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Practical  
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## INATTENTIVE



### Adult ADHD: Identify and treat symptoms beyond childhood

### An irritable, inattentive, and disruptive child: Is it ADHD or bipolar disorder in a child?

**GUEST EDITORIAL:** Jeffrey R. Strawn, MD

### Debunking pharmacotherapy myths in ADHD

**CASES THAT TEST YOUR SKILLS**

### ADHD symptoms are stable, then a sudden relapse

**PEARLS**

### Rule out these causes of inattention before diagnosing ADHD

### No more 'stickies': Help your patients tame their 'to-do' list **WEB EXCLUSIVE**

SHE HAS **DEPRESSION** AND/OR **ANXIETY**,  
BUT HER **ADHD** WASN'T REVEALED UNTIL  
**YOU TOOK A DEEPER LOOK**

Her inattention and impulsivity  
persisted despite treatment,  
so you kept looking.

APPROXIMATELY

**10%**

OF PATIENTS WITH  
CLINICAL DEPRESSION  
AND/OR ANXIETY

**MAY ALSO HAVE ADHD.<sup>1\*</sup>†**

<sup>\*</sup>Based on the National Comorbidity Survey  
Replication of 3,199 adults aged 18 to 44 years,  
conducted from 2001 to 2003.<sup>1</sup>

<sup>†</sup>Diagnosis should be based on a complete history  
and evaluation of the patient. Medication may not  
be appropriate for all patients.

Hypothetical patient portrayal.

Dig a little deeper for your adult patients with symptoms  
of inattention, hyperactivity, and impulsivity.

Download an **ADHD** screener at **UncoverADHD.com**

Reference: I. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry*. 2006;163(4):716-723.

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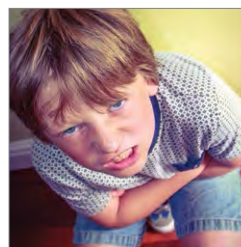
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Ken Braslow, MD



**Jeffrey R. Strawn, MD**  
Child and Adolescent Psychiatry  
Section Editor

# Hunting for ‘Woozles’ in the Hundred Acre Wood of ADHD

**Myths abound in the imagination of some clinicians, just as Winnie-the-Pooh believed that Woozles—imaginary, yet feared honey stealers—exist. Consider the following excerpt from a classic children’s book.**

One fine winter’s day when Piglet was brushing away the snow in front of his house he happened to look up, and there was Winnie-the-Pooh. Pooh was walking round and round in a circle, thinking of something else...

So begins the 1926 *Winnie-the-Pooh* story.<sup>1</sup> In this chapter, the well-meaning yellow bear, Winnie-the-Pooh, has found strange tracks in the snow, which he believes belong to a “Woozle.” Pooh follows the tracks, not realizing that he’s walking in a circle. As such, he begins to notice that the tracks have multiplied, which he interprets as evidence of several Woozles.

This “Woozle Effect” has been well described in research settings and is believed to have resulted in conclusions that are not supported by or are inconsistent with the original data, which are then propagated through successive citations, resulting in a scientific “urban legend.”<sup>2</sup>

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Throughout my training from medical school, through fellowship, and during my tenure as a faculty member, I have found myself, at times, searching for Woozles and often have joined my colleagues on these hunts. Herein, I would like to share with you 3 Woozles that have resulted in current false dogmas related to attention-deficit/hyperactivity disorder (ADHD) and stimulant psychopharmacology.

#### Stimulants worsen anxiety

FDA-required labeling for stimulants includes strong language noting that these drugs are “contraindicated in marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.”<sup>3</sup> However, data from randomized controlled trials and meta-analyses consistently have failed to demonstrate this effect. Moreover, sequenced treatment trials involving adolescents with anxiety disorders and co-occurring ADHD suggest that stimulants actually could reduce anxiety symptoms.

A recent meta-analysis<sup>4</sup> that evaluated nearly 2 dozen studies involving approximately 3,000 pediatric patients with ADHD reported that stimulant treatment was associated with a decreased relative risk of anxiety (relative risk: 0.86). The study also observed a dose-response relationship between stimulant dosage and anxiety (*Figure, page 6*).<sup>4</sup> Although the authors note that it is possible that some individu-

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als might experience increased anxiety with stimulants, many patients could show improvement in anxiety symptoms when treated with stimulants, and the authors also advise us, as clinicians, to “consider re-challenging children with ADHD who report ... anxiety with psychostimulants, as these symptoms are much more likely to be coincidental rather than caused by psychostimulants.”<sup>4</sup>

More evidence of a lack of stimulant-induced anxiety comes from a large randomized controlled trial of pediatric patients (age 6 to 17) who met DSM-IV criteria for ADHD and a co-occurring anxiety disorder who were treated with methylphenidate (open-label) and then randomized to fluvoxamine or placebo for treatment of anxiety symptoms.<sup>5</sup> However, in this trial >80% of the 32 medication-naïve youth improved after stimulant treatment to the point that they no longer had anxiety symptoms severe enough to be eligible for randomization to adjunctive fluvoxamine or placebo.

### Stimulants are contraindicated in patients with tic disorders

The package inserts for most stimulant medications warn clinicians that stimulants are “contraindicated in patients with motor tics or with a family history or diagnosis of Tourette’s syndrome.” This is particularly concerning, especially because of the medicolegal implications of the term “contraindicated” and given that as many as 1 in 5 pediatric patients with ADHD have a tic disorder.<sup>6</sup> Therefore, labels that list motor tics as a contraindication to stimulant use potentially eliminate the choice of stimulant pharmacotherapy—the most effective treatment for ADHD—for a large number of patients.

When hunting for the Woozle that linked stimulants and tics and led to this language in the package insert, it is worthwhile to review a recent meta-

analysis of 22 studies (involving nearly 2,400 youths with ADHD) that suggested new-onset tics or worsening of tics to be present in 5.7% of patients receiving stimulants and in 6.5% of patients receiving placebo. In addition, in this meta-analysis the class of stimulant, dosage, treatment duration, or patient age did not seem to be associated with onset or worsening of tics.<sup>7</sup>

### Polypharmacy represents a therapeutic failure and is not evidence-based

Although treatment guidelines generally have discouraged combination therapy for treating ADHD, there are—on the basis of efficacy—insufficient data to support this prohibition. Moreover, over the last decade, several studies have suggested benefits for combining ADHD medications that have complementary mechanisms. In this regard, 2 extended-release formulations of  $\alpha_2$  agonists have received FDA approval for as adjunctive treatments in pediatric patients with ADHD (extended-release guanfacine and extended-release clonidine). However, despite these FDA indications as adjunctive treatments, many clinicians remain concerned about combination therapy.

Several months ago, a large, 8-week, National Institutes of Health-sponsored trial shed more light on the use of  $\alpha_2$  agonist + stimulant combinations. Patients age 7 to 17 (N = 179) were randomized to (1) guanfacine + d-methylphenidate, (2) guanfacine monotherapy, or (3) d-methylphenidate monotherapy.<sup>8</sup> In addition to clinical outcomes, the authors evaluated the effects of the medication on background cortical activity. Of interest, monotherapies differed between one another and the combination treatment in their effects on cortical activity. Guanfacine decreased alpha band power and methylphenidate administration was associated with an

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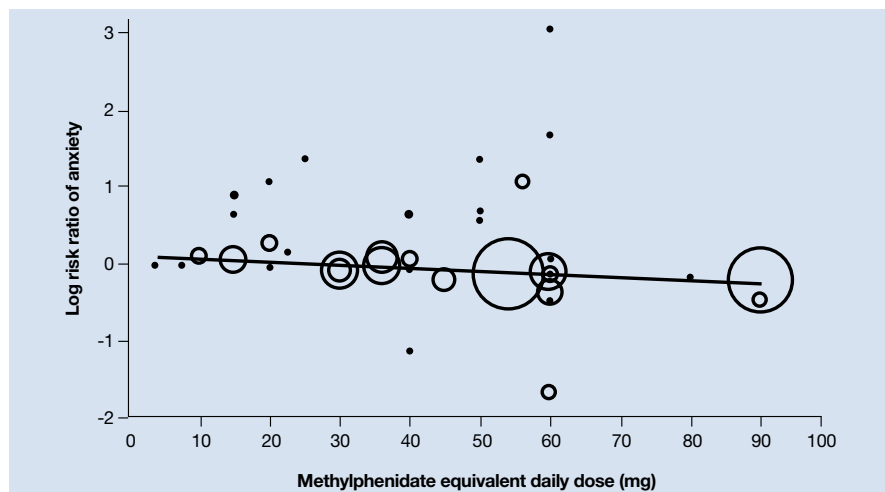
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As we evaluate evidence for our interventions, whether psychopharmacologic or psychotherapeutic, we will do well to relentlessly question the ‘evidence’ for our choices

Figure

### Is stimulant use associated with anxiety symptoms?



A recent meta-regression of stimulant dosage and risk of anxiety symptoms reveals that higher doses were associated with a slight decrease in the risk of anxiety (vs placebo,  $z = -2.34, P < .02$ ).

Source: Reprinted with permission from reference 4

increase in frontal/central beta power, while combination treatment dampened theta band power and was associated with specific, focal increases in beta power.<sup>8</sup> These results, although preliminary, suggest not only that medication results in changes in cortical activity that correlate with symptomatic improvement, but that combination treatment may be associated with a distinct cortical activity pattern that is more than the summation of the effects of the monotherapies. Moreover, these data raise the possibility that this synergistic effect on cortical activity may subtend—or at least—relate to the synergistic clinical effects of the 2 medications.

#### ‘Think it over, think it under’

Having discussed several important Woozles that have inhabited the Hundred Acre Wood of ADHD for decades, it is important to remember there are countless Woozles in the larger “Thousand Acre Wood” of psychiatry and medicine. As we evaluate evidence for our interventions, whether psycho-

pharmacologic or psychotherapeutic, we will do well to relentlessly question the “evidence” for our choices and in doing so strive to be like wise Christopher Robin rather than Winnie-the-Pooh.

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# An irritable, inattentive, and disruptive child: Is it ADHD or bipolar disorder?

## Clinical characteristics, rating scales, nomograms help guide diagnosis

**D**ifferentiating the irritable, oppositional child with attention-deficit/hyperactivity disorder (ADHD) from the child with bipolar disorder (BD) often is difficult. To make matters more complicated, 50% to 70% of patients with BD have comorbid ADHD.<sup>1,2</sup> Accordingly, clinicians often are faced with the moody, irritable, disruptive child whose parents want to know if he (she) is “bipolar” to try to deal with oppositional and mood behaviors.

In this article, we present an approach that will help you distinguish these 2 disorders from each other.

### Precision medicine

There is a lack of evidence-based methods for diagnosing psychiatric disorders in children and adolescents. DSM-5 provides clinicians with diagnostic checklists that rely on the clinician’s judgment and training in evaluating a patient.<sup>3</sup> In *The innovator’s prescription: a disruptive solution for health care*, Christensen et al<sup>4</sup> describe how medicine is moving from “intuitive medicine” to empirical medicine and toward “precision medicine.” Intuitive medicine depends on the clinician’s expertise, training, and exposure to different disorders, which is the traditional clinical model that predominates in child psychiatry. Empirical medicine relies on laboratory results, scans, scales, and other standardized tools.

Precision medicine occurs when a disorder can be precisely diagnosed and its cause understood, and when it can be treated with effective, evidence-based therapies. An



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## Bipolar disorder vs ADHD

### Clinical Point

Children with BD typically manifest with a ‘mood cycle’—a shift in mood and energy from one extreme to another



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example of this movement toward precision is Timothy syndrome (TS), a rare autosomal dominant disorder characterized by physical malformations, cardiac arrhythmias and structural heart defects, webbing of fingers and toes, and autism spectrum disorder. In the past, a child with TS would have been given a diagnosis of intellectual disability, or a specialist in developmental disorders might recognize the pattern of TS. It is now known that TS is caused by mutations in *CACNA1C*, the gene encoding the calcium channel  $\text{Ca}_v1.2$  subunit, allowing precise diagnosis by genotyping.<sup>5</sup>

Although there are several tools that help clinicians assess symptoms of ADHD and BD, including rating scales such as the Vanderbilt ADHD Diagnostic Rating Scale and Young Mania Rating Scale, none of these scales are diagnostic. Youngstrom et al<sup>6,7</sup> have developed an evidence-based strategy to diagnose pediatric BD. This method uses a nomogram that takes into account the base rate of BD in a clinical setting and family history of BD.

We will describe and contrast the epidemiologic and clinical characteristics of pediatric BD from ADHD and use the Youngstrom nomogram to better define these patients. Although still far from precision medicine, the type of approach represents an ongoing effort in mental health care to increase diagnostic accuracy and improve treatment outcomes.

### Pediatric bipolar disorder

**Prevalence** of pediatric BD is 1.8% (95% CI, 1.1% to 3.0%),<sup>8</sup> which does not include sub-threshold cases of BD. ADHD and oppositional defiant disorder (ODD) are 8 to 10 times more prevalent. For the purposes of the nomogram, the “base rate” is the rate at which a disorder occurs in different clinical settings. In general outpatient clinics, BD might occur 6% to 8% of the time, whereas in a county-run child psychiatry inpatient facility the rate is 11%.<sup>5</sup> A reasonable rate in an outpatient pediatric setting is 6%.

**Family history.** In the Bipolar Offspring Study,<sup>9</sup> the rate of BD in children of parents with BD was 13 times greater than that of

controls, and the rate of anxiety and behavior disorders was approximately twice that of children of parents without BD (*Table 1*).<sup>9</sup> This study evaluated 388 children of 233 parents with BD and 251 children of 143 demographically matched controls.

**Clinical characteristics.** Children and adolescents with BD typically manifest with what can be described as a “mood cycle”—a pronounced shift in mood and energy from one extreme to another. An example would be a child who wakes up with extreme silliness, high energy, and intrusive behavior that persists for several hours, then later becomes sad, depressed, and suicidal with no precipitant for either mood cycle.<sup>10</sup> Pediatric patients with BD also exhibit other symptoms of mania during mood cycling periods.

**Elevated or expansive mood.** The child might have a mood that is inappropriately giddy, silly, elated, or euphoric. Often this mood will be present without reason and last for several hours. It may be distinguished from a transient cheerful mood by the intensity and duration of the episode. The child with BD may have little to no insight about the inappropriate nature of their elevated mood, when present.

**Irritable mood.** The child might become markedly belligerent or irritated with intense outbursts of anger, 2 to 3 times a day for several hours. An adolescent might appear extremely oppositional, belligerent, or hostile with parents and others.

**Grandiosity or inflated self-esteem** can be confused with brief childhood fantasies of increased capability. Typically, true grandiosity can manifest as assertion of great competency in all areas of life, which usually cannot be altered by contrary external evidence. Occasionally, this is bizarre and includes delusions of “super powers.” The child in a manic episode will not only assert that she can fly, but will jump off the garage roof to prove it.

**Decreased need for sleep.** The child may only require 4 to 5 hours of sleep a night

**Table 1**

## A child's risk of bipolar disorder and other axis I disorders based on parents' bipolar disorder status

Lifetime axis I disorder	Child's lifetime risk when $\geq 1$ parents have a bipolar disorder	Child's lifetime risk with neither parent has a bipolar disorder (controls)
Any DSM-IV diagnosis	52%	29%
Bipolar I disorder	2.1%	0.0
Bipolar II disorder	1.3%	0.4%
Bipolar disorder, not otherwise specified	7.2%	0.4%
Major depressive disorder	9.1%	3.2%
Any anxiety disorder	26%	11%
Oppositional defiant disorder	17%	6%
Conduct disorder	3.6%	2.4%
Attention-deficit/hyperactivity disorder	24%	17%

**Source:** Reference 9

during a manic episode without feeling fatigued or showing evidence of tiredness. Consider substance use in this differential diagnosis, especially in adolescents.

**Increased talkativeness.** Lack of inhibition to social norms may lead pediatric BD patients to blurt out answers during class or repeatedly be disciplined for talking to peers in class. Speech typically is rapid and pressured to the point where it might be continuous and seems to jump between loosely related subjects.

**Flight of ideas or racing thoughts.** The child or adolescent might report a subjective feeling that his thoughts are moving so rapidly that his speech cannot keep up. Often this is differentiated from rapid speech by the degree of rapidity the patient expresses loosely related topics that might seem completely unrelated to the listener.

**Distractibility, short attention span.** During a manic episode, the child or adolescent might report that it is impossible to pay attention to class or other outside events because of rapidly changing focus of their thoughts. This symptom must be carefully distinguished from the distractibility and inattention of ADHD, which typically is a more fixed and long-standing pattern

rather than a brief episodic phenomenon in a manic or hypomanic episode.

**Increase in goal-directed activity.** During a mild manic episode, the child or adolescent may be capable of accomplishing a great deal of work. However, episodes that are more severe manifest as an individual starting numerous ambitious projects that she later is unable to complete.

**Excessive risk-taking activities.** The child or adolescent might become involved in forbidden, pleasurable activities that have a high risk of adverse consequences. This can manifest as hypersexual behavior, frequent fighting, increased recklessness, use of drugs and alcohol, shopping sprees, and reckless driving.

There are few studies comparing patients with comorbid BD and ADHD with patients with only ADHD. Geller et al<sup>11</sup> compared 60 children with BD and ADHD (mean age, 10) to age- and sex-matched patients with ADHD and no mood disorder. Compared with children who had ADHD, those with BD exhibited significantly greater elevated mood, grandiosity, flight and/or racing of ideas, decreased need for sleep, and hypersexuality (*Figure 1, page 10*).<sup>11</sup> Features common to both groups—and therefore not useful

### Clinical Point

**Lack of inhibition to social norms may lead pediatric BD patients to blurt out answers during class or be disciplined for talking to peers in class**

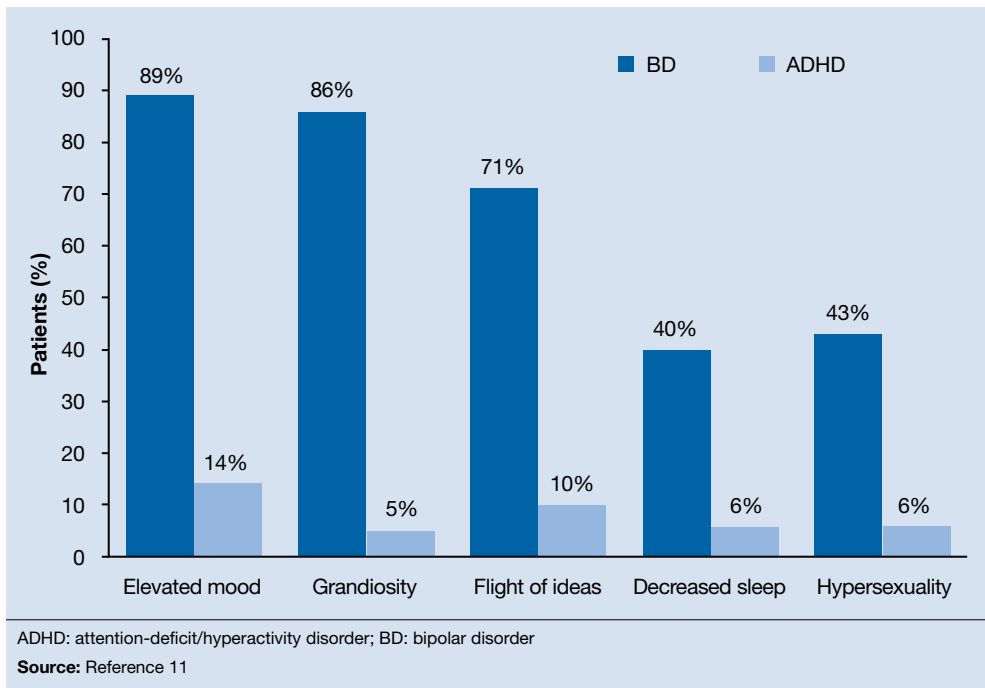


## Bipolar disorder vs ADHD

### Clinical Point

Irritability, hyperactivity, accelerated speech, and distractibility are not useful in differentiating ADHD and BD

**Figure 1**  
How symptoms and signs of BD and ADHD compare



in differentiating the disorders—including irritability, hyperactivity, accelerated speech, and distractibility.

### CASE REPORT

#### Irritable and disruptive

Bill, age 12, has been brought to see you by his mother because she is concerned about escalating behavior problems at home and school in the past several months. The school principal has called her about his obnoxious behavior with teachers and about other parents' complaints that he has made unwanted sexual advances to girls who sit next to him in class.

Bill, who is in the 7th grade, is on the verge of being suspended for his inappropriate and disruptive behavior. His parents report that he is irritable around them and stays up all night, messaging his friends on the internet from his iPad in his bedroom. They attribute his inappropriate sexual behavior to puberty and possibly to the Web sites he views.

Bill's mother is concerned about his:

- increasing behavior problems during the last several months at home and school

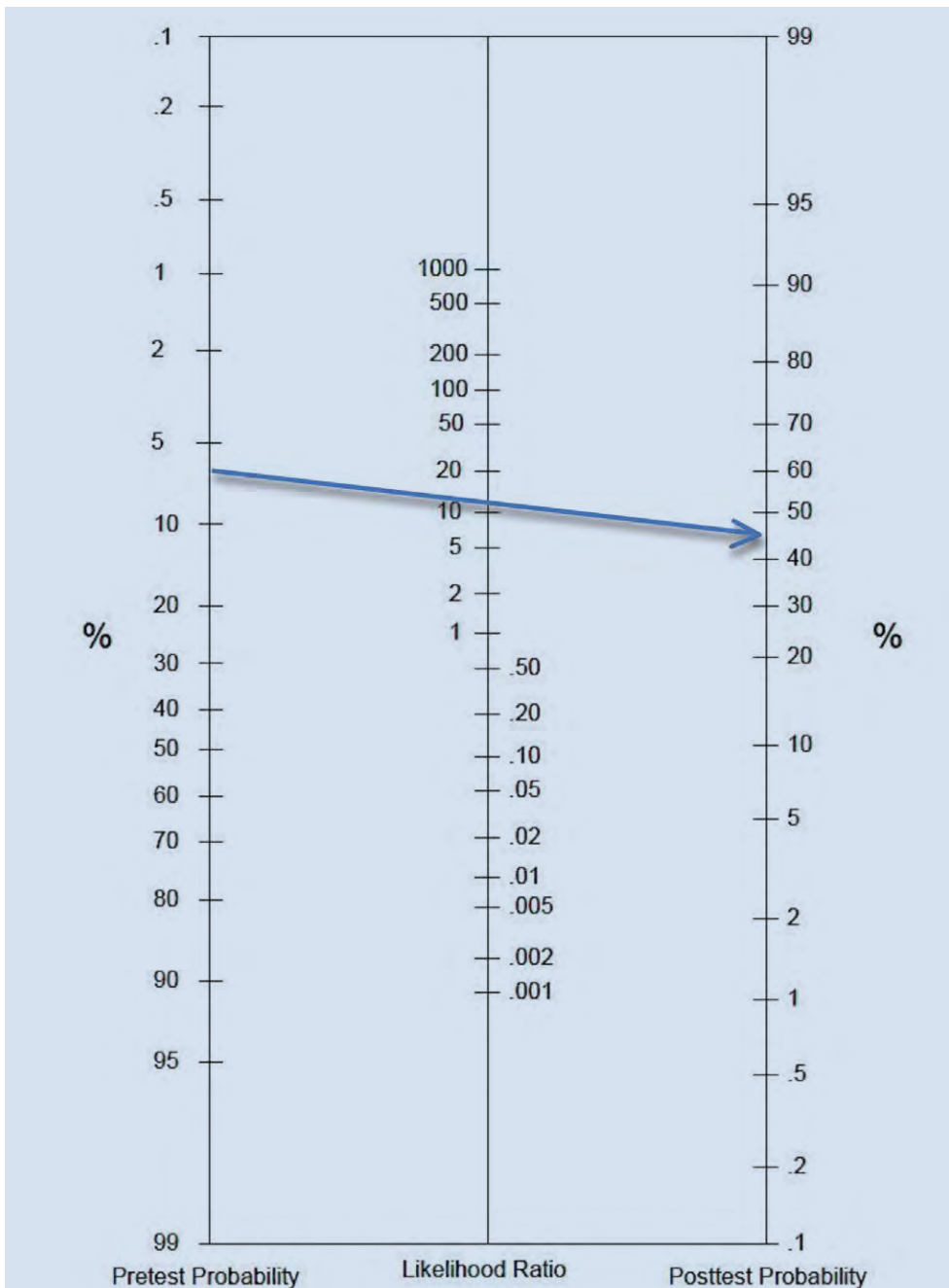
- intensifying irritability and depressive symptoms
- staying up all night on the internet, phoning friends, and doing projects
- frequent unprovoked, outbursts of rage occurring with increasing frequency and intensity (almost daily)
- moderate grandiosity, including telling the soccer coach and teachers how to do their jobs
- inappropriate sexual behavior, including kissing and touching female classmates.

During your history, you learn that Bill has been a bright and artistic child, with good academic performance. His peer relationships have been satisfactory, but not excellent—he tends to be “bossy” with his peers. He is medically healthy and not taking any medications. As part of your history, you also talk with Bill and his family about exposure to trauma or significant stressors, which they deny. You learn that Bill's father was diagnosed with BD I at age 32.

Completing the nomogram developed by Youngstrom et al<sup>6,7</sup> using these variables (**Figure 2**)<sup>6,7</sup> gives Bill a post-test probability of approximately 42%. The threshold for

Figure 2

### A Youngstrom et al nomogram for Bill



Bill's base rate in an outpatient clinic is approximately 6%, and you select a pre-test probability of 6. The middle column is completed using the family history rate; because one of his parents has bipolar disorder, his likelihood ratio based on data from the BIOS study is 13.

Source: References 6,7

#### Clinical Point

Few pediatric patients with BD will score low on externalizing behaviors

moving ahead with assessment and possible treatment, the "test-treatment threshold," depends on your clinical setting.<sup>12,13</sup> Our clinical experience is that, when the post-test probability exceeds 30%, further assessment for BD is warranted.

The next strategy is to look at Bill's scores on externalizing behaviors using an instrument such as the Vanderbilt ADHD Diagnostic Parent Rating Scale. Few pediatric patients with BD will score low on externalizing behaviors.<sup>14</sup> Bill scores in the



## Bipolar disorder vs ADHD

### Clinical Point

Common comorbidities in ADHD include ODD, conduct disorder, anxiety disorders, depression, and learning disability

Table 2

## Diagnostic criteria for attention-deficit/hyperactivity disorder

Inattention	Hyperactivity/impulsivity
Makes careless mistakes	Fidgets or squirms when sitting still is expected
Has trouble sustaining attention	Has trouble staying seated
Has trouble listening when spoken to directly	Runs or climbs excessively
Doesn't follow through with instructions	Has trouble playing quietly
Has trouble organizing activities	Is often on the go
Avoids or dislikes activities that require sustained mental effort	Talks excessively
Loses things	Blurts out answers
Easily distracted	Has trouble waiting his turn
Is forgetful	Interrupts or intrudes on others
Additional factors	
Signs and symptoms must be present before age 12 and present for >6 months	
Signs and symptoms must be present in ≥2 settings	
Signs and symptoms interfere with or reduce the quality of social, academic, or occupational functioning	
Signs and symptoms must not be better accounted for by another mental health or developmental disorder	
Source: Reference 20	

clinically significant range for hyperactivity/impulsivity and positive on the screeners for ODD, conduct disorder (CD), and anxiety/depression.

You decide that Bill is at high risk of pediatric BD; he has a post-test probability of approximately 45%, and many externalizing behaviors on the Vanderbilt. You give Bill a diagnosis of BD I and ADHD and prescribe risperidone, 0.5 mg/d, which results in significant improvement in mood swings and other manic behaviors.

### ADHD

**Epidemiology.** ADHD is one of the most common neurodevelopmental disorders in childhood, with prevalence estimates of 8% of U.S. children.<sup>15,16</sup> Overall, boys are more likely to be assigned a diagnosis of ADHD than girls.<sup>15</sup> Although ADHD often is diagnosed in early childhood, research is working to clarify the lifetime prevalence of ADHD into late adolescence and adulthood. Current estimates suggest that ADHD persists into adulthood in close to two-thirds of patients.<sup>17</sup> However, the symptom presentation can change during

adolescence and adulthood, with less overt hyperactivity and symptoms of impulsivity transitioning to risky behaviors involving trouble with the law, substance use, and sexual promiscuity.<sup>17</sup>

As in pediatric BD, comorbidity is common in ADHD, with uncomplicated ADHD being the exception rather than the rule. Recent studies have suggested that approximately two-thirds of children who have a diagnosis of ADHD have ≥1 comorbid diagnoses.<sup>15</sup> Common comorbidities are similar to those seen in BD, including ODD, CD, anxiety disorders, depression, and learning disability. Several tools and resources are available to help clinicians navigate these issues within their practices.

**Family history.** Genetics appear to play a large role in ADHD, with twin studies suggesting inheritance of approximately 76%.<sup>18</sup> Environmental factors contribute, either in the development of ADHD or in the exacerbation of an underlying familial predisposition. Interestingly, in children with BD, family history often is significant for several family members who have both ADHD and BD. However, in children with ADHD only,

family history often reflects an absence of family members with BD.<sup>19</sup> Although not diagnostic, this pattern can be helpful when considering a diagnosis of BD vs ADHD.

**Clinical picture.** ADHD often is recognized in childhood; DSM-5 criteria specify that symptoms be present before age 12 and persist for at least 6 months. This characterization of the timing of symptoms helps exclude behavioral disruptions related to external factors such as trauma (eg, death of a caregiver) or abuse. It also is important to note that symptoms might be present earlier but not come to attention clinically until a later age, perhaps because of increasing demands placed on the child by school, peer groups, and extracurricular activities. To make an ADHD diagnosis, symptoms must be present in >1 setting and interfere with functioning or development.

Core symptoms of ADHD include inattention, hyperactivity, and impulsivity that are out of proportion to the child's developmental level (*Table 2*).<sup>20</sup> When considering diagnosis of ADHD, 6 of 9 symptoms for inattention and/or hyperactivity-impulsivity must be present at a clinically significant level.

Three different ADHD presentations are recognized: combined, inattentive, and hyperactive impulsive. Children with predominant impulsive and hyperactive behaviors generally come to clinical attention at a younger age; inattentive symptoms often take longer to identify.

Children with ADHD have been noted to have lower tolerance for frustration, which might make anger outbursts and aggressive behavior more likely. Anger and aggression in ADHD often stem from impulsivity, rather than irritable mood seen with BD.<sup>18</sup> Issues related to self-esteem, depression, substance use, and CD can contribute to symptoms of irritability, anger, and aggression that can occur in children with ADHD. Although these symptoms can overlap with those seen in children with BD, other core symptoms of ADHD will not be present.

ODD is one of the most common comorbidities among children with ADHD, and the combination of ODD and ADHD may be confused with BD. Children with ODD

**Table 3**

### DSM-5 diagnostic criteria for oppositional defiant disorder

Symptoms and signs
Loses temper
Is touchy or easily annoyed by others
Is angry and resentful
Argues with adults
Actively defies adults' rules or requests
Deliberately annoys people
Blames other for his or her misbehavior or mistakes
Is spiteful or vindictive
Additional criteria
Signs and symptoms must be present for >6 months
Signs and symptoms cannot be better explained by another mental or developmental disorder
Signs and symptoms must result in impairment in functioning
<b>Source:</b> Reference 20

often are noted to exhibit a pattern of negative and defiant behavior that is out of proportion to what is seen in their peers and for their age and developmental level (*Table 3*).<sup>20</sup> When considering an ODD diagnosis, 4 out of 8 symptoms must be present at a clinically significant level.

The following case highlights the potential similarities between ADHD/ODD and BD, with tips on how to distinguish them.

#### CASE REPORT

#### Angry and destructive

Sam, age 7, has been given a diagnosis of ADHD, but his parents think that he isn't improving with methylphenidate treatment. They are concerned that he has anger issues like his uncle, who has "bipolar disorder."

Sam's parents find that he gets frustrated easily and note that he has frequent short "meltdowns" and "mood swings." During these episodes he yells, is aggressive toward others, and can be destructive. They are concerned because Sam will become angry quickly, then act as if nothing happened after the meltdown has blown over. Sam's parents feel that he doesn't listen to them and often argues when they make a request.

continued

#### Clinical Point

**Anger and aggression in ADHD often stem from impulsivity rather than irritable mood seen with BD**



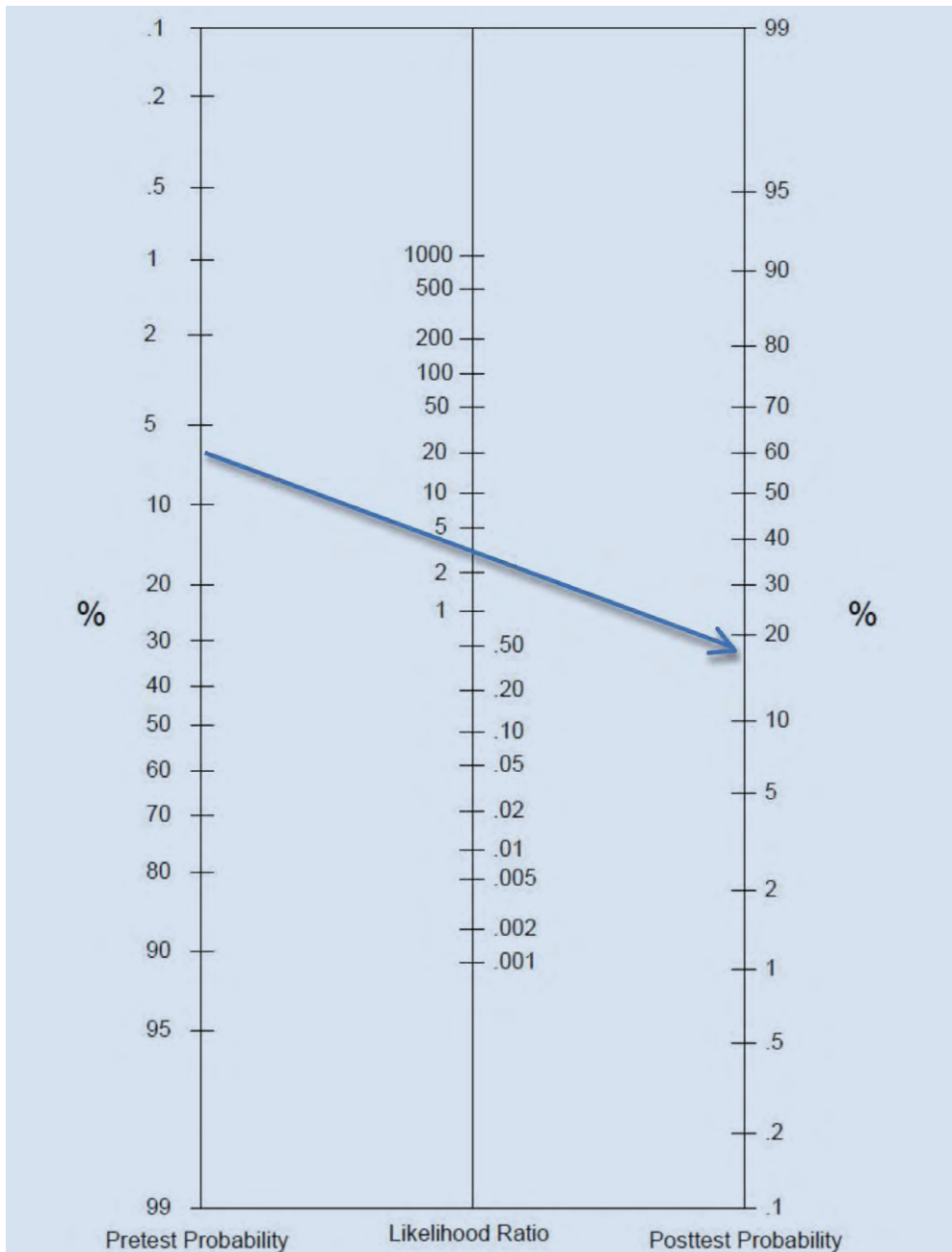
## Bipolar disorder vs ADHD

### Clinical Point

Children with ODD exhibit negative and defiant behavior that is out of proportion with their peers and for their age and development level

Figure 3

## A Youngstrom et al nomogram for Sam



Sam scores low on symptoms of inattention, hyperactivity, and impulsivity; however, scores on the oppositional defiant disorder screener are positive. You factor in Sam's base rate for bipolar disorder (BD) of approximately 6% and because none of his relatives have BD his likelihood ratio is 3%. Completing the nomogram using these variables gives Sam a post-test probability of <20%, below your threshold of considering BD in the differential diagnosis.

Source: References 6,7

His parents note that when they push harder, Sam digs in his heels, which can trigger his meltdowns.

Despite clearly disobeying his parents, Sam often says that things aren't his fault

and blames his parents or siblings instead. Sam seems to disagree with people often. His mother reports "if I say the water looks blue, he'll say it's green." Often, Sam seems to argue or pester others to get a rise out of



them. This is causing problems for Sam with his siblings and peers, and significant stress for his parents. Family history suggests that Sam's uncle may have ADHD with CD or a substance use disorder, rather than true BD. Other than Sam's uncle, there is no family history for BD.

Sam's parents say that extended release methylphenidate, 20 mg/d, has helped with hyperactivity, but they are concerned that other symptoms have not improved. Aside from the symptoms listed above, Sam is described as a happy child. There is no history of trauma, and no symptoms of anxiety are noted. Sam sometimes gets "down" when things don't go his way, but this lasts only for a few hours. Sam has a history of delayed sleep onset, which responded well to melatonin. No other symptoms that suggest mania are described.

You complete the pediatric bipolar nomogram (**Figure 3**)<sup>6,7</sup> and Sam's parents complete a Vanderbilt ADHD Diagnostic Parent Rating Scale. At first, Sam seems to have several factors that might indicate BD: aggressive behavior, mood swings, sleep problems, and, possibly, a family history of BD.

However, a careful history provides several clues that Sam has a comorbid diagnosis of ODD. Sam is exhibiting the classic pattern of negativist behavior seen in children with ODD. In contrast to the episodic pattern of BD, these symptoms are prevalent and persistent, and manifest as an overall pattern of functioning. Impulsivity seen in children with ADHD can complicate the picture, but, again, appears as a consistent pattern rather than bouts of irritability. Sam's core symptoms of ADHD (hyperactivity) improved with methylphenidate, but the underlying symptoms of ODD persisted.

## Bottom Line

Distinguishing the child who has bipolar disorder (BD) from one who has attention-deficit/hyperactivity disorder can be challenging. A careful history helps ensure that you are on the path toward understanding the diagnostic possibilities. Tools such as the Vanderbilt Rating Scale can further clarify possible diagnoses, and the nomogram approach can provide even more predictive information when considering a diagnosis of BD.

## Related Resources

- Children and Adults with Attention Deficit/Hyperactivity Disorder (CHADD). [www.chadd.org](http://www.chadd.org).
- American Academy of Child and Adolescent Psychiatry. Facts for Families. [www.aacap.org/cs/root/facts\\_for\\_families/facts\\_for\\_families](http://www.aacap.org/cs/root/facts_for_families/facts_for_families).
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## Drug Brand Names

Methylphenidate • Ritalin, Methylin, Metadate CD, Metadate ER, Methylin ER, Ritalin LA, Ritalin SR, Concerta, Quillivant XR, Daytrana  
Risperidone • Risperdal

Sleep problems are common in children who have ADHD *and* BD, but Sam's delayed sleep onset responded to melatonin, whereas the insomnia seen in BD often is refractory to lower-intensity interventions, such as melatonin. Taking a careful family history led you to believe that BD in the family is unlikely. Although this type of detail may not always be available, it can be helpful to ask about mental health symptoms that seem to "run in the family."

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continued on page 25

## Clinical Point

**Impulsivity seen in children with ADHD can complicate the diagnosis, but appears as a consistent pattern rather than bouts of irritability**

SHE HAS **DEPRESSION** AND/OR **ANXIETY**,  
BUT HER **ADHD** WASN'T REVEALED UNTIL  
**YOU TOOK A DEEPER LOOK**

Her inattention and impulsivity  
persisted despite treatment,  
so you kept looking.

APPROXIMATELY

**10%**

OF PATIENTS WITH  
CLINICAL DEPRESSION  
AND/OR ANXIETY

**MAY ALSO HAVE ADHD.<sup>1\*</sup>†**

<sup>\*</sup>Based on the National Comorbidity Survey  
Replication of 3,199 adults aged 18 to 44 years,  
conducted from 2001 to 2003.<sup>1</sup>

<sup>†</sup>Diagnosis should be based on a complete history  
and evaluation of the patient. Medication may not  
be appropriate for all patients.

Hypothetical patient portrayal.

Dig a little deeper for your adult patients with symptoms  
of inattention, hyperactivity, and impulsivity.

Download an **ADHD** screener at **UncoverADHD.com**

Reference: I. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry*. 2006;163(4):716-723.

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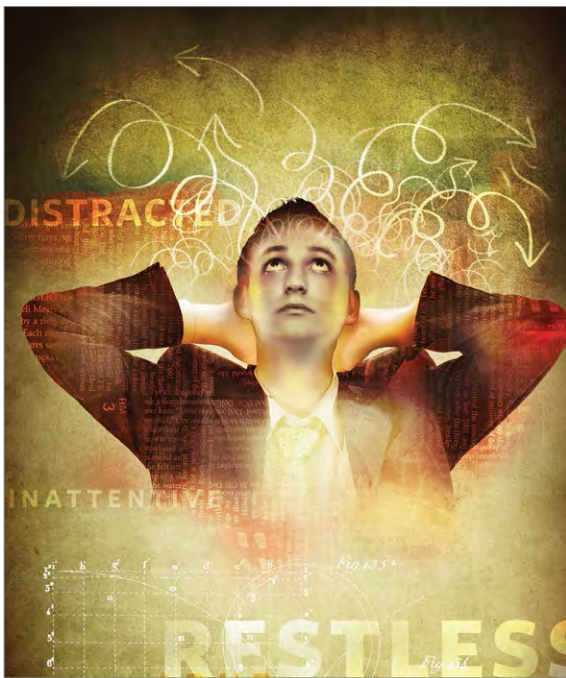
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# Adult ADHD: Pharmacologic treatment in the DSM-5 era



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## Revised diagnostic criteria reflect greater recognition of disease impact beyond childhood

**A**ttention-deficit/hyperactivity disorder (ADHD) is common; it affects 5% to 7% of children<sup>1,2</sup> and 4% to 5% of all adults.<sup>3,4</sup> Pediatric ADHD often persists into adulthood, as 65% of individuals diagnosed as children retain impairing symptoms by age 25.<sup>4</sup>

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

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

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

Adults with ADHD also are more likely to have a comorbid psychiatric disorder—in particular, substance use<sup>11</sup>—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.<sup>3,12</sup>

**Disclosures**

Dr. Parikh is a speaker for Sunovion. Dr. Baker reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

## Changes in DSM-5

Revisions within DSM-5 simplify ADHD's diagnosis—and make it more difficult to ignore in adults (*Table 1*).<sup>13</sup> For example, DSM-IV<sup>14</sup> 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.<sup>13,14</sup>

## 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*).<sup>15</sup> 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.<sup>16,17</sup>

**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.<sup>18</sup>

**Occupational history** also may be revealing:

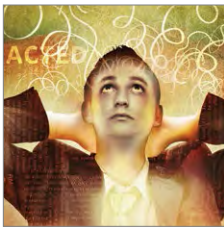
- How are they performing at work?
- Have they changed jobs multiple times in a short period?
- Do they have difficulty organizing tasks?

## 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.<sup>19,20</sup> No distinct psychometric cognitive test or profile is diagnostic of ADHD or its subtypes.<sup>21</sup>

### Treatment and follow-up care

Four general categories of medications are used to treat ADHD in children and adults: stimulant, noradrenergic,  $\alpha_2$  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.<sup>22</sup> 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.<sup>23</sup>

### 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.<sup>24</sup>

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.<sup>25</sup> 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.<sup>26</sup>

**Lisdexamfetamine** contains L-lysine, an essential amino acid, covalently bound to d-amphetamine via an amide linking group.<sup>27</sup> After absorption, lisdexamfetamine is metabolized by rate-limited, enzymatic hydrolysis to yield d-amphetamine and L-lysine.<sup>24,28,29</sup> 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.<sup>30</sup> 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.<sup>31</sup>

**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.<sup>22,32</sup> Optimized dosing is generally 1 mg/kg per day, and dosing up to 80 to 120 mg/d is not unusual.<sup>33</sup>

Dexmethylphenidate is the more pharmacologically active enantiomer of racemic

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

### 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.<sup>38</sup>

**Methylphenidate** has no interactions with CYP enzymes, making it an attractive option for patients taking CYP inhibiting or stimulating medications.<sup>39</sup> 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.<sup>40,41</sup> Methylphenidate inhibits the metabolism of tricyclic antidepressants; use methylphenidate with caution in patients taking monoamine oxidase inhibitors.<sup>42,43</sup>

**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.<sup>44</sup> 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.<sup>45</sup>

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.<sup>23</sup> 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.<sup>46</sup> Symptoms are usually mild, but in rare instances stimulants are associated with digital ulceration or soft tissue breakdown.<sup>47</sup>

### 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

### Clinical Point

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

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.<sup>46</sup> 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.<sup>48,49</sup> Atomoxetine may be a good alternative for adult patients with ADHD and comorbid anxiety.<sup>50</sup>

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.<sup>51</sup> 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.<sup>52</sup> Atomoxetine was found to have an effect size of 0.45 (medium) (number needed to treat [NNT] = 5).<sup>53-55</sup>

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.<sup>56-58</sup>

### 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  $\alpha$ -2A,  $\alpha$ -2B, and  $\alpha$ -2C (as well as to  $\alpha$ -1 and  $\beta$  subtypes, histamine receptors, and possibly dopamine receptors).<sup>59,60</sup> Guanfacine binds preferentially to postsynaptic  $\alpha$ -2A adrenoceptors in the prefrontal cortex, which have been implicated in attentional and organizational functions.<sup>61,62</sup>

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.<sup>63</sup>

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.<sup>64</sup>

**Adverse events.** Compared with clonidine, guanfacine has less CNS depressant and hypotensive activity.<sup>58</sup> 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.<sup>65</sup>

## 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.<sup>66,67</sup> 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.<sup>68</sup>

**Tricyclics.** Desipramine and nortriptyline have been found to be efficacious in childhood ADHD,<sup>69,70</sup> although cardiovascular risk and toxicity in overdose limit their use.<sup>71</sup>

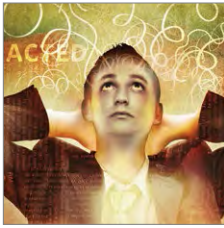
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## Clinical Point

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**

## Related Resources

- Christensen RC. Is he DISTRACTED? Considerations when diagnosing ADHD in an adult. *Current Psychiatry*. 2014;13(1):49-62.
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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
Dexmethylphenidate • Focalin	Pilocarpine • Salagen

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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**

### Bipolar disorder vs ADHD

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# ADHD symptoms are stable, then a sudden relapse

Muhammad Hassan Majeed, MD, and Muhammad Khalid Zafar, MD



## How would you handle this case?

Answer the **challenge questions** throughout this article

R, age 11, has ADHD, which has been stable on extended-release methylphenidate. Over 2 months, hyperactivity, inattention, and impulsivity reemerge. What could be causing his symptom relapse?

### **CASE** Sudden deterioration

R, age 11, has attention-deficit/hyperactivity disorder (ADHD), combined type, and oppositional defiant disorder, which has been stable for more than a year on extended-release (ER) methylphenidate (brand name: Concerta), 54 mg/d (1.2 mg/kg). With combined pharmacotherapy and behavioral management, his symptoms of hyperactivity, inattention, and impulsivity improved at school and at home. He shows some academic gains as evidenced by improved achievement at school.

Over 2 months, R experiences a substantial deterioration in behavioral and academic performance. Along with core symptoms of ADHD, he begins to exhibit physical and verbal aggression. A report from school states that R has been using obscene language and destroying property, and has had episodes of provoked aggression toward his peers. His grades drop and he receives 2 school suspensions because of aggressive behavior.

### What could be causing R's ADHD symptoms to reemerge?

- a) nonadherence to treatment
- b) substance abuse
- c) medication change
- d) all of the above

### **The authors' observations**

Worsening of psychiatric symptoms in a stable patient is relatively common. Many factors can contribute to patient destabilization. Treatment nonadherence is a leading cause, along with psychosocial stressors and substance use (*Table*).

### **EVALUATION** Adherence confirmed

R is hyperactive and distracted during his visit, a clear deterioration from his baseline status. R is oppositional and defiant toward his mother during the session, but shows good social skills when communicating with the physician.

R's mother reports that her son seldom forgets to take his medication, and she ensures that he is swallowing the pill, rather than chewing it. Data from the prescription drug-monitoring program show that the family is filling the prescriptions regularly. The ER methylphenidate dosage is raised to 72 mg/d. The clinicians provide psychoeducation about adherence to a medication regimen to R and his family. Also, his parents and teachers

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receive Vanderbilt Assessment Scales for ADHD to assess the symptoms in different settings.

At a follow-up visit a week later, R's mother reports that her son continues to have problems in school and at home. The Vanderbilt scales reveal that R is having clinically significant problems with attention, hyperactivity, impulse control, and oppositional behavior.

A urine drug screen is ordered to rule out the possibility of a sudden deterioration of ADHD symptoms secondary to substance use disorder. To ensure compliance, we recommend that R take his medication at the school nurse's office in the morning.

### A week later

Although R takes his medication at school, he continues to show core symptoms of ADHD without improvement. The urine drug screen is negative. A physical examination does not reveal any medical illness. The treatment team calls the pharmacist to obtain a complete list of medications R is taking, who confirms that he is only receiving ER methylphenidate, 72 mg/d. The pharmacist also notes that R's medication was switched from the brand-name drug to a generic 3 months ago because of a change in insurance coverage. This change coincided with the reemergence of his ADHD symptoms.

R's mother reports that the new pills do not look like the old ones even before the dosage was raised. A new brand-necessary prescription is sent to the pharmacy. With the brand-name medication, R's symptoms quickly improve, and remain improved when the dosage is decreased to the previous dosage of 54 mg/d.

### With osmotic-controlled release oral delivery system (OROS) and outer coating of ER methylphenidate, how much drug is released immediately vs slow release?

- 22% immediate release and 78% slow release
- 78% immediate release and 22% slow release
- 50% immediate release and 50% slow release

#### Table

### Considerations in patients whose symptoms have worsened following an initial stabilization

Nonadherence or partial adherence to treatment
Comorbid psychiatric or substance abuse disorder
Psychosocial factors or stress
Complicating physical health problems (eg, hypothyroidism or hyperthyroidism and temporal lobe epilepsy)
Drug–drug interactions (eg, inhibition of stimulant effect of amphetamines by lithium, introduction of a medication that competes with cytochrome P450 2D6-dependent metabolism)
Brand vs generic bioavailability
Decrease in effective weight-based dose secondary to growth in pediatric patients

### The authors' observations

Generic substitution of a brand medication can result in worsening of symptoms and increased adverse effects. Possible bioequivalence issues can lead to failure of drug therapy.<sup>1</sup>

In 2013, the FDA determined that 2 specific generic formulations of ER methylphenidate do not have therapeutic equivalency to the brand-name medication, Concerta. The FDA stated, "Based on an analysis of data, FDA has concerns about whether or not two approved generic versions of Concerta tablets (methylphenidate hydrochloride extended-release tablets), used to treat attention-deficit hyperactivity disorder in adults and children, are therapeutically equivalent to the brand-name drug."<sup>2</sup>

In an apparent confirmation of the FDA's concerns, a case series of children and adolescents with ADHD observed that almost all of the patients showed symptom improvement when they switched from a non-OROS formulation to an OROS preparation at the same dosage.<sup>3</sup>

### Clinical Point

Generic substitution of a brand-name medication can result in worsening of symptoms and increased adverse effects

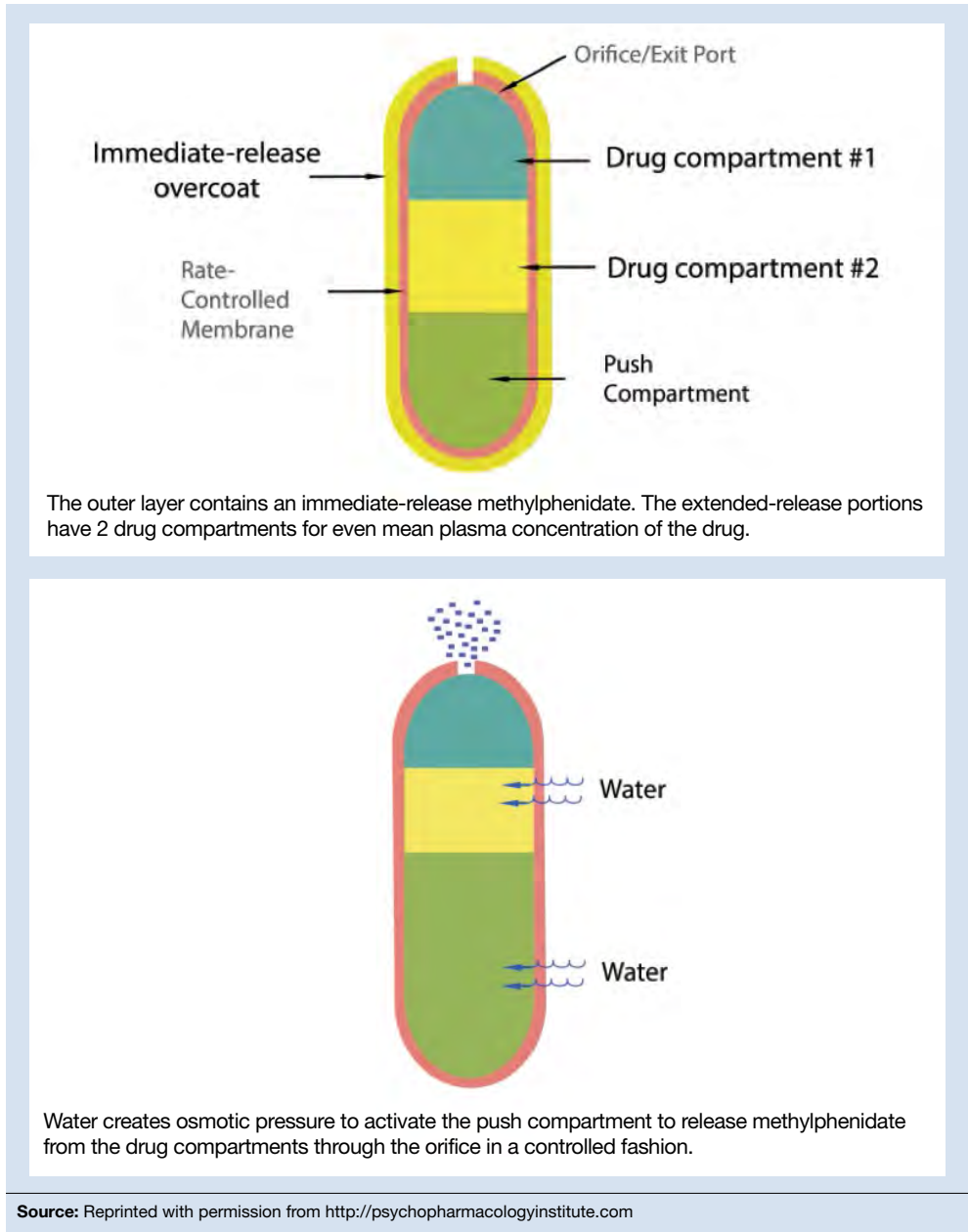
continued

**Clinical Point**

The OROS preparation is thought to provide more predictable medication delivery over an extended period of time

**Figure**

**Osmotic release oral system in Concerta**



The OROS preparation is thought to provide more predictable medication delivery over an extended period of time (Figure). A patient taking an ER formulation without OROS might lose this benefit, which could lead to symptom destabilization, even if the patient is taking the medication as instructed.

**Brand vs generic**

Under FDA regulations, companies seeking approval for generic formulations of approved drugs must demonstrate that their products are the same as the brand-name drug in terms of:

- active ingredients
- strength

- dosage form
- route of administration
- packaging label.

In addition, the pharmaceutical company must demonstrate that the generic form is absorbed and distributed to the part of the body at which it has its effect at acceptably similar levels to the brand-name drug. All medications—new or generic, in clinical trials or approved, prescription or over-the-counter—must be manufactured under controlled conditions that assure product quality.

However, some studies have disputed this equivalency. In 1 study, patients with schizophrenia receiving generic olanzapine had lower serum concentration than patients with schizophrenia taking equivalent dosages of brand-name olanzapine.<sup>4</sup> Similarly, studies comparing generic and brand-name venlafaxine showed significant differences in peak plasma concentration (C<sub>max</sub>) between generic and brand-name compounds.<sup>5</sup>

The FDA has considered upgrading the manufacturers' warnings about the risk of generic medications, but has delayed the decision to 2017.<sup>6</sup>

### FDA's approval process for generic drugs

To receive approval of a generic formulation in the United States, the FDA requires that the generic drug should be compared with the corresponding brand-name drug in small crossover trials involving at least 24 to 36 healthy volunteers.

Bioequivalence is then established based on assessments of the rate of absorption (C<sub>max</sub> and area under the plasma concentration-time curve [AUC]). The FDA's criteria are designed to achieve 90% confidence that the ratios of the test-to-reference log-transformed mean values for AUC and C<sub>max</sub> are within the interval of 80% to 125%. The FDA accepts –20% to 25% variation in C<sub>max</sub> and AUC in products that are considered bioequivalent. This is much less

stringent than its –5% to 5% standard used for brand-name products. The FDA publishes a list of generic drugs that have been certified as bioequivalent, known as the "Orange Book."<sup>5</sup>

### Considerations when substituting generic medication

Because of the growing number of generic formulations of the same medication, generic–generic switches are becoming more commonplace. Theoretically, any 2 generic versions of the same medication can have a variation of up to 40% in AUC and C<sub>max</sub>. Generic medications are tested in healthy human controls through single-dose studies, which raises concerns about their applicability to the entire patient population.

**Bioequivalence.** It is a matter of debate whether bioequivalence translates to therapeutic equivalency. For medications with a narrow therapeutic index, the FDA has accepted that these 2 phenomena are not necessarily linked. With the exception of a few medications, including lithium and some anticonvulsants such as divalproex sodium and carbamazepine, serum level of the medications usually does not predict clinical response.

**Inert ingredients.** Generic medications can include inert ingredients (excipients) that are different from those in their branded counterparts. Some of these inactive ingredients can cause adverse effects. A study comparing paroxetine mesylate and paroxetine hydrochloride showed differences in bioequivalence and clinical efficacy.<sup>7</sup>

In some cases, brand-to-generic substitution can thwart clinical progress in a stable patient. This small change in the medication could destabilize the patient's condition, which, in turn, may lead to unnecessary and significant social and financial burdens on the patient's family, school, community, and the health care system.

### Clinical Point

**Theoretically, any 2 generic versions of the same medication can have a variation of up to 40% in AUC and C<sub>max</sub>**

## Clinical Point

Prescribers should remain cognizant of drug switches from brand to generic and from one generic to another

## Related Resources

- U.S. Food and Drug Administration. Fact sheet: what's involved in reviewing and approving generic drug applications? [www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm506040.htm](http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm506040.htm).
- Desmarais JE, Beauclair L, Margolese HC. Switching from brand-name to generic psychotropic medications: a literature review. *CNS Neurosci Ther.* 2011;17(6):750-760.

### Drug Brand Names

Carbamazepine • Tegretol	Olanzapine • Zyprexa
Divalproex • Depakote	Paroxetine • Paxil
Lithium • Eskalith, Lithobid	
Methylphenidate extended-release • Concerta	

## Recommendations

In the event of a change in clinical response, clinicians first should evaluate adherence and explore other factors, such as biological, psychological, medical, and social issues. Adherence can be adversely affected by a change in the physical characteristics of the pill. Prescribers should remain cognizant of brand–generic and generic–generic switches. It may be reasonable to adjust the dosage of the new generic medication to address changes in clinical effectiveness.

If these strategies are ineffective, consider switching to a brand-name medication. Write “Dispense As Written” on the pre-

scription to ensure delivery of the branded medication or a specific generic version of the medication.

An insurance company might require prior authorization to approve payment for the brand medication. To save time, use electronic forms or fax for communicating with the insurance company. Adding references to FDA statements and research papers, along with the patient’s history and presentations, would be prudent to demonstrate doubts about efficacy of the generic medication.

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## Bottom Line

Generic medications can differ in bioequivalence and clinical response from their brand-name or other generic counterparts. When a stable patient shows signs of sudden clinical deterioration, consider a brand–generic switch as a possible factor.



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## Rule out these causes of inattention before diagnosing ADHD

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### Disclosure

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Inattention and distractibility are highly prevalent, and can exist secondary to a number of underlying causes. When a patient (or the patient's family) asks whether he (she) might have attention-deficit/hyperactivity disorder (ADHD), you must perform a comprehensive assessment to rule out other medical and psychiatric disorders that might be manifesting as inattention. It is important not to miss a diagnosis of ADHD, and it is vital not to mistake another medical or psychiatric condition as ADHD.

Pay attention to components of the differential diagnosis while you are evaluating a patient with possible ADHD.

**Medical conditions.** Several disorders can present with cognitive, attentional, and executive functioning deficits that resemble the presentation of ADHD. These include absence seizures and other types of seizures, Lyme disease, HIV infection, and encephalopathy.<sup>1</sup>

People who have completed chemotherapy (particularly children) often exhibit attentional and executive functioning deficits similar to those found in ADHD.<sup>1</sup>

**Anxiety disorders,** the most prevalent of psychiatric disorders, correlate highly with difficulty concentrating. Chronic stress can have negative effects on hippocampus- and prefrontal cortical-based memory and cognitive functions.<sup>2</sup> Be cautious, therefore, when diagnosing ADHD in a patient who suffers from significant, acute, or inadequately controlled anxiety—especially one who does *not* have a history of a childhood onset of attentional difficulties.

On the other hand, untreated ADHD can lead to anxiety symptoms.

**Drugs.** A number of substances of abuse—marijuana, cocaine, ecstasy, and caffeine—can produce symptoms of poor attention or impulsivity, similar to what is seen in ADHD, through their effects on the hippocampus and prefrontal cortex.<sup>3,4</sup> MRI studies of the brains of 8-year-olds prenatally exposed to cocaine have found changes in frontal lobes suggesting potential long-term effects on attention and impulse control in these children.<sup>5,6</sup>

Use of certain medications, such as anticholinergics, also can contribute to attentional difficulties in some patient populations.

**Abuse or trauma.** Difficulty concentrating is one of the core symptoms of posttraumatic stress disorder (PTSD). Rule out PTSD and recent abuse or trauma when assessing for ADHD. Children with recent trauma often present with agitation, restlessness, and behavioral disturbance—symptoms that mimic ADHD.

**Mood and adjustment disorders.** Difficulty concentrating also is a criterion for major



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depressive disorder. On the other hand, untreated ADHD also can lead to, or contribute to, development of a depressive disorder. If a patient is experiencing a major depressive episode, obtain a thorough collateral history delineating a timeline of attention difficulties, which should allow for an accurate diagnosis.

In children, ADHD and bipolar disorder can have symptom overlap; both can present with distractibility, increased energy, and mood lability—therefore making a careful history a diagnostic necessity. Furthermore, ADHD and bipolar disorder can coexist in a small percentage of ADHD patients.

**Hypothyroidism.** Studies show a decrease in memory, attention, and concentration in patients with overt hypothyroidism, and at least a small decrease in these domains in patients with subclinical hypothyroidism.<sup>7</sup> Decreased cerebral blood flow in brain regions that mediate attention and executive functioning, and decreased hippocampal volume, have been observed in patients with hypothyroidism.<sup>7</sup> Therefore, the cognitive profile in these patients can look similar to, and can be confused with, ADHD, inattentive type.

**Insomnia.** Sleep plays a key role in memory consolidation and maintaining attention. Sleep disorders (eg, sleep apnea, restless legs syndrome, delayed sleep phase-onset disorder) can produce chronic tiredness and significantly affect attention, concentration, and cognitive functioning in children, adolescents, and adults.<sup>8</sup>

Studies in adults have shown that sleep deprivation is linked to attentional difficulty secondary to changes in prefrontal cortex activity.<sup>9</sup> Other studies suggest that short sleep duration in healthy children is associated with inattention and poorer academic functioning, and also was found linked to teacher reports of inattention and a cognitive profile similar to what is seen in ADHD.<sup>8</sup>

**Learning disorders and developmental disabilities.** Children with an undiagnosed

learning disorder often present with symptoms akin to those of ADHD.<sup>1</sup> An undiagnosed reading or mathematics disorder, for example, can have a significant impact on academic functioning, in which the child might not be paying attention because of his (her) restricted ability to grasp the subject matter.

On the other hand, keep in mind that ADHD is highly comorbid with learning disorders.<sup>10</sup>

Last, children and adults with a developmental disability can present with signs and symptoms similar to those of ADHD.<sup>1</sup>

## Summing up

Comprehensive assessment and management of any underlying condition is important to address the attention deficits you observe in a patient. A collateral history from parents and significant others, school reports, relevant laboratory tests, and a full physical examination are important tools for making an accurate diagnosis.

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Untreated ADHD can lead to, or contribute to, anxiety symptoms or a depressive disorder

SHE HAS **DEPRESSION** AND/OR **ANXIETY**,  
BUT HER **ADHD** WASN'T REVEALED UNTIL  
**YOU TOOK A DEEPER LOOK**

Her inattention and impulsivity  
persisted despite treatment,  
so you kept looking.

APPROXIMATELY

**10%**

OF PATIENTS WITH  
CLINICAL DEPRESSION  
AND/OR ANXIETY

**MAY ALSO HAVE ADHD.<sup>1\*</sup>†**

<sup>\*</sup>Based on the National Comorbidity Survey  
Replication of 3,199 adults aged 18 to 44 years,  
conducted from 2001 to 2003.<sup>1</sup>

<sup>†</sup>Diagnosis should be based on a complete history  
and evaluation of the patient. Medication may not  
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