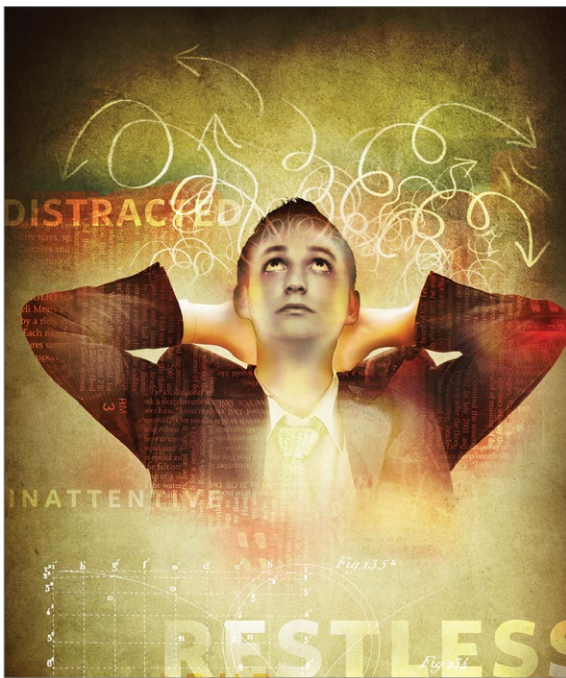


Adult ADHD: Pharmacologic treatment in the DSM-5 era



ALICIA BUELOW FOR CURRENT PSYCHIATRY

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Revised diagnostic criteria reflect greater recognition of disease impact beyond childhood

Attention-deficit/hyperactivity disorder (ADHD) is common; it affects 5% to 7% of children^{1,2} and 4% to 5% of all adults.^{3,4} Pediatric ADHD often persists into adulthood, as 65% of individuals diagnosed as children retain impairing symptoms by age 25.⁴

The prevalence of ADHD in childhood is 2 to 3 times greater among boys than girls, but more comparable between the sexes in adulthood.² Symptoms could be more easily overlooked in women because of the greater prominence of hyperactivity and impulsivity-type symptoms in men.⁵

Untreated ADHD is associated with significant costs. Adults with ADHD have increased unemployment rates, poor work performance, and comparatively lower educational performance.^{6,7} Compared with non-ADHD adults, those with ADHD have:

- more traffic violations and accidents and a higher rate of criminal convictions and incarcerations^{8,9}
- a mortality rate almost 2 times higher, with the greatest differences seen in deaths by suicide and accidents.^{10,11}

Adults with ADHD also are more likely to have a comorbid psychiatric disorder—in particular, substance use¹¹—and often are in treatment for other mental or substance use disorders. Among adults who meet diagnostic criteria for ADHD, approximately only 10% are receiving treatment for ADHD symptoms.^{3,12}

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Changes in DSM-5

Revisions within DSM-5 simplify ADHD's diagnosis—and make it more difficult to ignore in adults (*Table 1*).¹³ For example, DSM-IV¹⁴ required symptoms to be present by age 7, but DSM-5 raises the age to 12. Additionally, fewer ADHD symptoms are now required for the diagnosis in adults. DSM-IV required 6 of 9 symptoms in the areas of inattention or hyperactivity/impulsivity, whereas DSM-5 requires only 5 symptoms in either category.

DSM-5 also provides examples of behaviors more commonly found in adults, such as “feelings of restlessness,” compared with DSM-IV's “often runs about or climbs excessively in situations in which it is inappropriate.” Finally, ADHD now may be diagnosed in a person with an autism spectrum disorder who meets diagnostic criteria for both disorders.^{13,14}

Identifying ADHD in adults

ADHD diagnosis in adults is made through careful clinical interviewing. For example, ask about what factors motivated an individual to seek evaluation for ADHD. Often, patients present after a change in responsibility at work or at home, such as a promotion or birth/adoption of a new child.

Consider incorporating a brief screen for adult ADHD in all new outpatient evaluations (*Table 2, page 21*).¹⁵ Screen for other psychiatric disorders as well; comorbidity with ADHD is high, and hyperactivity and inattention symptoms may result from anxiety, depression, or substance use.

Screen for learning disorders, which can present with ADHD symptoms (such as poor concentration) when the individual attempts difficult tasks. Evaluate for risk factors associated with ADHD medications, such as a history of cardiac problems, hypertension, or tachycardia. A family history of ADHD is found in approximately 80% of cases.^{16,17}

Determine the presence of ADHD symptoms in childhood. A careful review of the educational history often reveals long-

Table 1

DSM-5 criteria for diagnosis of ADHD in adults

≥5 symptoms per category in adults, persisting at least 6 months; present prior to age 12; several symptoms are present in ≥2 settings; symptoms interfere with, or reduce the quality of social, academic, or occupational functioning

Inattention

- Lack of attention to details/careless mistakes
- Difficulty sustaining attention in tasks
- Does not seem to listen when spoken to directly
- Does not follow through on instructions
- Difficulty organizing tasks and activities
- Avoids tasks that require sustained mental effort
- Loses or misplaces objects
- Easily distracted
- Forgetful in daily activities

Hyperactivity and impulsivity

- Fidgetiness (hands or feet)/squirms in seat
- Leaves seat frequently
- Feeling restless
- Unable to engage in leisure activities quietly
- Always “on the go,” difficulty being still for extended time
- Talks excessively
- Blurts out answers
- Difficulty waiting his or her turn
- Interrupts or intrudes on others

ADHD: attention-deficit/hyperactivity disorder

Source: Reference 13

term underachievement and struggles in school. Patients may report a chronic history of poor attention or feelings of restlessness in school. Sometimes problems do not become apparent until high school or college; some individuals, especially those with high intelligence, compensate for deficits and show fewer overt symptoms of impairment until later in their education.¹⁸

Occupational history also may be revealing:

- How are they performing at work?
- Have they changed jobs multiple times in a short period?
- Do they have difficulty organizing tasks?

Clinical Point

Revisions within DSM-5 simplify ADHD's diagnosis—and make it more difficult to ignore in adults



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Adult ADHD

Clinical Point

Stimulants are associated with the highest treatment response rates in adult ADHD

Subtle ADHD signs include time of arrival to appointments (eg, late or extremely early), missing data on intake paperwork, and a history of losing keys or phones.

Neuropsychological testing. Some clinicians routinely include neuropsychological testing in an adult ADHD evaluation, but these studies have shown inconsistent cognitive deficits in people with ADHD.^{19,20} No distinct psychometric cognitive test or profile is diagnostic of ADHD or its subtypes.²¹

Treatment and follow-up care

Four general categories of medications are used to treat ADHD in children and adults: stimulant, noradrenergic, α_2 adrenergic agonist, and antidepressants (*Table 3, page 22*). Stimulants are associated with the highest treatment response rates in adult ADHD. Amphetamine and methylphenidate products are associated with a response rate >80%, with a large effect size of 0.99 for short-acting agents and 0.95 for long-acting agents.²² Other medications are useful options for patients intolerant to stimulants' side effects.

After starting a patient on medication, at each follow-up appointment ask about new cardiac symptoms or diagnoses, new family history of cardiac problems, or new medications. Measure pulse and blood pressure every 1 to 3 months. Measure vital signs more frequently during titration and weaning periods.²³

Stimulant medications

Amphetamines have dual action: they block the reuptake of dopamine and noradrenaline by competitive inhibition of the transporters and promote the release of dopamine and noradrenaline by competitive inhibition of the intraneuronal vesicular monoamine transporter.²⁴

For most amphetamine products, including dextroamphetamine and amphetamine mixed salts, the target dosage is approximately 0.5 mg/kg. Start at a lower dosage, however, and rapidly titrate weekly so

patients can adjust to the medication while not becoming frustrated with a lack of efficacy. Some patients may require short-acting forms with dosing 3 times per day, and twice daily dosing is not uncommon with extended-release (ER) formulations.

Metabolism of most amphetamine products—with the exception of lisdexamfetamine—involves the cytochrome P450 (CYP) enzyme CYP2D6, leading to the formation of the metabolite 4-hydroxyamphetamine.²⁵ The pharmacokinetics of lisdexamfetamine in slow or ultra-rapid CYP2D6 metabolizers has not been evaluated (Shire US Inc., written communication, July 2014).

Agents that alter urinary pH can affect blood levels of amphetamine. Acidifying agents decrease amphetamine blood levels, while alkalinizing agents increase amphetamine blood levels.²⁶

Lisdexamfetamine contains L-lysine, an essential amino acid, covalently bound to d-amphetamine via an amide linking group.²⁷ After absorption, lisdexamfetamine is metabolized by rate-limited, enzymatic hydrolysis to yield d-amphetamine and L-lysine.^{24,28,29} A starting dose of 40 mg is advised; twice-daily dosing rarely is required.

A meta-analysis of 5 randomized, controlled trials in the treatment of adult ADHD showed a response rate of 70% for lisdexamfetamine compared with 37% for placebo. Trial duration ranged from 4 to 14 weeks, with dosages of 30 to 70 mg/d.³⁰ Another analysis of data from lisdexamfetamine trials predicted an effect size of 1.07 for European adults, which is larger than the 0.8 threshold for large effect sizes.³¹

Methylphenidate products. Methylphenidate's main action is through enhancement of dopamine signaling by blockade of the dopamine transporter, leading to increases in extracellular dopamine as well as norepinephrine.^{22,32} Optimized dosing is generally 1 mg/kg per day, and dosing up to 80 to 120 mg/d is not unusual.³³

Dexmethylphenidate is the more pharmacologically active enantiomer of racemic

methylphenidate and is twice as potent.³⁴⁻³⁶ Target dosing of dexamethylphenidate should be one-half as much (ie, 0.5 mg/kg per day) as other methylphenidate products.³⁷

Managing stimulants' side effects

Amphetamines' side effects may include insomnia, dry mouth, decreased appetite, weight loss, headaches, and anxiety. To help minimize sleep problems, advise patients to take a second immediate-release dose at noon, rather than later in the afternoon. The longer-acting formulation taken once per day in the morning may be offered as an alternative. Some patients may experience improved sleep because of diminished bedtime ruminations.

Oral rinses, such as Biotène, could help reduce discomfort associated with dry mouth. Pilocarpine, which stimulates saliva production, is another option if rinses are not effective. To address decreased appetite, advise patients to take their medication after they eat. Switching from an immediate-release amphetamine to a longer-acting formulation also may lessen symptoms. Lisdexamfetamine might be a good choice for adults with ADHD who have undergone bariatric surgeries because it is absorbed in the small bowel.³⁸

Methylphenidate has no interactions with CYP enzymes, making it an attractive option for patients taking CYP inhibiting or stimulating medications.³⁹ The most common side effects of methylphenidate products include appetite loss, insomnia, irritability, and tachycardia. Some side effects will abate after 1 to 2 weeks of treatment, but persistence of insomnia and appetite loss may require a decrease in dosage. In rare cases, methylphenidate may produce tics, exacerbate an existing tic disorder, or produce mania or psychosis.^{40,41} Methylphenidate inhibits the metabolism of tricyclic antidepressants; use methylphenidate with caution in patients taking monoamine oxidase inhibitors.^{42,43}

Cardiovascular risks. Possible cardiovascular risks associated with stimulant use have gained widespread attention, although research has not demonstrated an increased

Table 2

Ultra-short screening list for ADHD in adults

1. Do you usually feel restless? (for example: nervous, difficulty sitting still, fidgeting, a lot of exercising or being active) Yes/no

2. Do you usually act first and then think? (for example: blurting things out, spending too much money or being impatient) Yes/no

3. Do you usually have concentration problems? (for example: being easily distracted, not finishing things, being easily bored, forgetful, or chaotic) Yes/no

If the answer to questions 1 and/or 2 and/or 3 is yes:

4. Have you always had this? (as long as you can remember, or have you been like this most of your life) Yes/no

If the answer to question 4 is yes, consider further diagnostic assessment for ADHD

ADHD: attention-deficit/hyperactivity disorder

Source: Reprinted with permission from reference 15

risk of serious cardiovascular events in young and middle-aged adults receiving stimulant medications for ADHD.⁴⁴ Nonetheless, obtain a thorough medical history in adult patients, including cardiac history, family history of cardiac disease, history of any cardiac symptoms, and a medication history. Baseline ECG is not required.⁴⁵

Screen for a family history of sudden death in a young person, sudden death during exercise, cardiac arrhythmia, cardiomyopathies (including hypertrophic cardiomyopathy, dilated cardiomyopathy, and right ventricular cardiomyopathy), prolonged QT interval, short QT syndrome, Brugada syndrome, Wolff-Parkinson-White syndrome, Marfan syndrome, and an event requiring resuscitation in a family member younger than 35, including syncope requiring resuscitation.²³ If fainting spells, palpitations, chest pain, or other symptoms suggest preexisting cardiovascular disease, refer the patient promptly to a cardiologist.

Peripheral vasculopathy, including Raynaud's phenomenon, is a lesser known side effect associated with stimulants.⁴⁶ Symptoms are usually mild, but in rare instances stimulants are associated with digital ulceration or soft tissue breakdown.⁴⁷

continued

Clinical Point

Lisdexamfetamine might be a good choice for adults who have undergone bariatric surgeries because it is absorbed in the small bowel



Adult ADHD

Table 3

FDA-approved medications for ADHD in adults

Medication	Brand names
Amphetamine mixed salts	Adderall XR
Atomoxetine	Strattera
Dexmethylphenidate	Focalin XR
Lisdexamfetamine	Vyvanse
Methylphenidate	Aptensio, Concerta, Metadate, Metadate ER, Ritalin

Amphetamine mixed salts IR and dextroamphetamine ER frequently are used off-label to treat adult ADHD
ADHD: attention-deficit/hyperactivity disorder; ER: extended release; IR: immediate release

Clinical Point

No trials have been published regarding the efficacy of extended-release clonidine in adults with ADHD

Advise patients to tell you if they experience any new symptoms of numbness, pain, skin color changes, or sensitivity to temperature in fingers and toes. Signs and symptoms generally improve after dosage reduction or discontinuation of the stimulant medication.⁴⁶ Referral to a rheumatologist might be appropriate if symptoms persist.

A noradrenergic medication

Atomoxetine is a potent, selective inhibitor of the presynaptic noradrenaline transporter that increases the availability of extracellular noradrenaline in the prefrontal cortex.^{48,49} Atomoxetine may be a good alternative for adult patients with ADHD and comorbid anxiety.⁵⁰

For adults, the optimal starting dosage is 40 mg in the morning for 1 week, followed by an increase to 80 mg. Insufficient dosing is common with atomoxetine, and the dosage could be increased to 100 mg/d.⁵¹ Dosing twice per day may be associated with higher rates of insomnia.

Atomoxetine's efficacy for managing ADHD in adults has been consistently demonstrated by 6 placebo-controlled trials of 10 to 16 weeks, 3 placebo-controlled 6-month trials, and a 1-year maintenance-of-response trial.⁵² Atomoxetine was found to have an effect size of 0.45 (medium) (number needed to treat [NNT] = 5).⁵³⁻⁵⁵

The most common adverse effects include nausea, dry mouth, insomnia, and erectile dysfunction. Small increases in

heart rate and blood pressure have been reported, so use this medication with caution in patients for whom this might be problematic. Atomoxetine is metabolized by CYP2D6; 7% of white individuals have a genotype corresponding to a nonfunctional CYP2D6 enzyme.⁵⁶⁻⁵⁸

Alpha-2 adrenergic agonists

Clonidine and guanfacine are antihypertensive drugs that induce peripheral sympathoinhibition via the stimulation of receptors. Clonidine binds equally to adrenergic receptor subtypes α -2A, α -2B, and α -2C (as well as to α -1 and β subtypes, histamine receptors, and possibly dopamine receptors).^{59,60} Guanfacine binds preferentially to postsynaptic α -2A adrenoceptors in the prefrontal cortex, which have been implicated in attentional and organizational functions.^{61,62}

ER guanfacine and ER clonidine are FDA-approved as monotherapy for ADHD in children and adolescents.

Efficacy in adults. A small (N = 17), double-blind, placebo-controlled, crossover study comparing immediate-release guanfacine and dextroamphetamine found that both medications significantly reduced adult ADHD symptoms, as measured with the DSM-IV Adult Behavior Checklist for Adults.⁶³

No trials have been published regarding the efficacy of ER clonidine in adults with ADHD; adverse effects including sedation, bradycardia, and hypotension may limit its use. One study compared the supplemental use of ER guanfacine (1 to 6 mg/d) or a matching placebo in 26 adults with ADHD who had suboptimal response to stimulant-only treatment. After 10 weeks, both the guanfacine ER and placebo groups showed statistically significant improvements in ADHD symptoms and general functioning. The treatments did not differ in efficacy, safety, or tolerability.⁶⁴

Adverse events. Compared with clonidine, guanfacine has less CNS depressant and hypotensive activity.⁵⁸ A phase I trial of ER guanfacine in healthy adults found its sin-

gle-dose pharmacokinetic properties in 1-, 2-, and 4-mg tablets appeared to be statistically linear. Somnolence—the most common treatment-emergent adverse effect—occurred in 33 of 52 participants (63.5%). All mean vital-sign measurements and ECG parameters remained within normal limits after dosing, and no marked changes from baseline measurements were noted.⁶⁵

Antidepressants

Antidepressants used in ADHD treatment include bupropion and tricyclic antidepressants.

Bupropion is a noradrenaline and dopamine reuptake inhibitor and is considered to be a mild psychostimulant because of its amphetamine-derived chemical structure.^{66,67} It generally is considered a third-line medication when stimulants have not improved ADHD symptoms or are not tolerated.

A 2011 meta-analysis examined 5 randomized, controlled trials including 175 adults treated with bupropion for ADHD. Bupropion was found to be more effective than placebo (NNT = 5), although bupropion's therapeutic benefits were not observed until weeks 5 and 6. Its effects were less pronounced than those of methylphenidate. Mean daily dosages were 362 mg for the bupropion SR trials and 393 mg for the bupropion XL trial.⁶⁸

Tricyclics. Desipramine and nortriptyline have been found to be efficacious in childhood ADHD,^{69,70} although cardiovascular risk and toxicity in overdose limit their use.⁷¹

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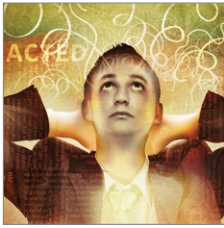
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Clinical Point

Compared with clonidine, guanfacine has less CNS depressant and hypotensive activity



Adult ADHD

Clinical Point

Bupropion generally is considered a third-line medication when stimulants have not improved ADHD symptoms or are not tolerated

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Drug Brand Names

Amphetamine Mixed Salts • Adderall	Guanfacine extended-release • Intuniv
Atomoxetine • Strattera	Guanfacine immediate-release • Tenex
Bupropion • Wellbutrin	Lisdexamfetamine • Vyvanse
Clonidine extended-release • Kapvay	Methylphenidate • Ritalin
Desipramine • Norpramin	Nortriptyline • Pamelor
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Bottom Line

Attention-deficit/hyperactivity disorder (ADHD) in adults impairs work functioning and increases mortality risk but remains underdiagnosed and undertreated. DSM-5 changes to diagnostic criteria reflect growing recognition of ADHD impairments in adulthood. Although stimulants for adult ADHD are associated with the highest treatment response rates, other medications are options for patients intolerant to stimulants' side effects.

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Clinical Point

Desipramine and nortriptyline are efficacious in childhood ADHD, although cardiovascular risk and toxicity in overdose limit their use