

CLINICAL PRACTICE

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Adult Attention Deficit–Hyperactivity Disorder

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 31-year-old middle-school teacher sought medical help because she was having trouble keeping up with her job assignments and responsibilities. Her primary symptoms were an inability to stay focused and being easily distracted. She reported daydreaming with multiple thoughts at the same time, an inability to complete tasks on time, frequently forgetting to do things at work, and being unable to remain still during solitary activities (e.g., watching a movie and reading a book). Her friends described her as excessively talkative, disorganized, impatient, and careless. From childhood, her teachers noted that she was inattentive and messy and often did not turn in homework. She was able to do reasonably well in school despite her symptoms, but more recently, her job demands have overwhelmed her, and she is considering quitting. What would you advise?

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THE CLINICAL PROBLEM

ADHD IN CHILDHOOD AND ADULTHOOD

According to the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5),¹ attention deficit–hyperactivity disorder (ADHD) is characterized by symptoms of impulsivity, inattention, and hyperactivity that emerge in childhood (Table 1). ADHD was initially considered to be solely a childhood disorder, and the diagnosis of adult ADHD² was controversial.³ However, long-term follow-up studies revealed that in 40 to 60% of children with ADHD, the disorder persists into adulthood.⁴⁻⁷

The presentation of ADHD in adults is different from that in children,^{2,3} in part because of a greater decrease in symptoms of hyperactivity than in symptoms of inattention.⁸ Also, impairment related to ADHD in adulthood is manifested differently from impairment in childhood.² In the transition from childhood to adulthood, the diminishing symptoms of hyperactivity may be manifested as restlessness,² whereas the persisting symptoms of inattention⁸ may be manifested as difficulties in carrying out tasks (e.g., keeping appointments, meeting deadlines, or focusing on a single task) and may affect important functions in various aspects of life. Consequences of ADHD in adulthood^{5,9,10} include employment and financial difficulties (e.g., frequent job changes, unemployment, and lower socioeconomic status), interpersonal problems (e.g., social maladjustment and marital problems), and coexisting psychiatric disorders (e.g., depression and anxiety). There is also an increased risk of substance abuse, including smoking.

In a representative sample of U.S. adults who were 18 to 44 years of age, 5.4% of



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KEY CLINICAL POINTS

ATTENTION DEFICIT–HYPERACTIVITY DISORDER IN ADULTS

- The recognition that attention deficit–hyperactivity disorder (ADHD) persists after adolescence has led to an increase in its diagnosis and treatment in adults.
- Randomized trials show clinically significant improvements in ADHD symptoms and in daily functioning with the use of approved medications (stimulants and atomoxetine) for ADHD in adults.
- Clinical trials of medications for ADHD have been largely short-term and have predominantly involved young and middle-aged adults. Data are lacking on long-term benefits and risks and on risks among elderly patients.
- The absolute risk of serious cardiovascular adverse events associated with ADHD medications appears to be very low. However, the observed increases in pulse rate and blood pressure with stimulant use underscore the need for caution in prescribing these agents for patients with cardiovascular disease.
- The risk of addiction to stimulant medications prescribed for the treatment of ADHD in adults is low, but the clinician should be aware of their potential for abuse and dependence.

men and 3.2% of women met the criteria for ADHD.¹¹ In some clinical series, the ratio of men to women with ADHD is close to 1:1,¹² whereas the ratio of boys to girls with ADHD is at least 4:1.

GENETIC AND NONGENETIC FACTORS

ADHD has a strong genetic component, with heritability of approximately 0.8, suggesting that genetic factors would account for about 65% of phenotypic variance. However, only a few genes associated with ADHD have been identified, mostly in studies of candidate genes, and these genes account for only about 3% of phenotypic variation¹³; genomewide association studies have not identified any additional common variants.¹⁴ This suggests that many unidentified common variants with small effects, gene–environment or gene–gene interactions, rare variants, or a combination of these factors play a prominent role in the genetic cause of ADHD.¹⁵

Nongenetic factors are also associated with ADHD. Observational studies have shown that the risk of ADHD is doubled or tripled among offspring of mothers who smoked during pregnancy and among persons with evidence of lead exposure in childhood.¹⁶ Persons with obesity or diabetes¹⁷ and those whose mothers had these conditions during pregnancy have also been reported to have an increased risk of ADHD.^{18,19} It is not known whether these associations are causal.

NEUROBIOLOGIC FACTORS

Brain imaging studies in persons with ADHD (Table 2) have identified dysfunction of dopamine pathways involved in attention, executive function, and motivation and reward,^{20–22} as well as dysfunction in noradrenergic pathways, particularly those that innervate the prefrontal cortex, which is a central region for executive function.²³ Moreover, stimulant medications, which are the most effective treatments for ADHD, enhance dopaminergic and noradrenergic signaling; this provides support for the involvement of these neurotransmitters in the pathologic process of ADHD.

STRATEGIES AND EVIDENCE

DIAGNOSIS

The *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association provides guidelines for the diagnosis of ADHD. The current edition (DSM-5), which was approved in December 2012,¹ replaces the fourth edition. New to the DSM-5 is the inclusion of specific examples of how ADHD is manifested in adults (Table 1).¹ This change is based on a recognition of the chronic nature of ADHD and its varying manifestations across the lifespan.

The DSM-5 diagnosis in adults is based on the presence of at least five of nine symptoms in each of two domains — inattention, and hyperactivity

Table 1. Criteria for the Diagnosis of Attention Deficit–Hyperactivity Disorder (ADHD).*

ADHD consists of a pattern of behavior that is present in multiple settings and gives rise to difficulties with social and academic or work performance. The diagnosis requires evidence of inattention, hyperactivity and impulsivity, or both.

Inattention

Six or more of the following symptoms (five or more in adolescents and adults 17 years of age or older) have persisted for at least 6 months to a degree that is inconsistent with the person's developmental level and that directly affects social and academic or occupational activities:†

- Often fails to give close attention to details and makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
- Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures or conversations or when reading lengthy writings).
- Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
- Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked; does not finish schoolwork, household chores, or tasks in the workplace).
- Often has difficulty organizing tasks and activities (e.g., has difficulty managing sequential tasks and keeping materials and belongings in order; has messy, disorganized work; has poor time management; tends to fail to meet deadlines).
- Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., doing schoolwork or homework; preparing reports, completing forms, or reviewing lengthy papers).
- Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, or mobile phones).
- Is often easily distracted by extraneous stimuli (in older adolescents and adults, may include unrelated thoughts).
- Is often forgetful in daily activities (e.g., performing chores and running errands, returning telephone calls, paying bills, and keeping appointments).

Hyperactivity and impulsivity

Six or more of the following symptoms (five or more in adolescents and adults 17 years of age or older) have persisted for at least 6 months to a degree that is inconsistent with the person's developmental level and that directly affects social and academic or occupational activities:‡

- Often fidgets with or taps hands or feet or squirms in seat.
- Often leaves seat in situations in which one is expected to remain seated (e.g., leaves his or her place in the classroom or office).
- Often runs about or climbs in situations in which it is inappropriate. (In adolescents or adults, this symptom may be limited to feeling restless.)
- Often is unable to play or engage in leisure activities quietly.
- Often is "on the go," acting as if "driven by a motor" (e.g., is unable to be still or feels uncomfortable being still for an extended period of time in restaurants or meetings; other people may perceive him or her as being restless and difficult to keep up with).
- Often talks excessively.
- Often blurts out an answer before a question has been completed (e.g., completes people's sentences and "jumps the gun" in conversations, cannot wait for next turn in conversation).
- Often has difficulty waiting his or her turn (e.g., while waiting in line).
- Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities or uses other people's things without asking or receiving permission; adolescents or adults may intrude in or take over what others are doing).

Symptoms that cause impairment

Several symptoms of inattention or hyperactivity and impulsivity were present before 12 years of age.

Criteria for the disorder are met in two or more settings (e.g., at home, school, or work or with friends or relatives).

There is clear evidence that the symptoms interfere with or reduce the quality of social, academic, or occupational functioning.

The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better accounted for by another mental disorder (e.g., a mood disorder, an anxiety disorder, a dissociative disorder, or a personality disorder).

Current presentation§

Combined presentation: criteria for both inattention and hyperactivity and impulsivity have been present for the past 6 months.

Predominantly inattentive presentation: criteria for inattention are met but criteria for hyperactivity and impulsivity are not met.

Predominantly hyperactive and impulsive presentation: criteria for hyperactivity and impulsivity are met and criteria for inattention are not met.

* The criteria are based on the *Diagnostic and Statistical Manual of Medical Disorders*, fifth edition (DSM-5). ADHD denotes attention deficit–hyperactivity disorder. The table is adapted from the American Psychiatric Association.¹

† The DSM-5 committee considered reducing the cutoff to four symptoms for the diagnosis in adults (as suggested by some follow-up studies), but this was not accepted or included in the final version.

‡ An earlier revision of the DSM-5 added four additional symptoms of impulsivity to give this domain more prominence, but this addition was not included in the final version.

§ In persons (especially adolescents and adults) who currently have symptoms with impairment that no longer meet the full criteria, "in partial remission" should be specified.

Table 2. Neurobiologic Mechanisms of ADHD.**Anatomical correlates**

Smaller total brain volume (including frontal lobe, caudate nucleus, and cerebellum)

Reduced thickness of prefrontal and other cortical regions

Functional correlates

Alterations in connectivity in frontostriatal, frontoparietal, frontocerebellar, and parieto-occipital pathways and in the cingulate cortex

Decreased activity in the networks involved with executive function and with attention, and increased activity in the default mode network, which is deactivated during cognitive tasks and is implicated in mind wandering and interoception

Delayed brain maturation

Neurochemical factors

Dysregulation of dorsal striatal and ventral striatal dopamine systems

Dysregulation of noradrenergic systems

Genetic risk factors

Heritability of approximately 0.8

At least 18 ADHD-susceptibility genes (including the dopamine receptors D4 (DRD4) and D5, dopamine transporter (DAT1), serotonin receptor 1B, and synaptosomal-associated protein 25), but without specificity; 7-repeat allele of DRD4 most strongly implicated

Small effect sizes in molecular genetic analyses and genomewide association studies

Environmental and clinical risk factors

Prenatal exposure to alcohol, tobacco, and lead

Complications of pregnancy and birth

Neonatal anoxia, seizures, and brain injury

Obesity and diabetes

Gene–environment interactions

Interaction between genetic variants (*DRD4* and *DAT1*) and environmental factors such as maternal smoking during pregnancy

and impulsivity. The previous enumeration of three “subtypes” (ADHD characterized by a predominance of inattentive symptoms, ADHD characterized by hyperactive and impulsive symptoms, and ADHD characterized by both types of symptoms) was eliminated in the DSM-5, which instead focuses on “presentations at the time of assessment.” This change reflects the developmental instability of ADHD symptoms. The definition of the age at which ADHD symptoms began, which previously was an age younger than 7 years, was changed to an age younger than 12 years. For adults who do not receive a diagnosis in childhood, this criterion requires a retrospective report of childhood ADHD, which may

not be accurate.²⁴ Self-report of current symptoms in adults can also be problematic, since it is less predictive than reports from others regarding problems with employment (e.g., job dismissal and failure to be promoted), domestic life (e.g., strained relationships with one’s spouse and children or divorce), and social activities (e.g., friendship breakups).⁷ Thus, the DSM-5 recommends obtaining information from a friend or family member with long-term knowledge of the person.

The diagnosis of adult ADHD is complicated by the common co-occurrence of psychiatric conditions,^{11,25} most frequently substance-use disorders, generalized anxiety disorders, and mood disorders. Some psychiatric conditions, such as depression and bipolar disorder, and some medical conditions, such as thyroid diseases and sleep disorders, may underlie ADHD symptoms,²⁶ but these diagnoses can be ruled out by confirming that symptoms were present during childhood, except in instances in which these disorders might have been unrecognized. Assessment in adults is further complicated because some persons feign ADHD “symptomlike behaviors” to obtain stimulant medications for diversion to nonmedical use²⁷ and because the symptomlike behaviors can be present in adults without a pathologic condition.

MANAGEMENT*Pharmacotherapy*

Randomized, controlled trials of pharmacotherapeutic agents in adults with ADHD (Table 3) have consistently shown positive short-term effects, including symptom reduction and improvement in daily functioning.²⁹ However, evidence of positive effects on long-term outcomes is limited and mostly derived from observational studies that show some benefits in functioning, self-esteem, and work performance^{29,30}; a Swedish registry-based study (which included hospitalized persons) showed reduced risks of criminal behavior among persons with ADHD who were receiving treatment for the disorder than among those who were untreated.³¹ Although the consensus is that sustained treatment is necessary for ADHD, few randomized trials have assessed the efficacy and safety of approved ADHD medications in the long term (≥ 6 months) for adults.³² The determination of benefit is complicated by poor adherence to medication and discontinuation of treat-

ment and by coexisting psychiatric conditions.²⁹ One recommended strategy is to temporarily discontinue the medication after 1 or 2 years of treatment to determine whether benefits are lost; a loss of benefits would suggest that the medication is still useful.

Stimulant Medications

Stimulants (amphetamine and methylphenidate) are the most effective medications for the treatment of adult ADHD. Initially, immediate-release formulations were used, with multiple doses administered during the day (up to four doses) to maintain efficacy. ADHD symptoms diminish shortly after the administration of these agents, but symptoms reappear 3 to 4 hours later, as the medication starts to clear from the body. (The elimination half-life of methylphenidate is approximately 2 to 3 hours, and the elimination half-life of amphetamine is approximately 4 to 6 hours.) Subsequently, controlled-release formulations, which release medication gradually throughout the day and are intended for once-daily dosing, were developed, and they are currently used more commonly than immediate-release formulations.³³ In controlled studies,³⁴ most adults with ADHD have had a favorable clinical response to either methylphenidate or amphetamine, so there is no recommendation to start with one as opposed to the other. Approximately 70% of adults with ADHD have immediate improvement in attentiveness and reduced distractibility, with moderate-to-large effect sizes; effects are seen within 1 hour after administration (with both immediate-release and controlled-release formulations). Controlled-release formulations with a duration of efficacy of 6 to 10 hours might result in higher compliance than immediate-release formulations, since they may require only once-daily dosing (with a maximum of two doses), but data comparing rates of adherence to these medications are lacking. Clinical studies reveal considerable variation among persons with respect to the most effective dose of stimulant medication, and adjustments in the dose are necessary to maximize control of symptoms while minimizing adverse effects.

Methylphenidate and amphetamine have similar adverse effects. These include insomnia, dry mouth, decreased appetite, weight loss, headaches, depression, and anxiety. Some patients have fewer side effects with one of the agents

than with the other; thus, it is reasonable to try the alternative if these effects limit the use of the initial agent. Stimulants are contraindicated in patients with hypertension, psychosis, or tics, since these conditions might be exacerbated by these medications.²⁸ In a large retrospective cohort study, current use of stimulant drugs was not associated with an increased risk of serious adverse cardiovascular events among young or middle-aged adults.³⁵ A meta-analysis of treatment trials, however, showed significant increases in the resting heart rate (5.7 beats per minute) and systolic and diastolic blood pressure (1.2 mm Hg) with stimulant medications, as compared with placebo.³⁶ The Food and Drug Administration (FDA) recognizes that data on long-term risks among adults with ADHD are limited and recommends that stimulants (or atomoxetine [discussed below]) should not be used in “patients with serious heart problems or for whom increased blood pressure or heart rate would be problematic.”³⁷ For patients who are being treated with stimulants, the FDA advises that the heart rate and blood pressure be monitored periodically (every 3 months).

Stimulant medications have a potential for abuse and thus are classified by the Drug Enforcement Agency as Schedule II substances. They increase levels of dopamine in the human brain, which is the mechanism by which drugs of abuse exert their rewarding effects. The risk of abuse is increased among persons with a history of a substance-use disorder.^{28,38} The controlled-release formulations are harder to inject or snort than the immediate-release formulations and thus are less likely to be abused. Stimulants are also abused for their purported cognitive-enhancing effects.³⁹ In adolescents and college students, this nonmedical use may be as prevalent as medical use for the treatment of ADHD.²⁷ About 5% of persons without ADHD who use stimulants for nonmedical purposes are expected to increase their use, leading to abuse and dependence.

Nonstimulant Medications

The only nonstimulant medication approved for adult ADHD is atomoxetine. Atomoxetine is a blocker of norepinephrine transporters that enhances noradrenergic signaling in the brain and dopaminergic signaling in the frontal cortex, since in this brain region, norepinephrine trans-

Table 3. Pharmacotherapeutic Agents for the Treatment of ADHD in Adults.*

Drug and Formulation	Trade Name	Dose	Common Adverse Effects
Stimulant medications			
Immediate-release			
Methylphenidate	Ritalin, Methylin, Metadate	10–60 mg/day in divided doses	Nervousness, insomnia, hypersensitivity, anorexia, nausea, dizziness, headache, dyskinesia, drowsiness, blood-pressure and pulse changes, tachycardia, weight loss, abdominal pain, decreased appetite
Dexmethylphenidate	Focalin IR†	Initial dose, 5 mg/day (2.5 mg twice daily); can be increased weekly in increments of 2.5 to 5 mg/day to a maximum of 20 mg/day	Abdominal pain, fever, anorexia, nausea, nervousness, insomnia
Amphetamine	Adderall	Initial dose, 10 mg/day; can be increased by 10 mg/day every week; usual dose, 5–60 mg/day	Dry mouth, loss of appetite, insomnia, headache, weight loss, nausea, anxiety, agitation, dizziness, tachycardia, diarrhea, asthenia, urinary tract infections
Dextroamphetamine	Dexedrine, Dextrostat	Initial dose, 10 mg/day; can be increased by 10 mg/day at weekly intervals until best response is obtained; usual dose, 5–60 mg/day in divided doses	Blood-pressure elevation, tachycardia, palpitations, dizziness, insomnia, tremor, diarrhea, constipation, dry mouth, urticaria, impotence, changes in libido, euphoria, dyskinesia, headache
Sustained-release			
Methylphenidate	Concerta, Metadate CD, Metadate ER, Metadate ER, Ritalin LA	Concerta: 18–72 mg/day; Metadate CD, Metadate ER, and Ritalin LA: 10–60 mg per day	Decreased appetite, headache, dry mouth, nausea, insomnia, anxiety, dizziness, decreased weight, irritability, upper abdominal pain, hyperhidrosis, palpitations, tachycardia, depressed mood, nervousness
Dexmethylphenidate	Focalin XR	Initial dose, 10 mg; can be increased weekly in 10-mg increments to a maximum of 40 mg/day	Dyspepsia, headache, anxiety, insomnia, anorexia, dry mouth, pharyngolaryngeal pain, jittery feeling, dizziness, decreased appetite, vomiting
Amphetamine	Adderall XR	Typically, 20 mg every morning; for persons switching from immediate-release amphetamine, the total daily dose should be the same; the dose can be adjusted at weekly intervals as indicated	Dry mouth, loss of appetite, insomnia, headache, abdominal pain, weight loss, agitation, anxiety, nausea, vomiting, dizziness, tachycardia, nervousness, asthenia, diarrhea
Dextroamphetamine	Dexedrine Spansule	5–60 mg/day in divided doses	Blood-pressure elevation, tachycardia, palpitations, dizziness, insomnia, tremor, diarrhea, constipation, dry mouth, urticaria, impotence, changes in libido, euphoria, dyskinesia, headache

Lisdexamfetamine dimesylate	Vyvanse [‡]	Initial dose, 30 mg; can be increased in increments of 10 or 20 mg/day at weekly intervals to a maximum of 70 mg/day	Appetite decreased, insomnia, upper abdominal pain, irritability, nausea, vomiting, weight decreased, dry mouth, dizziness, affect lability, rash, diarrhea, anxiety, anorexia, jittery feeling
Nonstimulant medications			
Atomoxetine (selective norepinephrine-reuptake inhibitor)	Strattera	Initial dose, 40 mg/day; can be increased to maximum of 100 mg/day	Abdominal pain, nausea, vomiting, fatigue, decreased appetite, somnolence, increased heart rate, headache, dry mouth, insomnia, constipation, hot flushes, urinary hesitancy and retention, erectile dysfunction

* Typical doses in published studies of medications to treat ADHD in adults are shown. Data are from Wilens et al.²⁸

[‡] This agent contains only the D-isomer, unlike Ritalin, which contains both the D- and L-isomers.

[‡] This prodrug of dextroamphetamine lasts longer and may be less addictive when misused than other stimulants.

porters also remove dopamine. Two randomized phase 3 clinical trials involving a total of 536 patients followed for 10 weeks⁴⁰ showed the efficacy of atomoxetine in adults with ADHD. Atomoxetine has a lower potential for abuse than stimulants and may be preferred in patients with ADHD and substance-use disorders and those who have tics, anxiety, or psychosis.²⁸ However, atomoxetine appears to be less effective than stimulant drugs in reducing ADHD symptoms (on the basis of comparisons of effect sizes separately reported for each medication), and 1 to 2 weeks of treatment are required for full benefits to emerge. There is no evidence that atomoxetine has a better safety profile than stimulant medications, and it should be used cautiously in patients with cardiovascular disease (including hypertension) or cerebrovascular disease.

Other nonstimulant medications are used on an off-label basis in adults with ADHD; examples include modafinil, guanfacine, venlafaxine, bupropion, and desipramine. However, the evidence base for these medications is limited to a few randomized trials of short duration and small overall samples.⁴¹ Modafinil (approved by the FDA for the management of excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift-work sleep disorder in adults) has been suggested as an option for patients with ADHD who do not benefit from stimulants or atomoxetine or in whom these agents have unacceptable side effects.³⁴ This suggestion is based on short-term randomized trials showing a benefit of modafinil in reducing ADHD symptoms in patients, mostly in children and adolescents. However, patients should be informed of the small risk of the Stevens-Johnson syndrome; five cases of severe cutaneous reactions were reported in postmarketing follow-up of 673,000 adults treated with modafinil.⁴²

Nonpharmacologic Treatments

Psychotherapeutic interventions are recommended for adults with ADHD.^{43,44} The most empirical evidence of efficacy involves cognitive behavioral therapy. Randomized trials have shown that training in behavioral and cognitive strategies to manage impairments from ADHD (i.e., training in time management, prioritization, organization, problem solving, motivation, and emotional regulation) results in reduced symptoms and improved functioning, regardless of whether patients are receiving medications for ADHD. These

interventions are usually used as adjuncts to pharmacologic therapy.⁴⁵

AREAS OF UNCERTAINTY

The long-term benefits versus harms of stimulant treatments and nonstimulant treatments in adults with ADHD have not been investigated adequately. Overall results of six open-label trials of 6 to 24 months' duration suggest that the clinical response is sustained, but data from controlled follow-up studies of medication benefits and adverse effects with longer, consistent use have not been reported.^{34,46}

Clinical trials of medications for ADHD have been largely short-term and have predominantly involved young and middle-aged adults. Data are lacking on long-term benefits and risks and on risks among elderly patients. Nonmedical use of prescription stimulants is increasing, including use that is intended to enhance performance in persons without ADHD.³⁹ The consequences of these patterns of misuse are poorly understood.

The genetic and pathophysiological features of ADHD in adults remain incompletely understood. This incomplete knowledge contributes in part to the persistent controversy over the assignment of a pathologic label to behaviors that some view as variants on a spectrum of normal functioning.

The DSM-5 definition of ADHD highlights the attention deficit, but the clinical manifestations include deficits in reward and motivation.^{21,22,47,48} Adults with ADHD have reduced responses to rewards and are less motivated to engage in and follow through on everyday activities.⁴⁹ Thus, a motivation deficit might contribute to ADHD symptoms and should be considered in treatment.

GUIDELINES

The DSM-5 provides guidelines for the diagnosis of ADHD in adults.¹ Recommendations for the diagnosis and management of ADHD have been published by the Centers for Disease Control and Prevention (www.cdc.gov/ncbddd/adhd/treatment.html).

The National Institute for Health and Care Excellence⁵⁰ and the European Network Adult ADHD⁵¹ have provided guidelines for nonphar-

macologic and pharmacologic treatments for ADHD in adults. The recommendations in this article are consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The woman described in the vignette has symptoms of inattention and distractibility that suggest ADHD. Medical assessment and psychiatric evaluation are required to make the diagnosis and to rule out coexisting conditions that could account for her presentation or that might complicate or contraindicate treatment. Given the limitations associated with self-reported symptoms, corroboration of the nature of the symptoms by a friend or family member and an onset of symptoms dating back at least to 12 years of age are helpful in establishing the diagnosis.

Once the diagnosis is confirmed, we would discuss treatment options: pharmacotherapy to ameliorate her symptoms and cognitive behavioral therapy to help her develop skills to compensate for the deficits. She should be informed about the paucity of long-term data regarding the use of stimulant medications in adults and about the risks, including increases in the pulse rate and blood pressure, as well as the possibility, though unlikely, of abuse. If the patient had no contraindication to stimulant medication (e.g., cardiovascular disease, seizures, or psychosis), we would prescribe a stimulant (either controlled-release methylphenidate or amphetamine), and we would adjust the dose in the ensuing weeks as needed for efficacy and on the basis of any adverse effects. The patient should be followed regularly for any adverse events that would warrant discontinuation of the drug.

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REFERENCES

1. DSM-5 development. Arlington, VA: American Psychiatric Association, 2012 (<http://www.dsm5.org>).
2. Wender PH. Attention-deficit hyperactivity disorder in adults. *Psychiatr Clin North Am* 1998;21:761-74.
3. Spencer T, Biederman J, Wilens TE, Faraone SV. Adults with attention-deficit/hyperactivity disorder: a controversial diagnosis. *J Clin Psychiatry* 1998;59:Suppl 7:59-68.
4. Hechtman L. Predictors of long-term outcome in children with attention-deficit/hyperactivity disorder. *Pediatr Clin North Am* 1999;46:1039-52.
5. Hinshaw SP, Owens EB, Zalecki C, et al. Prospective follow-up of girls with attention-deficit/hyperactivity disorder into early adulthood: continuing impairment includes elevated risk for suicide attempts and self-injury. *J Consult Clin Psychol* 2012;80:1041-51.
6. Klein RG, Mannuzza S, Olazagasti MA, et al. Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. *Arch Gen Psychiatry* 2012;69:1295-303.
7. 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;111:279-89.
8. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychol Med* 2006;36:159-65.
9. Barkley R, Murphy K, Fischer M. ADHD in adults: what the science says. New York: Guilford Press, 2008.
10. Weiss G, Hechtman L. Hyperactive children grown up: ADHD in children, adolescents, and adults. New York: Guilford Press, 1993.
11. 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;163:716-23.
12. Biederman J, Fried R, Petty CR, et al. Cognitive development in adults with attention-deficit/hyperactivity disorder: a controlled study in medication-naïve adults across the adult life cycle. *J Clin Psychiatry* 2011;72:11-6.
13. Kuntsi J, Neale BM, Chen W, Faraone SV, Asherson P. The IMAGE project: methodological issues for the molecular genetic analysis of ADHD. *Behav Brain Funct* 2006;2:27.
14. Neale BM, Medland SE, Ripke S, et al. Meta-analysis of genome-wide association studies of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2010;49:884-97.
15. Zuk O, Hechter E, Sunyaev SR, Lander ES. The mystery of missing heritability: genetic interactions create phantom heritability. *Proc Natl Acad Sci U S A* 2012;109:1193-8.
16. Froehlich TE, Lanphear BP, Auinger P, et al. Association of tobacco and lead exposures with attention-deficit/hyperactivity disorder. *Pediatrics* 2009;124(6):e1054-e1063.
17. Campbell BC, Eisenberg D. Obesity, attention deficit-hyperactivity disorder and the dopaminergic reward system. *Coll Antropol* 2007;31:33-8.
18. Buss C, Entringer S, Davis EP, et al. Impaired executive function mediates the association between maternal pre-pregnancy body mass index and child ADHD symptoms. *PLoS One* 2012;7(6):e37758.
19. Rodriguez A, Miettunen J, Henriksen TB, et al. Maternal adiposity prior to pregnancy is associated with ADHD symptoms in offspring: evidence from three prospective pregnancy cohorts. *Int J Obes (Lond)* 2008;32:550-7.
20. Cortese S, Kelly C, Chabernaud C, et al. Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. *Am J Psychiatry* 2012;169:1038-55.
21. Volkow ND, Wang GJ, Kollins SH, et al. Evaluating dopamine reward pathway in ADHD: clinical implications. *JAMA* 2009;302:1084-9 [Erratum, *JAMA* 2009;302:1420.]
22. Sonuga-Barke EJ. The dual pathway model of AD/HD: an elaboration of neurodevelopmental characteristics. *Neurosci Biobehav Rev* 2003;27:593-604.
23. Arnsten AF, Rubia K. Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: disruptions in neurodevelopmental psychiatric disorders. *J Am Acad Child Adolesc Psychiatry* 2012;51:356-67.
24. Sibley MH, Pelham WE Jr, Molina BS, et al. Diagnosing ADHD in adolescence. *J Consult Clin Psychol* 2012;80:139-50.
25. McGough JJ, Smalley SL, McCracken JT, et al. Psychiatric comorbidity in adult attention deficit hyperactivity disorder: findings from multiplex families. *Am J Psychiatry* 2005;162:1621-7.
26. Kolar D, Keller A, Golfopoulos M, Cumyn L, Syer C, Hechtman L. Treatment of adults with attention-deficit/hyperactivity disorder. *Neuropsychiatr Dis Treat* 2008;4:107-21.
27. Teter CJ, McCabe SE, LaGrange K, Cranford JA, Boyd CJ. Illicit use of specific prescription stimulants among college students: prevalence, motives, and routes of administration. *Pharmacotherapy* 2006;26:1501-10.
28. Wilens TE, Morrison NR, Prince J. An update on the pharmacotherapy of attention-deficit/hyperactivity disorder in adults. *Expert Rev Neurother* 2011;11:1443-65.
29. Shaw M, Hodgkins P, Caci H, et al. A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder: effects of treatment and non-treatment. *BMC Med* 2012;10:99.
30. Lensing MB, Zeiner P, Sandvik L, Opjordsmoen S. Four-year outcome in psychopharmacologically treated adults with attention-deficit/hyperactivity disorder: a questionnaire survey. *J Clin Psychiatry* 2013;74(1):e87-e93.
31. Lichtenstein P, Halldner L, Zetterqvist J, et al. Medication for attention deficit-hyperactivity disorder and criminality. *N Engl J Med* 2012;367:2006-14.
32. Fredriksen M, Halmøy A, Faraone SV, Haavik J. Long-term efficacy and safety of treatment with stimulants and atomoxetine in adult ADHD: a review of controlled and naturalistic studies. *Eur Neuropsychopharmacol* 2013;23:508-27.
33. Swanson JM, Volkow ND. Psychopharmacology: concepts and opinions about the use of stimulant medications. *J Child Psychol Psychiatry* 2009;50:180-93.
34. Moriyama TS, Polanczyk GV, Terzi FS, Faria KM, Rohde LA. Psychopharmacology and psychotherapy for the treatment of adults with ADHD — a systematic review of available meta-analyses. *CNS Spectr* 2013 June 6 (Epub ahead of print).
35. Habel LA, Cooper WO, Sox CM, et al. ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. *JAMA* 2011;306:2673-83.
36. Mick E, McManus DD, Goldberg RJ. Meta-analysis of increased heart rate and blood pressure associated with CNS stimulant treatment of ADHD in adults. *Eur Neuropsychopharmacol* 2013;23:534-41.
37. FDA drug safety communication: safety review update of medications used to treat attention-deficit/hyperactivity disorder (ADHD) in children and young adults. November 1, 2011 (<http://www.fda.gov/drugs/drugsafety/ucm277770.htm>).
38. Volkow ND, Swanson JM. Variables that affect the clinical use and abuse of methylphenidate in the treatment of ADHD. *Am J Psychiatry* 2003;160:1909-18.
39. Smith ME, Farah MJ. Are prescription stimulants "smart pills"? The epidemiology and cognitive neuroscience of prescription stimulant use by normal healthy individuals. *Psychol Bull* 2011;137:717-41.
40. Christman AK, Fermo JD, Markowitz JS. Atomoxetine, a novel treatment for attention-deficit-hyperactivity disorder. *Pharmacotherapy* 2004;24:1020-36.
41. Faraone SV, Glatt SJ. A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. *J Clin Psychiatry* 2010;71:754-63.
42. Modafinil (CEP- 1538) tablets: supplemental NDA 20-717/S-019 ADHD indication

- briefing document for Psychopharmacologic Drugs Advisory Committee Meeting. Frazer, PA: Cephalon, 2006 (<http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4212b1-01-cephalon-background.pdf>).
43. Young S, Amarasinghe JM. Practitioner review: non-pharmacological treatments for ADHD: a lifespan approach. *J Child Psychol Psychiatry* 2010;51:116-33.
44. Seixas M, Weiss M, Müller U. Systematic review of national and international guidelines on attention-deficit hyperactivity disorder. *J Psychopharmacol* 2012;26:753-65.
45. Mongia M, Hechtman L. Cognitive behavior therapy for adults with attention-deficit/hyperactivity disorder: a review of recent randomized controlled trials. *Curr Psychiatry Rep* 2012;14:561-7.
46. Goodman DW. Sustained treatment effect in attention-deficit/hyperactivity disorder: focus on long-term placebo-controlled randomized maintenance withdrawal and open-label studies. *Ther Clin Risk Manag* 2013;9:121-30.
47. Volkow ND, Wang GJ, Newcorn JH, et al. Motivation deficit in ADHD is associated with dysfunction of the dopamine reward pathway. *Mol Psychiatry* 2011;16:1147-54.
48. Torrente F, Lischinsky A, Torralva T, López P, Roca M, Manes F. Not always hyperactive? Elevated apathy scores in adolescents and adults with ADHD. *J Atten Disord* 2011;15:545-56.
49. Conzelmann A, Mucha RF, Jacob CP, et al. Abnormal affective responsiveness in attention-deficit/hyperactivity disorder: subtype differences. *Biol Psychiatry* 2009; 65:578-85.
50. National Institute for Health and Clinical Excellence. Attention deficit hyperactivity disorder: the NICE guideline on diagnosis and management of ADHD in children, young people and adults. London: British Psychological Society and Royal College of Psychiatrists, 2009 (<http://www.nice.org.uk/nicemedia/pdf/adhdfullguideline.pdf>).
51. Kooij SJ, Bejerot S, Blackwell A, et al. European consensus statement on diagnosis and treatment of adult ADHD: the European Network Adult ADHD. *BMC Psychiatry* 2010;10:67.

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