blood pressure and heart rate. Patients should be monitored for the development of liver toxicity or suicidal thoughts.[20,22]

Additionally, less than one-half of patients will respond to atomoxetine.[35] This represents a pressing need for more nonstimulant options, particularly in adults with conditions limiting the use of stimulants or where substance abuse may represent a significant hurdle. On April 29, 2022, viloxazine extended-release was approved by the FDA for the treatment of adult ADHD. Viloxazine extended release had previously been approved by the FDA for the treatment of pediatric ADHD. Similar to atomoxetine, it binds to the norepinephrine transporter, but also has affinity for serotonin $5HT_{2B}$, $5HT_{2C}$, and $5HT_{7}$ receptors.[36,37] It is available as a once-a-day extended-release preparation, has shown efficacy in adult patients with ADHD, and may be effective in patients with comorbid depression or anxiety.[36,38] It is also associated with a low risk of substance use liability, representing an attractive alternative to Schedule II stimulants for the treatment of ADHD.[36]

In a phase 3, randomized, double-blind, placebo-controlled clinical trial in adults with ADHD, treatment with viloxazine extended release (flexible dose of 200 mg to 600 mg/d) resulted in significant reductions in AISRS total scores (least square mean ± standard error: -15.5 ± .91) compared with placebo (-11.7 ± .90, P = .004). There were also significant reductions in Clinical Global Impressions-Severity of Illness (CGI-S) scores in patients who were treated with viloxazine ER (-1.4 ± .10), compared with patients receiving placebo (-1.0 ± .10, P = .0023).[38]

The most common adverse events associated with viloxazine use are insomnia, fatigue, nausea, decreased appetite, dry mouth, and headache.[38] All patients receiving viloxazine should be monitored for the development of or clinical worsening of suicidal thoughts and behaviors.[36]

What treatments are on the immediate horizon for the treatment of adult ADHD?

One drug currently in late-phase development is centanafadine, an inhibitor of norepinephrine, dopamine, and serotonin transporters (triple reuptake inhibitor) that acts as a stimulant but with nonstimulant characteristics.[34] The results of 2 phase 3 randomized clinical trials demonstrated that treatment with centanafadine 200 or 400 mg/d resulted in significant improvements in AISRS total scores. The overall rate of treatment-emergent adverse events (TEAEs) was low, though there was a small increase in TEAEs with increasing dose. The most commonly occurring TEAEs, headache and decreased appetite, were mild or moderate in nature. Other TEAEs considered potentially related to treatment included dry mouth and nausea. The occurrences of adverse events related to substance use were low.[34]

A potential benefit of centanafadine is that, like extended-release viloxazine, it may be an effective treatment for both ADHD and other behavioral and mood disorders, such as depression and anxiety, that are linked to norepinephrine, dopamine, and serotonin reuptake.[34]

Which patients could benefit most from treatment with nonstimulant ADHD medications?

Although stimulant medications are effective at controlling symptoms in most patients with ADHD, approximately 10% to 30% will not respond adequately to stimulant treatment, and many may experience intolerable adverse effects.[39] Further, all adult patients with ADHD are potential candidates for treatment with nonstimulants; this includes younger adults who are transitioning from adolescence into adulthood and may be leaving home for the first time. These patients are particularly suited for nonstimulant medication because they can be at a higher risk of abuse, misuse, and diversion of stimulants, although early treatment may help prevent the development of comorbid psychiatric disorders in this population.[5] Clinicians may also be more comfortable prescribing a nonstimulant, and this type of medication may be easier for the patient to manage. Nonstimulants are also appropriate for patients with a history of substance use disorders. Another group well suited for nonstimulants is adults with cardiovascular issues such as hypertension, where stimulants may pose a serious risk, although, as

noted earlier, atomoxetine should be used with caution in this patient population.

What risks and benefits are associated with today's ADHD treatments?

Stimulant medications are very effective treatments for adult ADHD, with a quick onset of action (ie, within the first week) for most patients. Stimulant therapies have been associated with such adverse effects as insomnia, anorexia, nausea, decreased appetite, weight loss, headache, and mood liability. Further, stimulant use may pose a cardiovascular risk for patients, as they increase blood pressure and elevate pulse.[39] Care should be taken, therefore, to ensure that blood pressure is properly monitored and managed in adult patients with ADHD. Stimulant medications are contraindicated for patients with psychiatric risk factors, such as bipolar disorder, severe anorexia, and Tourette syndrome, as well as those with hypertension, tachycardia, and arrhythmias. These medications have been associated with psychosis and mania. There are also warnings about abuse potential, vasoconstriction, such as Raynaud phenomenon, and priapism (methylphenidates).[12,39]

Nonstimulant medications may be more suitable for older adults with cardiovascular issues. These medications also have the potential to treat the patient's ADHD as well as some underlying comorbidities, such as anxiety or depression. Because they are not scheduled medications, nonstimulants are easier to prescribe and easier for the patient to access and manage. Though stimulants have a swifter onset of action compared with nonstimulants, treatment with the nonstimulant viloxazine has resulted in significant improvements in ADHD symptoms after 2 weeks of treatment,[38] while atomoxetine may require 3 weeks or more to reach the maximum clinical effect.[34] As stated earlier, the most common adverse effects of viloxazine include decreased appetite, fatigue, nausea, vomiting, insomnia, constipation, and headache. Patient heart rate and blood pressure should be monitored regularly; patients should also be screened for bipolar disorder. Viloxazine should not be used in combination with cytochrome P450 (CYP) 1A2 substrates.[38] As mentioned previously, atomoxetine has been associated with constipation, dry mouth, nausea, decreased appetite, dizziness, erectile dysfunction, and urinary hesitation. Atomoxetine may also result in drug-drug interactions with CYP2D6 inhibitors and should not be used in combination with monoamine oxidase inhibitors, antihypertensive drugs, or albuterol. Patients should also be monitored for suicidal ideation.[19,39]

What are the most important considerations when making ADHD treatment decisions with adult patients?

Several considerations should be taken into account. These include: the age of the patient, cost of treatment, patient/caregiver time demand, medical and psychiatric comorbidities, concomitant medications, expected effectiveness of treatment, adverse effects, tolerability, and safety. Patient preferences for specific treatments also play a substantial role. Also, the acceptance of the proposed treatment by the patient and caregiver can have a significant impact on the patient's treatment adherence.[40,41] Drug therapy should also only be initiated under the guidance of a primary care provider (PCP), psychiatrist, or other clinical prescriber with training in the diagnosis and management of ADHD.[41]

Patients and clinicians should also always discuss the potential risks and benefits of treatment, and shared decision making should be used to explain the various options and to explain the possible need for dose adjustments for optimal dose responses.[40] Further, patients with psychiatric comorbidities or those who experience adverse effects may be less likely to adhere to treatment, and may be at increased risk of treatment discontinuation in the long term. Careful monitoring is therefore necessary to address comorbidities and possible adverse effects in order to optimize treatment outcomes.[42] A combination of drug therapy and nonpharmacologic intervention, such as cognitive behavioral therapy or other psychotherapeutic approaches, can also benefit adult patients with ADHD, and can be effective for patients who also have comorbid psychiatric disorders.[5]

How do you monitor adults with ADHD long term?

Several scales are useful in the monitoring of adult patients with ADHD. For example, the ADHD-RS is readily available, and monitors the 18 specific symptoms that are listed in the *DSM-5*.[43] Ideally, ADHD-RS scores should be below 18. Scales used to monitor treatment effects include the AISRS; the CAARS, which includes a self-reported and observer-rated version; the ADHD-RS; and the ADHD-RS with adult prompts.[44]

Further, clinicians can also monitor real-life measurable parameters of functional and quality-of-life benefits that accompany symptom control. After symptoms have been stabilized, follow-up appointments to monitor treatment adherence and response, as well as assessments of adverse effects, should be performed for at least 1 year.[40] Weight, blood pressure, and heart rate should be routinely monitored, and psychiatric symptoms including suicidality should be assessed.

What types of specialists might be involved in team-based strategies to help patients manage their ADHD?

Primary care providers (PCPs) are becoming increasingly involved in ADHD screening in undiagnosed adult patients,[7] and can help manage their adult patients with ADHD with input from other specialists. For example, PCPs may request that a specialist see the patient initially or to help them with initiating or adjusting therapy. Neuropsychological testing can be helpful when monitoring comorbidities, cognitive impairment, or learning disabilities but it is not required nor is it useful in making the initial diagnosis.[7] ADHD coaches, who are specifically trained to help adults with ADHD better manage their lives, may be a useful adjunct to help patients learn valuable coping strategies.[45] Website resources, such as the Children and Adults with ADHD (CHADD)[46] and the Attention Deficit Disorder Association (ADDA)[47] sites, are also useful tools for patients and caregivers. ●

REFERENCES

1. American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
2. Magnin E, Maurs C. Attention-deficit/hyperactivity disorder during adulthood. *Rev Neurol (Paris)*. 2017;173:506-515.
3. Feifel D. Why diagnose and treat ADHD in adults? *Postgrad Med*. 2008;120:13-15.
4. Ghosh S, Sinha M. ADHD, ODD, and CD: do they belong to a common psychopathological spectrum? A case series. *Case Rep Psychiatry*. 2012;2012:520689.
5. Katzman MA, Bilkey TS, Chokka PR, et al. Adult ADHD and comorbid disorders: clinical implications of a dimensional approach. *BMC Psychiatry*. 2017;17:302.
6. Perugi G, Pallucchini A, Rizzato S, et al. Current and emerging pharmacotherapy for the treatment of adult attention deficit hyperactivity disorder (ADHD). *Expert Opin Pharmacother*. 2019;20:1457-1470.
7. Young JL, Goodman DW. Adult attention-deficit/hyperactivity disorder diagnosis, management, and treatment in the DSM-5 Era. *Prim Care Companion CNS Disord*. 2016;18.
8. Sibley MH, Arnold LE, Swanson JM, et al. Variable patterns of remission from ADHD in the Multimodal Treatment Study of ADHD. *Am J Psychiatry*. 2022;179:142-151.
9. Anbarasan D, Kitchin M, Adler, LA. Screening for adult ADHD. *Curr Psychiatry Rep*. 2020;22:72.
10. Silverstein MJ, Faraone SV, Alperin S, et al. Validation of the expanded versions of the Adult ADHD Self-Report Scale v1.1 symptom checklist and the Adult ADHD Investigator Symptom Rating Scale. *J Atten Disord*. 2019;23:1101-1110.
11. United States Food and Drug Administration. Osmotic release oral system methylphenidate hydrochloride (OROS-MPH) [prescribing Information]. Approved 2000. Revised May 2017.
12. United States Food and Drug Administration. Dexmethylphenidate hydrochloride extended-release (d-MPH XR) [prescribing Information]. Approved 2005. Revised 2017.
13. United States Food and Drug Administration. Methylphenidate hydrochloride extended-release (MPH DR/ER) [prescribing Information]. Approved 1955. Revised 2018.
14. United States Food and Drug Administration. Methylphenidate hydrochloride (MPH XR MLR) [prescribing Information]. Approved 1955. Revised 2019.
15. United States Food and Drug Administration. Serdexmethylphenidate and dexmethylphenidate (Serdex MPH/d-MPH) [prescribing Information]. Approved 2021. Revised 2017.
16. United States Food and Drug Administration. Mixed amphetamine salts (MAS XR double bead) [prescribing Information]. Approved 2001. Revised 2017.
17. United States Food and Drug Administration. Mixed amphetamine salts (MAS XR triple bead) [prescribing Information]. Approved 2001. Revised 2017.
18. United States Food and Drug Administration. Lisdexamfetamine [prescribing Information]. Approved 2007. Revised 2017.
19. United States Food and Drug Administration. Amphetamine XR liquid and tablets [prescribing Information]. Approved 1960. Revised 2017.
20. United States Food and Drug Administration. Atomoxetine hydrochloride [prescribing Information]. Approved 2002. Revised 2010.
21. United States Food and Drug Administration. Viloxazine XR [prescribing Information]. Approved 2021. Revised 2021.
22. Zalsman G, Tal S. Adult ADHD: a new disease? *Int J Psychiatry Clin Pract*. 2016;20:70-76.
23. Biederman J, Mick E, Surman C, et al. A randomized, 3-phase, 34-week, double-blind, long-term efficacy study of osmotic-release oral system-methylphenidate in adults with attention-deficit/hyperactivity disorder. *J Clin Psychopharmacol*. 2010;30:549-553.
24. Moen MD, Kearn SJ. Dexmethylphenidate extended release: a review of its use in the treatment of attention-deficit hyperactivity disorder. *CNS Drugs*. 2009;23:1057-1083.
25. Weiss MD, Childress AC, Connelly GAE. Efficacy and safety of PRC-063, extended-release multilayer methylphenidate in adults with ADHD including 6-month open-label extension. *J Atten Disord*. 2021;25:1417-1428.
26. Childress AC, Cutler AJ, Po MD, et al. Symptomatic and functional response and remission from the open-label treatment-optimization phase of a study with DR/ER-MPH in children with ADHD. *J Clin Psychiatry*. 2021;82:21m13914.
27. Kollins SH, Braeckman R, Guenther S, et al. A randomized, controlled laboratory classroom study of serdexmethylphenidate and d-methylphenidate capsules in children with attention-deficit/hyperactivity disorder. *J Child Adolesc Pychopharmacol*. 2021;31:597-609.
28. Kuczenski R, Segal DS. Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. *J Neurochem*. 1997;68:2032-2037.
29. Adler LA, Goodman DW, Kollins SH, et al. Double-blind, placebo-controlled study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2008;69:1364-1373.
30. Weisler RH. Safety, efficacy and extended duration of action of mixed amphetamine salts extended-release capsules for the treatment of ADHD. *Expert Opin Pharmacother*. 2005;6:1003-1018.
31. Frick G, Yan B, Adler LA. Triple-bead mixed amphetamine salts (SHP465) in adults with ADHD: results of a phase 3, double-blind, randomized, forced-dose trial. *J Atten Disord*. 2020;24:402-413.
32. Cutler AJ, Childress AC, Pardo A, et al. Randomized, double-blind, placebo-controlled, fixed-dose study to evaluate the efficacy and safety of amphetamine extended-release tablets in adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2022;83:22m14438.
33. Asherson P, Bushe C, Saylor K, et al. Efficacy of atomoxetine in adults with attention deficit hyperactivity disorder: an integrated analysis of the complete database of multicenter placebo-controlled trials. *J Psychopharmacol*. 2014;28:837-846.

34. Adler LA, Adams J, Madera-McDonough J, et al. Efficacy, safety, and tolerability of centanafadine sustained-release tablets in adults with attention-deficit/hyperactivity disorder: results of 2 phase 3, randomized, double-blind, multicenter, placebo-controlled trials. *J Clin Psychopharmacol*. 2022;42:429-439.
35. Childress AC. A critical appraisal of atomoxetine in the management of ADHD. *Ther Clin Risk Manag*. 2015;12:27-39.
36. Lamb YN. Viloxazine: Pediatric first approval. *Pediatr Drugs*. 2021;23:403-409.
37. Yu C, Garcia-Olivares J, Candler S, et al. New insights into the mechanism of action of viloxazine: serotonin and norepinephrine modulating properties. *J Exp Pharmacol*. 2020;12:285-300.
38. Nasser A, Hull JT, Chaturvedi SA, et al. A phase III, randomized, double-blind, placebo-controlled trial assessing the efficacy and safety of viloxazine extended-release capsules in adults with attention-deficit/hyperactivity disorder. *CNS Drugs*. 2022;33:897-915.
39. Kolar D, Keller A, Golfinopoulos M, et al. Treatment of adults with attention-deficit/hyperactivity disorder. *Neuropsychiatr Dis Treat*. 2008;4:389-403.
40. Caye A, Swanson JM, Coghill D, et al. Treatment strategies for ADHD: an evidence-based guide to select optimal treatment. *Mol Psychiatry*. 2019;24:390-408.
41. Faraone SV, Silverstein MJ, Antshel K, et al. The adult ADHD quality measures initiative. *J Atten Disord*. 2019;23:1063-1078.
42. Fredricksen M, Dahl AA, Martinsen EW, et al. Effectiveness of one-year pharmacological treatment of adult attention-deficit/hyperactivity disorder (ADHD): an open-label prospective study of time in treatment, dose, side-effects and comorbidity. *Eur Neuropsychopharmacol*. 2014;24:1873-1884.
43. Zhang S, Faries DE, Vowles M, et al. ADHD Rating Scale IV: Psychometric properties from a multinational study as clinician-administered instrument. *Int J Methods Psychiatr Res*. 2005;14:186-201.
44. Ramsay JR. Assessment and monitoring of treatment response in adult ADHD patients: current perspectives. *Neuropsychiatr Dis Treat*. 2017;13:221-232.
45. ADHD Coaches Organization. Accessed September 15, 2022. https://acoo.memberclicks.net/
46. Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD). Updated 2022. Accessed July 11, 2022. https://chadd.org/adhd-information-library/
47. Attention Deficit Disorder Association (ADDA). Updated 2022. Accessed July 11, 2022. https://add.org/adda-virtual-programs/

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