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# **Risk-Benefit Considerations in ADHD Pharmacotherapy**

**A review of the safety issues related to pharmacologic treatment  
of ADHD and strategies for the management of medication misuse**



Jointly sponsored by the University of Cincinnati College of Medicine and Princeton Media Associates

November 2006

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# Risk-Benefit Considerations in ADHD

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This activity is designed for pediatricians and psychiatrists.

## STATEMENT OF NEED

Attention-deficit/hyperactivity disorder (ADHD) is a common disorder affecting both children and adults, often with a severe impact in daily functioning and quality of life. While stimulant treatment has long been the standard of care for ADHD, concerns still exist regarding the safety of these agents, and their potential for abuse, misuse, and diversion. Due to these concerns, a variety of other treatment options—from long-acting stimulants to nonstimulants—have been added and are currently being studied as additions to the treatment armamentarium. With the growing burden of ADHD and new prospective challenges and opportunities in ADHD management, clinicians require additional education on the new and emerging strategies for the management of ADHD, particularly with regard to medication compliance and issues of abuse and misuse of pharmacologic treatments.

## LEARNING OBJECTIVES

After completing this activity, participants should be able to:

- Define the prevalence of ADHD and its effect on overall health and quality of life
- Describe the liability of medication abuse, its measurement, and its impact on clinical practice
- Summarize safety and tolerability challenges associated with traditional ADHD pharmacotherapies
- Outline the potential opportunities with emerging pharmacotherapies to improve safety and tolerability in the management of ADHD
- Apply the latest data to advance the safe and effective management of ADHD

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There is no fee associated with this activity.

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The following off-label/unapproved drugs or devices are discussed: bupropion, guanfacine, modafinil, and lisdexamfetamine in the treatment of ADHD

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# Risk-Benefit Considerations in ADHD Pharmacotherapy

By Jeffrey H. Newcorn, MD, and Iliyan Ivanov, MD

Attention-deficit/hyperactivity disorder (ADHD) is the most prevalent neuropsychiatric disorder in childhood, with rates that range from 3% to 18% in children, depending on age, gender, and the definition and specific assessment methods used.<sup>1</sup> Consistent with the recognition that ADHD is a developmental disorder with early childhood onset, at least some symptoms of ADHD must be present by age 7.<sup>2</sup> However, the full syndrome may not be apparent until much later. This is more likely the case in individuals who have a predominance of inattentive rather than hyperactive/impulsive symptoms, and especially in females. In clinical settings, the gender ratio of males to females with ADHD ranges from 6:1 to 9:1 in children, owing to the popular conceptualization of ADHD as a male condition. However in epidemiologic settings, the gender ratio is closer to 3:1,<sup>1</sup> suggesting there is substantial gender bias in case identification. ADHD symptoms often persist across the entire life span, although hyperactive/impulsive symptoms often decrease with age.<sup>3</sup> An even larger number of individuals have residual or subthreshold pathology.<sup>4</sup> A recent epidemiologic survey of ADHD among 3199 18- to 44-year-olds estimated the current adult ADHD prevalence to be 4.4% at a gender ratio that approaches 1:1.<sup>5</sup> A substantial and growing data base indicates that ADHD is a disorder of brain function, which is highly heritable. However, a variety of other factors, such as central nervous system insults and environmental elements, may also contribute to its etiology.

ADHD is often highly impairing, and carries a well-documented social and economic impact. In 2000, the estimated total cost of ADHD in the United States was \$31.6 billion, comprising \$1.6 billion in ADHD treatment costs, \$12.1 billion for other medical treatment of ADHD patients, \$14.2 billion for healthcare costs of family members of ADHD patients, and \$3.7 billion in work loss of adult ADHD patients and adult family members of ADHD patients.<sup>6</sup> The financial impact of ADHD also extends to costs associated with impairments in the workplace or the inability to consistently find and maintain employment.<sup>7</sup>

Although the functional impact of ADHD has been linked to poor academic performance and underachievement in school-age children and college students, including overall lower educational level and higher dropout rates,<sup>8</sup> the impact of ADHD extends well beyond educational attainment. Adult ADHD drivers have more incidents of reckless driving, driving without a license, hit-and-run crashes, and having had their licenses suspended or revoked.<sup>9</sup> Impulsive and risk-taking behaviors among adolescents and adults with ADHD have also been linked to the increased risk for a range of medical and psychiatric con-

ditions, including human immunodeficiency virus/acquired immune deficiency syndrome (as a result of risky sexual practices), addiction (high risk for experimenting with illicit substances and more difficulty quitting once using), and criminal acts and behaviors. While those with comorbid conditions such as conduct or bipolar disorder are at highest risk, untreated ADHD alone appears to confer intermediate risk for substance use disorders (SUDs).<sup>10</sup>

While treatment of ADHD appears to decrease the risk for impairments such as academic performance, conduct problems, and risk for SUD,<sup>11,12</sup> alteration of a long-term outcome is adversely affected by poor adherence to treatment. It has been estimated that less than 50% of patients treated with medication for ADHD remain on treatment after 6 months; one recent review estimates that less than 10% of ADHD patients in several child studies (the phenomenon is also recognized in adults but the data are less highly developed) persist with treatment over the long term.<sup>13</sup> It is therefore important to consider factors that might contribute to improved adherence. The need to take multiple daily doses of medications has been linked to poor adherence in a variety of medical conditions; it is presumed that the recent introduction of longer-acting medications for ADHD may lead to improved adherence. In children and adolescents, longer-acting formulations have the additional benefits of taking medication treatment out of the classroom, thereby reducing stigmatization of the ADHD patient and costs to the system.<sup>14</sup>

The decision whether to initiate and maintain pharmacotherapy in individuals with ADHD must take into consideration the nature of present and potential impairments, the developmental course of the disorder, and the safety of available treatments. Treatment decisions must be mindful of the well-recognized poor adherence to long-term treatment and the substantial risk from nontreatment. This *First Report*<sup>®</sup> will review issues related to the risk-benefit ratio of existing and emerging medication treatments for ADHD, including both safety and tolerability considerations, and the potential for reducing the burden of the disorder and its associated impairments.

## FOOD AND DRUG ADMINISTRATION (FDA)- APPROVED TREATMENTS FOR ADHD

**Psychostimulants.** Psychostimulants have long been considered the “gold standard” of pharmacotherapy for children with ADHD, and recent studies have extended their utility to the adolescent and adult populations. Stimulants are highly efficacious—70% of patients will have at least some response when either one of the 2 classes of stimulant medication (amphetamine [AMP] and methylphenidate

[MPH]) are used.<sup>15</sup> When both AMP and MPH have been nonconcurrently administered and dosed appropriately, the response is as high as 90%.<sup>16</sup> Although most patients will respond to either agent, there are individual differences in both response and tolerability, consistent with similarities and differences in their mechanisms of action. In addition to their effects on ADHD symptoms, psychostimulants are also beneficial in a variety of associated domains, such as oppositional and aggressive behaviors, academic achievements, and social skills.<sup>17</sup> Initially, only immediate-release formulations were available, but new extended-release formulations have been developed that can provide either the equivalent of 2 immediate-release doses or continuous-release dosing. Due to convenience and possible advantages in clinical response and tolerability, the newer extended-release formulations have largely replaced the immediate-release medications as first-line therapy.

**Nonstimulants.** Atomoxetine is the first FDA-approved nonstimulant agent for childhood and adult ADHD. The duration of activity is longer than would typically be predicted from the half-life in extensive metabolizers;<sup>18</sup> thus atomoxetine is labeled for either qd or bid use. Dosing follows a weight-based schedule because plasma levels vary considerably as a function of body weight, with a recommended target dose of 1.2 mg/kg. Although there is some immediate improvement with treatment, a longer period is often required before the full effects are observed. Therapeutic effects may persist into the evening and even the next morning.<sup>19</sup> Effect sizes have averaged 0.7 in children and adolescents but were lower in adults,<sup>20</sup> owing either to differences between treatment of adults and children or factors related to the nature and measurement of ADHD symptoms in adults.

**Impact of Pharmacotherapy on the Burden of ADHD.** A number of investigators have assessed the clinical and cost-effectiveness of currently approved medications for ADHD. MPH use in children has a cost-effectiveness ratio (assessed through estimating both the incremental costs and incremental effects associated with treatment) that clearly favors treatment on a short-term basis (eg, 6 months or less).<sup>21</sup> While the cost-benefit ratio of more extended treatment has been more controversial, the National Institute of Mental Health-sponsored Multimodal Treatment Study of Children with ADHD (MTA) found that medication management alone was more cost-effective in children with uncomplicated ADHD, particularly for those without comorbid disorders. In the treatment of children with comorbid disorders, combined medication and psychosocial treatment—although considerably more expensive—may be more cost-effective than medication alone, when considering the reduction in cost to society that accompanies the increased response to treatment.<sup>22</sup>

Pharmacologic treatment of ADHD, either with stimulants or nonstimulants, is often best conceptualized within a comprehensive management plan, including psychosocial treatment.

### SAFETY OF FDA-APPROVED TREATMENTS FOR ADHD

**Stimulants.** The most common adverse effects of stimulants include insomnia, nervousness, irritability, anxiety, jitteriness, headache, stomachache, and decreased appetite. Stimulants can increase pulse and blood pressure modestly, but this is rarely a clinical problem. There has been concern regarding the worsening of tic disorders; however, usual doses of stimulants do not exacerbate or precipitate tic disorders in most children,<sup>23</sup> and apparent medication-induced exacerbations may decline spontaneously even without discontinu-

ing or changing the medication.<sup>24</sup> Stimulants can often be used in children with tics, particularly when the magnitude and severity of ADHD symptoms have an impairing effect on quality of life.<sup>25</sup>

The extent to which stimulant treatment may be associated with growth retardation remains controversial. At the group level, chronic use of stimulants appears to decrease the velocity of growth acutely. Although the effects on weight and height have generally been considered to be of minimal clinical significance,<sup>26</sup> it is important to consider the possible impact on individuals at risk. The presumption has been that growth stabilizes and catches up over time, as was shown in an early study.<sup>27</sup> In the MTA study, acute use of immediate-release stimulants, administered 3 times daily, 7 days per week, produced a slowing of growth by approximately 1 cm per year over the first 24 months of treatment in medication-treated versus unmedicated subjects.<sup>28</sup> The decrease in growth trajectory flattened after the initial treatment period, but did not “catch up” to the curve for the unmedicated group by 36 months. Interpretation of these data is complicated by the fact that the ADHD children in this and most other clinical trials are larger than the age- and gender-based norms, so it is not clear whether this degree of slowing of growth is actually of concern. It is also not clear what the proper comparison is—to unmedicated youth with ADHD or national norms. In the MTA study, children have not yet been followed long enough to determine their ultimate growth status, but the study is ongoing. Finally, it should be noted that the MTA study was conducted with immediate-release stimulants, as the newer, long-acting formulations were not yet available. Industry-funded trials with long-acting agents have found only small changes relative to normative values, with some variability as a function of medication class.

The issue of cardiotoxicity and stimulant treatment has received considerable recent attention. The debate has been quite passionate, as indicated by several recent opinion papers in high-profile journals.<sup>29,30</sup> Reports of 12 cases of sudden cardiac death in children taking mixed amphetamine salts (MAS) prompted an initial review by the FDA and led to a decision by Health Canada to temporarily withdraw MAS-extended release (XR) from the Canadian market (MAS immediate release was not available for use in Canada, and thus was not pulled from the market). The Health Canada decision was based on preliminary review of US data, since there were no apparent treatment-related deaths in Canada. Of the 12 reported cases, 5 occurred in patients with underlying structural heart defects (abnormal arteries or valves, abnormally thickened walls, etc). In several of the other cases, there were problems complicating the assessment of medication-related risk (family history of ventricular tachycardia; association of death with heat exhaustion, dehydration, and near-drowning; very rigorous exercise; fatty liver; heart attack; and type 1 diabetes mellitus). Consistent with this information, as well as the large number of patients who are safely and effectively treated with this medication, MAS-XR was reinstated by Health Canada after careful review.

The most recent information indicates that the risk for sudden death in patients taking stimulants does not exceed the base rate in the general population (0.6-6/100,000 per year), and this outcome is often associated with preexisting structural cardiac defects, other complicating circumstances, or a positive family history.<sup>31</sup> Because the number of cases of sudden death reported for MAS is only slightly greater than for MPH, the most recent FDA review (2005-2006) of cardiac risk considered possible risk from all classes and formulations of stimulants. In February 2006, an FDA safety subcommittee recommended that stimulants receive a “black box” warning for risk of sudden death. However, in the subsequent FDA pediatric advisory panel review, which includ-

ed examination of available research data, public testimony, and expert opinion, it was determined that there was not sufficient risk to warrant a “black box.” Instead, a less severe warning was issued, along with a recommendation to improve the information made available regarding the benefits and risks of stimulants for patients and families.<sup>31</sup>

The labeling for dextroamphetamine was also recently updated, warning that use of the agent may exacerbate symptoms of behavior disturbance and thought disorder in patients with preexisting psychotic disorders, and that treatment-emergent psychotic or manic symptoms may result from use at usual doses of the agent in children and adolescents without a prior history of psychotic illness or mania.<sup>32</sup>

Another issue that has received recent media attention is the potential for acute overdose with stimulants, and the frequency with which stimulants are implicated in emergency department (ED) visits.<sup>33</sup> Data from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, which reviews clinical records from ED visits, found that there were 188 ED visits in 64 NEISS-CADES facilities attributable to stimulant-related adverse events, excluding intentional overdose, from August 1, 2003, to December 31, 2005; 26% were related to cardiovascular events (chest pain, stroke, syncope, tachycardia, hypertension, or dyspnea).<sup>33</sup> Based on the fact that 81 stimulant-related adverse events were reported to these facilities in 2004, Cohen et al estimated that in calendar year 2004, approximately 3075 patients presented nationally to EDs for stimulant-related adverse events.<sup>33</sup> The report also found that 36% of the patients who presented for an ED visit related to stimulant side effects ingested medications that were not prescribed to them.<sup>33</sup>

Stimulant overdose may occur in the context of individual hypersensitivity to these agents or as a result of accidental or deliberate overuse. The strong sympathomimetic activity (mimicking the effects of a stimulated sympathetic nervous system) of stimulants can produce a wide range of clinical manifestations—most notably irritability, agitation, euphoria, dizziness, restlessness, hallucinations, delusions, psychosis, lethargy, seizures, tremors, and hyperreflexia. Cardiovascular manifestations include tachycardia, hypertension, atrial and ventricular tachydysrhythmias, and chest pain. In addition, affected individuals may also experience mydriasis, diaphoresis, tachypnea, fever, vomiting, and abdominal pain. Hyperthermia, arrhythmias, and seizures may occur in severe intoxications.

**Atomoxetine.** The most commonly occurring adverse effects of atomoxetine include sedation, nausea and vomiting, decreased appetite, weight loss, and increase in pulse and blood pressure. Irritability and increased aggression can also be seen, particularly in individuals with comorbid mood or behavioral syndromes. Longitudinal data from industry-funded clinical trials suggest that the effects of atomoxetine on growth are relatively small in comparison to national norms, particularly after accounting for the initial effects of decreased appetite.<sup>34</sup> There were no changes in electrocardiogram (ECG) results observed in any of the clinical trials; however, use of atomoxetine is cautioned in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease, because it can increase blood pressure and heart rate.<sup>35,36</sup> There are 2 additional warnings in effect for atomoxetine, for liver toxicity and suicidal ideation. In 2004, postmarketing surveillance identified 2 cases (out of approximately 2 million exposures) of acute hepatotoxicity, which resulted in the FDA warning. Both were characterized by abdominal pain, jaundice, and substantially elevated liver function tests, which resolved with medication discontinua-

tion. One of these cases developed liver toxicity a second time after rechallenge with atomoxetine. A subsequent case report described 2 additional children with acute hepatitis after receiving atomoxetine, but neither met the criteria for medication-induced liver toxicity in the FDA analysis.<sup>37</sup> A “black box” warning was issued in 2005 regarding the potential for suicidal ideation. This action was based on the presence of increased risk of suicidal ideation occurring in the first few months of treatment in a review by the FDA of approximately 2200 children and adolescents in 12 short-term clinical trials (1357 treated with atomoxetine and 852 with placebo). The average risk of suicidal thinking was about 4 per 1000 patients treated with atomoxetine, compared to no events in placebo-treated patients. In one of the cases reviewed, there was a nonlethal medication overdose, deemed to represent a suicide attempt.<sup>38</sup> Atomoxetine is not a controlled substance, and results of a randomized, double-blind, crossover, likeability study of atomoxetine in a drug-abusing population indicate that it does not produce stimulant or euphoric properties.<sup>39</sup>

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### STIMULANT ABUSE, MISUSE, AND DIVERSION

Data from several studies indicate that a subgroup of youth who are prescribed stimulants misuse their medication or divert it to others. A school-based, self-administered Web survey of students in grades 6 through 11 (n=1536) from a Midwestern public school district found that students in higher grades were more likely to be approached by others for their stimulant medications.<sup>40</sup> Illicit use was reported by 4.5% of the overall sample. Of the students who reported prescription stimulant use, 23.3% reported being approached to sell, give, or trade their prescription drugs.<sup>40</sup> Findings from a longitudinal study indicate that 11% of youth with ADHD report selling their medications.<sup>41</sup> An additional 22%, all of whom had a comorbid diagnosis of conduct disorder or SUD, reported misusing their medications. A minority of subjects reported either escalation of their dose or concomitant use with alcohol and drugs.<sup>41</sup> It is thought that new extended-release formulations of stimulants have lower abuse liability. Data from the National Survey on Drug Use and Health in 2002 identified only 5 cases of misuse (not necessarily abuse) of osmotic release oral system-MPH (the only new long-acting formulation available at the time of the study) out of thousands of individuals screened.<sup>42</sup> However, given the subjective nature of this report, the authors urged caution in extrapolating from these data.

College students appear to be at particular risk for stimulant misuse and abuse. An online survey of 1025 students at a northeastern university found that 16% of the respondents reported abusing or misusing stimulant medication.<sup>43</sup> The preferred method was swallowing pills, but 40% used the medications intranasally. These results con-

cur with those from another report, which indicate that up to 70% of college students who abused MPH, but were not treated with the stimulant reported recreational MPH use, while 30% reported that they used MPH for study purposes.<sup>44</sup> Recreational users were more likely to report using MPH intranasally, as well as coadministering MPH with other substances. There has been some controversy as to whether MPH has abuse potential similar to that of other psychostimulants, since MPH is believed to be abused at rates much lower than those for other stimulants. However, a review of both human and nonhuman studies indicated that the physiologic properties of MPH and self-administration and/or preference are similar to those of other classes of stimulants.<sup>45</sup>

In contrast to diversion, frank abuse of stimulants and dependence generally occur in the context of other addiction disorders. As with all addiction disorders, stimulant abuse starts in early adolescence and quickly escalates. Although stimulants can be synthesized, drug diversion rather than manufacture is believed to be the primary source.

### MANAGING ADVERSE EFFECTS, ENHANCING SAFETY, AND MINIMIZING POTENTIAL FOR MISUSE AND ABUSE

In the management of ADHD, attention to the safety issues (Table), including adverse events and misuse/abuse, is critical. Both pharmacologic management and psychoeducation and counseling are integral to any ADHD management strategy for both children and adults.

**Medical Management Strategies.** As a general rule, both stimulants and nonstimulants should be initiated at a low dose and sequentially titrated upward to a maximally effective level. Higher starting doses may produce unpleasant sensations and compromise adherence to treatment. The American Academy of Child and Adolescent Psychiatry (AACAP) guidelines for the use of stimulants recommend that all children have a routine physical examination prior to starting the medication, including blood pressure and pulse, and should have their vital signs checked annually during routine physical examinations.<sup>46</sup> AACAP also recommends that adults treated with stimulants have their blood pressure and pulse checked on a quarterly basis.<sup>46</sup> Similar recommendations are offered regarding treatment with atomoxetine in the product insert.<sup>36</sup> The baseline clinical evaluation should also include a history and/or examination for tics and other neurologic conditions.

It is not essential to obtain ECGs routinely in initiating treatment, since even a normal ECG will not guarantee the absence of a structural cardiac defect. However, it may be important to consider obtaining further consultation, possibly including an ECG and echocardiogram, in high-risk cases such as patients with arrhythmias, hypertension, structural cardiac defects, or a family history of untoward cardiac events, both with stimulants and atomoxetine treatment. It is not currently recommended that liver function tests be routinely obtained before initiating atomoxetine treatment, due to the very low frequency of liver toxicity, and the fact that it could not be predicted from baseline laboratory indices. However, in patients at risk or in those who develop abdominal pain or jaundice in association with treatment, a thorough work-up is indicated. Height and weight should be monitored in patients on either stimulants or atomoxetine.

Patients should be examined frequently at the beginning of treatment, with particular attention to acute emotional changes, including increased sadness, tearfulness, irritability, anger, or euphoria.

Although the risk for actual suicidal behavior seems to be quite low, the potential for such behavior must be thoroughly discussed prior to treatment and monitored carefully. The recommended schedule for atomoxetine includes daily monitoring by parents and caretakers, and weekly or biweekly follow-up visits with the treating physician for the first few months after treatment initiation.<sup>36</sup>

In many cases, lowering the medication dose is the first step to minimizing the occurrence of adverse events. However, some adverse events are idiosyncratic and cannot be managed successfully by dose reduction. Problems in tolerability or suboptimal response should be managed by switching to a different agent.

**Psychoeducation and Counseling.** It is important to counsel patients and parents/guardians regarding the benefits and adverse effects of all psychopharmacologic treatments. Patients should understand why a medication is being given, and what positive and negative effects to look for. This will help to develop realistic expectations regarding treatment, and minimize anxiety should adverse effects develop. Patients should be advised that most side effects are usually transient, and do not limit long-term treatment. It is also essential to review the manner in which medications are to be stored and administered, and the importance of keeping medications away from young children. Finally, with adolescents and adults, it is important to directly discuss issues related to abuse and diversion. Because a large number of college students taking medication are likely to be approached regarding their medication, it is useful to anticipate and discuss this problem.

**Role of New and Emerging Treatments.** Concerns regarding stimulant misuse, diversion, and abuse have promoted the search for alternative agents that might offer comparable efficacy to existing treatments but have lower potential for abuse. As described above, atomoxetine is an FDA-approved treatment for ADHD in children and adults that is not scheduled by the Drug Enforcement Administration and therefore does not have abuse potential. Additionally, extended-release formulations of stimulants have become the standard of care due to their potential to increase adherence and improve tolerability. They may also possess a reduced abuse potential due to their delivery method, however there is currently a lack of clinical data to support this belief. A variety of other agents that potentially reduce risk of abuse or diversion are currently either available or in clinical trials.

The MPH transdermal system (MTS) was recently approved by the FDA for the treatment of ADHD in children 6 to 12 years old. Results of clinical trial data, which have been presented at national meetings, have found that MTS is statistically significantly superior to placebo ( $P < .0001$ ),<sup>47,48</sup> with efficacy ratings and tolerability comparable to oral MPH.<sup>49</sup> Mild skin irritation is the most frequently encountered adverse effect, which can generally be managed by rotating the site of administration or by application of topical ointments.<sup>50</sup> The primary advantage of the transdermal system is its long and flexible duration of action. Although full extent of duration of action is not known, the medication appears to last until 3 hours after the patch is removed and has been studied out to 12 hours.<sup>48</sup> Diversion is potentially minimized by the fact that once the patch is applied, it usually cannot be reapplied to another individual. It is apparently difficult to extract the medication from the patch, which could also minimize the potential for abuse.

Lisdexamfetamine (LDX, NRP104) is a novel, pharmacologically inactive prodrug of dextroamphetamine, which is currently under

**Table. Safety Considerations and Management Strategies for the Pharmacologic Treatment of ADHD**

Pharmacologic Treatment	Safety Considerations	Management Strategies
<i>Methylphenidate</i>		
Immediate release (dextro,levo-MPH, dextro-MPH)	<ul style="list-style-type: none"> <li>- Risk for tachycardia, arrhythmia, sudden death</li> <li>- Risk for growth suppression</li> <li>- Risk for tics</li> <li>- Potential for abuse and diversion</li> </ul>	<ul style="list-style-type: none"> <li>- Heart rate/BP monitoring, ECG and/or echocardiogram in high-risk cases; baseline ECG not recommended</li> <li>- Baseline height/weight with periodic monitoring; dietary consultation and/or nutritional supplementation</li> <li>- Decrease anxiety; monitor for appearance/exacerbation of tics; adjust dose; change medication</li> <li>- Counsel; nonstimulants; extended-release formulations of stimulants</li> </ul>
Extended release (MPH-LA, MPH-CD, OROS MPH, d-MPH XR)	<ul style="list-style-type: none"> <li>- Presumed same risk for cardiovascular adverse events as IR, but not studied</li> <li>- Risk for growth suppression and tics similar to or lower than IR formulations</li> <li>- Possible lower potential for abuse and diversion, but not well studied</li> </ul>	<ul style="list-style-type: none"> <li>- See recommendations for IR formulations</li> </ul>
Transdermal system	<ul style="list-style-type: none"> <li>- Risk for skin erythema</li> <li>- Risk for other side effects similar to oral MPH</li> <li>- Possible lower potential for abuse and diversion, but no data currently</li> </ul>	<ul style="list-style-type: none"> <li>- Observation; topical creams; rotation of administration site</li> </ul>
<i>Amphetamine</i>		
Immediate release (d-AMP, MAS)	<ul style="list-style-type: none"> <li>- Overall risks are similar to MPH, with some individual variations</li> </ul>	<ul style="list-style-type: none"> <li>- See recommendations for MPH</li> </ul>
Extended release (d-AMP, spansule, MAS-XR)	<ul style="list-style-type: none"> <li>- Presumed risks similar to IR formulation</li> <li>- Possible lower potential for abuse and diversion</li> </ul>	<ul style="list-style-type: none"> <li>- See recommendations for MPH</li> </ul>
<i>Atomoxetine</i>		
	<ul style="list-style-type: none"> <li>- Risk for hepatotoxicity</li> <li>- Possibility of suicidal thinking</li> <li>- Risk for sedation</li> <li>- Risk of tachycardia, arrhythmia, sudden death</li> <li>- No abuse potential</li> </ul>	<ul style="list-style-type: none"> <li>- Baseline history; follow clinically for abdominal pain/jaundice</li> <li>- Weekly monitoring for suicidal ideation/behavior when beginning treatment or changing dose</li> <li>- Dose bid, or bedtime dosing</li> <li>- Heart rate/BP monitoring; ECG and/or echocardiogram in high-risk cases; baseline ECG not recommended</li> </ul>
<i>Off-label/Investigational Treatments</i>		
Bupropion IR, Bupropion SR or XL	<ul style="list-style-type: none"> <li>- Decreased seizure threshold</li> <li>- Risk for suicidal thinking</li> <li>- No abuse potential</li> </ul>	<ul style="list-style-type: none"> <li>- Do not exceed 150 mg in a single dose for IR or 300 mg for XL</li> <li>- Weekly monitoring for mood changes when beginning treatment or changing dose</li> </ul>
Lisdexamfetamine	<ul style="list-style-type: none"> <li>- Risk for side effects generally similar to other stimulants</li> <li>- Abuse potential limited by requirement for GI metabolism</li> </ul>	<ul style="list-style-type: none"> <li>- See recommendations for MPH</li> </ul>
Guanfacine	<ul style="list-style-type: none"> <li>- Risk for hypotension, rebound hypertension</li> <li>- Risk for sedation</li> <li>- No abuse potential</li> </ul>	<ul style="list-style-type: none"> <li>- Heart rate and BP monitoring</li> <li>- Dose bid, or bedtime dosing</li> </ul>

MPH = methylphenidate; BP = blood pressure; ECG = electrocardiogram; LA = long acting; OROS = osmotic release oral system; XR = extended release; d-AMP = dextroamphetamine; MAS = mixed amphetamine salts; IR = immediate release; SR = sustained release; XL = extended release; GI = gastrointestinal.

review by the FDA. The dextroamphetamine molecule is gradually released after the prodrug is metabolized in the gastrointestinal (GI) tract, which makes tampering with the drug impractical.<sup>51,52</sup> Additionally, acute medication effects are limited until the medication passes through the GI tract, regardless of the route of administration. Furthermore, saturation of the metabolic system at excessively high dose levels may potentially limit the amount of drug that can be absorbed at any one time. Thus, LDX may have the potential to decrease frank abuse (although not diversion) of prescription stimulants and may offer some protection against accidental stimulant overdose. In 2 preliminary reports, LDX was found to have comparable efficacy to MAS-XR and to be significantly more effective than placebo in children with ADHD ( $P < .001$ ).<sup>51</sup> It was also well-tolerated with a side-effect profile similar to other stimulants.<sup>52</sup> Two recent studies reviewed the abuse potential of LDX in adults with a history of stimulant abuse (one study of intravenous LDX, and one of oral LDX).<sup>53,54</sup> In the study of intravenous LDX compared to dextroamphetamine and placebo, only 1 of 9 patients studied said they would choose to use LDX again for abuse purposes (6 chose dextroamphetamine).<sup>53</sup> In the study of oral LDX, LDX was found to have a slower release than amphetamine sulfate, with an attenuation of the maximum concentration at higher doses.<sup>54</sup> Both of these findings would seem to support the lower abuse liability of this agent, but more extensive testing is required.

**Off-Label Treatments.** Guanfacine (nonstimulant) is an alpha-2 adrenergic agonist, which has been used off-label for ADHD often in the context of comorbid tic or behavior disorders. The alpha-2 agonists have positive effects on hyperactive and impulsive behaviors. Although there is less certainty regarding their potential for treating inattention, initial reports with guanfacine have been promising.<sup>55</sup> Sedation is the most frequently encountered adverse effect, in addition to decreased pulse and blood pressure. A limitation of guanfacine is a relatively short duration, generally requiring multiple daily dosing. A long-acting formulation of guanfacine is currently in clinical trials, but is not yet available for use. Guanfacine is a nonstimu-

lant and thus does not possess abuse potential. However, more extensive study is required to better understand the safety profile of guanfacine and how it compares with currently approved treatments.

The nonstimulant, mixed catecholaminergic agonist bupropion is an antidepressant that is FDA approved for treatment of depression in adults. It is often used off-label to treat depression in children or adolescents, and to treat ADHD in both children and adults. Bupropion may be particularly useful in the treatment of adolescents with comorbid ADHD and depression<sup>56</sup> as well as comorbid ADHD and SUD/conduct disorder.<sup>57</sup> It has demonstrated efficacy as an alternative treatment for ADHD in adults, with a study finding bupropion to reduce ADHD symptoms by 42% at 6 weeks, compared to 24% with placebo.<sup>58</sup> The most common adverse events associated with bupropion include headache, nausea, dry mouth, constipation, and insomnia.<sup>59</sup> Bupropion is associated with a minimally increased risk for seizures at higher doses; therefore, it is recommended to not exceed 150 mg in a single immediate-release dose, or 300 mg for the extended-release formulation. Finally, although bupropion is structurally different from the selective serotonin reuptake inhibitor (SSRI) antidepressants, it now carries the same warning for suicidality in children and adolescents as the SSRIs and other classes of antidepressants.<sup>59</sup>

## CONCLUSION

There are a variety of stimulant and nonstimulant medications available for the treatment of ADHD. Given the high degree of impairment often associated with the disorder and the well-documented efficacy of approved ADHD treatments, the risk-benefit ratio strongly favors pharmacologic treatment. Nevertheless, because there is risk for adverse events, it is essential to be mindful of updated information on the various medications and strategies for their use. The emergence of new medication treatments may further extend our ability to provide effective and safe treatment to individuals with ADHD across the lifespan. Concomitant use of psychosocial treatment may both improve treatment response (in selected individuals) and assist in the management of risk. ■

## References

1. Jensen PS. Epidemiologic Research on ADHD: What We Know and What We Need to Learn. ADHD: A Public Health Perspective Conference. Available at: <http://www.cdc.gov/ncbddd/adhd/dadabepi.htm>. Accessed October 4, 2006.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*. Washington, DC: American Psychiatric Press; 2000.
3. Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. *Am J Psychiatry*. 2000;157(5):816-818.
4. Faraone SV, Biederman J, Doyle A, et al. Neuropsychological studies of late onset and subthreshold diagnoses of adult attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2006;July 27 (epub ahead of print).
5. 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.
6. Birnbaum HG, Kessler RC, Lowe SW, et al. Costs of attention deficit-hyperactivity disorder (ADHD) in the US: excess costs of persons with ADHD and their family members in 2000. *Curr Med Res Opin*. 2005;21(2):195-206.
7. Kessler RC, Adler L, Ames M, et al. The prevalence and effects of adult attention deficit/hyperactivity disorder on work performance in a nationally representative sample of workers. *J Occup Environ Med*. 2005;47(6):565-572.
8. Barkley RA, Fischer M, Edelbrock CS, Smallish L. The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study. *J Am Acad Child Adolesc Psychiatry*. 1990;29(4):546-557.
9. Fischer M, Barkley RA, Smallish L, Fletcher K. Hyperactive children as young adults: driving abilities, safe driving behavior, and adverse driving outcomes. *Accid Anal Prev*. 2006;Aug 16 (epub ahead of print).
10. Wilens TE. Attention-deficit/hyperactivity disorder and the substance use disorders: the nature of the relationship, subtypes at risk, and treatment issues. *Psychiatr Clin North Am*. 2004;27(2):283-301.
11. Raggi VL, Chronis AM. Interventions to address the academic impairment of children and adolescents with ADHD. *Clin Child Fam Psychol Rev*. 2006;Sep 14 (epub ahead of print).
12. Connor DF, Carlson GA, Chang KD, et al. Juvenile maladaptive aggression: a review of prevention, treatment, and service configuration and a proposed research agenda. *J Clin Psychiatry*. 2006;67(5):808-820.
13. Weiss MD, Gadow K, Wasdell MB. Effectiveness outcomes in attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2006;67(suppl 8):38-45.
14. Grcevich S, Rowane WA, Marcellino B, Sullivan-Hurst S. Retrospective comparison of Adderall and methylphenidate in the treatment of attention deficit hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2001;11(1):35-41.
15. Spenser T, Biederman J, Wilens T, Greene R. Attention-deficit hyperactivity disorder. In: Martin A, Scahill L, Charney DS, Leckman JF, eds. *Pediatric Psychopharmacology*. New York, NY: Oxford University Press; 2003:447-465.
16. Elia J. Stimulants and antidepressant pharmacokinetics in hyperactive children. *Psychopharmacol Bull*. 1991;27(4):411-415.

17. Spencer T, Biederman J, Wilens T, Harding M, O'Donnell D, Griffin S. Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle. *J Am Acad Child Adolesc Psychiatry*. 1996;35(4):409-432.
18. Michelson D, Allen AJ, Busner J, et al. Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: a randomized, placebo-controlled study. *Am J Psychiatry*. 2002;159(11):1896-1901.
19. Kelsey DK, Sumner CR, Casat CD, et al. Once-daily atomoxetine treatment for children with attention-deficit/hyperactivity disorder, including an assessment of evening and morning behavior: a double-blind, placebo-controlled trial. *Pediatrics*. 2004;114(1):e1-e8.
20. Michelson D, Adler L, Spencer T, et al. Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. *Biol Psychiatry*. 2003;53(2):112-120.
21. Gilmore A, Milne R. Methylphenidate in children with hyperactivity: review and cost-utility analysis. *Pharmacoeconom Drug Saf*. 2001;10:85-94.
22. Jensen PS, Garcia JA, Glied S, et al. Cost-effectiveness of ADHD treatments: findings from the multimodal treatment study of children with ADHD. *Am J Psychiatry*. 2005;162(9):1628-1636.
23. Treatment of ADHD in children with tics: a randomized controlled trial. *Neurology*. 2002;58(4):527-536.
24. Castellanos FX, Giedd JN, Elia J, et al. Controlled stimulant treatment of ADHD and comorbid Tourette's syndrome: effects of stimulant and dose. *J Am Acad Child Adolesc Psychiatry*. 1997;36(5):589-596.
25. Erenberg G. The relationship between tourette syndrome, attention deficit hyperactivity disorder, and stimulant medication: a critical review. *Semin Pediatr Neurol*. 2005;12(4):217-221.
26. Zachor DA, Roberts AW, Hodgins JB, Isaacs JS, Merrick J. Effects of long-term psychostimulant medication on growth of children with ADHD. *Res Dev Disabil*. 2006;27(2):162-174.
27. Mattes JA, Gittelman R. Growth of hyperactive children on maintenance regimen of methylphenidate. *Arch Gen Psychiatry*. 1983;40(3):317-321.
28. National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: changes in effectiveness and growth after the end of treatment. *Pediatrics*. 2004;113(4):762-769.
29. Biederman J, Spencer TJ, Wilens TE, Prince JB, Faraone SV. Treatment of ADHD with stimulant medications: response to Nissen Perspective in *The New England Journal of Medicine*. *J Am Acad Child Adolesc Psychiatry*. 2006;Jul 12 (epub ahead of print).
30. Nissen SE. ADHD drugs and cardiovascular risk. *N Engl J Med*. 2006;354(14):1445-1448.
31. Wilens TE, Prince JB, Spencer TJ, Biederman J. Stimulants and sudden death: what is a physician to do? *Pediatrics*. 2006;118(3):1215-1219.
32. Dextrotrine® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2006.
33. Cohen AL, Jhung MA, Budnitz DS. Stimulant medications and attention deficit-hyperactivity disorder. *N Engl J Med*. 2006;354(21):2294-2295.
34. Spencer TJ, Newcorn JH, Kratochvil CJ, Ruff D, Michelson D, Biederman J. Effects of atomoxetine on growth after 2-year treatment among pediatric patients with attention-deficit/hyperactivity disorder. *Pediatrics*. 2005;116(1):e74-e80.
35. Wernicke JF, Faries D, Girod D, et al. Cardiovascular effects of atomoxetine in children, adolescents, and adults. *Drug Saf*. 2003;26(10):729-740.
36. Strattera® [package insert]. Indianapolis, Ind: Eli Lilly & Company; 2006.
37. Lim JR, Faught PR, Chalasani NP, Molleston JP. Severe liver injury after initiating therapy with atomoxetine in two children. *J Pediatr*. 2006;148(6):831-834.
38. Food and Drug Administration. FDA Alert [9/2005]: Suicidal Thinking in Children and Adolescents. Available at: <http://www.fda.gov/cder/drug/infopage/atomoxetine/default.htm>. Accessed October 4, 2006.
39. Jasinski DR, Faries D, Moore RJ, Allen AJ. Abuse liability assessment of atomoxetine in a drug-abusing population. Poster presented at: XXIVth Collegium Internationale Psychopharmacologicum Congress; June 20-24, 2004; Paris, France.
40. McCabe SE, Teter CJ, Boyd CJ. The use, misuse and diversion of prescription stimulants among middle and high school students. *Subst Use Misuse*. 2004;39(7):1095-1116.
41. Wilens TE, Gignac M, Swezey A, Monuteaux MC, Biederman J. Characteristics of adolescents and young adults with ADHD who divert or misuse their prescribed medications. *J Am Acad Child Adolesc Psychiatry*. 2006;45(4):408-414.
42. Kroutil LA, Van Brunt DL, Herman-Stahl MA, Heller DC, Bray RM, Penne MA. Nonmedical use of prescription stimulants in the United States. *Drug Alcohol Depend*. 2006;84(2):135-143.
43. White BP, Becker-Blease KA, Grace-Bishop K. Stimulant medication use, misuse, and abuse in an undergraduate and graduate student sample. *J Am Coll Health*. 2006;54(5):261-268.
44. Barrett SP, Darredeau C, Bordy LE, Pihl RO. Characteristics of methylphenidate misuse in a university student sample. *Can J Psychiatry*. 2005;50(8):457-461.
45. Kollins SH, MacDonald EK, Rush CR. Assessing the abuse potential of methylphenidate in nonhuman and human subjects: a review. *Pharmacol Biochem Behav*. 2001;68(3):611-627.
46. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. *J Am Acad Child Adolesc Psychiatry*. 2002;41(2 suppl):S26-S49.
47. Turnbow JM, Wigal SB, Abikoff H, et al. Parent rated effects of transdermal methylphenidate in children with ADHD. Poster NR726 presented at: 159th Annual Meeting of the American Psychiatric Association; May 24, 2006; Toronto, Ontario, Canada.
48. Wigal SB, Turnbow JM, Abikoff H, et al. Attention and department ratings of transdermal methylphenidate in ADHD. Poster NR734 presented at: 159th Annual Meeting of the American Psychiatric Association; May 24, 2006; Toronto, Ontario, Canada.
49. Arnold LE, Patel A, Rugino T, et al. Abrupt conversion from oral methylphenidate to a transdermal patch. Poster NR623 presented at: 159th Annual Meeting of the American Psychiatric Association; May 24, 2006; Toronto, Ontario, Canada.
50. López FA, Findling RL, Squires L, Livolsi M. Skin response to methylphenidate transdermal system in pediatric subjects. Poster NR690 presented at: 159th Annual Meeting of the American Psychiatric Association; May 24, 2006; Toronto, Ontario, Canada.
51. Biederman J, Boellner SW, Childress A, et al. Improvements in symptoms of attention-deficit/hyperactivity disorder in school-aged children with lisdexamfetamine (NRP104) and mixed amphetamine salts, extended-release versus placebo. Poster presented at: 159th Annual Meeting of the American Psychiatric Association; May 24, 2006; Toronto, Ontario, Canada.
52. Biederman J, Krishnan S, Hodgkins P, Findling RL. Efficacy and safety of lisdexamfetamine (NRP104) in children aged 6 to 12 years with attention-deficit/hyperactivity disorder (ADHD). Poster NR632 presented at: 159th Annual Meeting of the American Psychiatric Association; May 24, 2006; Toronto, Ontario, Canada.
53. Jasinski DR, Krishnan S. Abuse liability of intravenous L-lysine-d-amphetamine (NRP104). Poster presented at: The College on Problems of Drug Dependence 68th Annual Meeting; June 20, 2006; Scottsdale, Arizona.
54. Krishnan S, Jasinski DR. Pharmacokinetics of oral NRP104/SPD489 (lisdexamfetamine dimesylate) versus d-amphetamine in healthy adults with a history of stimulant abuse. Poster presented at: The College on Problems of Drug Dependence 68th Annual Meeting; June 18, 2006; Scottsdale, Arizona.
55. Scahill L, Chappell PB, Kim YS, et al. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. *Am J Psychiatry*. 2001;158(7):1067-1074.
56. Daviss WB, Bentivoglio P, Racusin R, Brown KM, Bostic JQ, Wiley L. Bupropion sustained release in adolescents with comorbid attention-deficit/hyperactivity disorder and depression. *J Am Acad Child Adolesc Psychiatry*. 2001;40(3):307-314.
57. Riggs PD, Leon SL, Mikulich SK, Pottle LC. An open trial of bupropion for ADHD in adolescents with substance use disorders and conduct disorder. *J Am Acad Child Adolesc Psychiatry*. 1998;37(12):1271-1278.
58. Wilens TE, Spencer TJ, Biederman J, et al. A controlled clinical trial of bupropion for attention deficit hyperactivity disorder in adults. *Am J Psychiatry*. 2001;158(2):282-288.
59. Wellbutrin XL® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2006.

## Pediatric Commentary

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The public perception of stimulant medications has been affected by a combination of lack of information, abundance of misinformation, and unresolved research issues. This perception creates one of the greatest challenges faced by clinicians—educating parents and patients about attention-deficit/hyperactivity disorder (ADHD) amidst the profusion of information sources.

While the Internet in particular includes sources that generally provide accurate information (eg, the Web site for Children and Adults with Attention Deficit Disorders, [www.CHADD.org](http://www.CHADD.org)), there are an equal or perhaps greater number of inaccurate sites that disseminate false and potentially harmful information. Additionally, the popular media often highlights concerns about potential overdiagnosis of ADHD, leading parents to question the validity of the diagnosis in their child. One particular concern relates to the perception that schools are too quick to suggest ADHD as an explanation for a child's academic struggles.

This challenge is confounded by the fact that clinicians have great difficulty staying abreast of new information about ADHD treatment, including new treatment options and information about the safety of existing treatments. While news reports often exaggerate or sensationalize information about the safety of ADHD treatment, popular media may be a primary, initial source of information for practicing physicians. Clinicians need accu-

rate, concise information that they can then pass on to parents and patients in the context of regular follow-up visits. Reputable organizations such as the American Academy of Pediatrics serve a vitally important role in providing clinicians with succinct, accurate summaries of information about potential side effects of stimulant treatment that have emerged in the wake of the recent Food and Drug Administration review of stimulant risks.

Ideally, information should be provided to clinicians who can then, in turn, provide the information to their patients in the context of an established therapeutic relationship. Information must come from unbiased sources, such as respected individual experts or national organizations.

It is essential for physicians to provide accurate information about medical treatment, including frequency of visits and mechanisms for refilling prescriptions. Furthermore, it is critically important to identify the behaviors and symptoms that are targets for pharmacotherapy (ie, core ADHD symptoms) and to distinguish these from symptoms or behaviors that are not responsive to pharmacotherapy (eg, longstanding oppositional behavior, learning disability). Finally, assessment of treatment effectiveness requires that accurate feedback is collected from both the home and school settings, ideally in the form of ADHD-specific rating scales. ■

## Psychiatric Commentary

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Psychiatrists and pediatricians alike are in need of scientific information regarding the safety of medications in order to properly educate their patients regarding the issues related to attention-deficit/hyperactivity disorder (ADHD) treatment. Although many clinicians are very knowledgeable about and comfortable with prescribing stimulants for ADHD, they may have less experience in the clinical use of new and emerging treatment options that may reduce safety concerns in the treatment of ADHD. As more clinicians are provided with proper education as to the available ADHD treatments and their safety profiles, more parents of children with ADHD and patients with ADHD will come to understand the issues related to ADHD treatment.

Despite the widespread use of stimulants, and their documented generally good tolerability and efficacy in the treatment of ADHD and the advances in research into the safety of ADHD medications, there continues to be public concern about medication safety, one area in particular is stimulant misuse.

Parents may be reluctant to consent to stimulant use for their ADHD child because of fears that stimulants will sensitize their child to later substance abuse problems. Reviewing the available scientific information with parents on the abuse potential of clinically administered stimulants and reviewing the studies suggesting ADHD treatment reduces risk could be beneficial in this instance. Additionally, it is helpful for anxious parents to understand that effective nonstimulant medications with low abuse and misuse potential are available, and that long-acting and alternative stimulant delivery systems also may reduce potential risk for abuse.

The issue of abuse and misuse may also impact the decision to use stimulants on the part of clinicians, especially in situations in which the ADHD patient is already struggling with ongoing substance abuse issues or when the patient is routinely exposed to family or friends with ongoing substance abuse issues. In these situations, it is recommended to use alternative treatments for ADHD with lower abuse potential.

The following points should be made prior to initiation of ADHD pharmacologic treatment, and should be reinforced throughout the course of treatment:

- The probability of stimulant misuse and diversion appears to rise with the age of the ADHD patient.
- The probability of stimulant misuse and diversion rises with ADHD comorbidity, particularly conduct disorder and substance abuse disorders, and especially for ADHD adolescents and young adults with such comorbidities.
- Stimulant prescriptions should be kept in a safe place, and patients, particularly college students with ADHD, should be helped to develop effective assertiveness skills to cope with the possibility of being asked to sell or otherwise divert their prescription medication.
- The risk for substance abuse is conferred by the ADHD diagnosis itself, especially when accompanied by conduct disorder or a preexisting substance use disorder, and not by the ADHD treatment. In fact, treatment of ADHD reduces the risk for young adult substance abuse in ADHD patients. ■

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