

## Do stimulants for ADHD increase the risk of substance use disorders?



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### For some patients, stimulants might protect against future SUDs

Does prescribing stimulants to patients with attention-deficit/hyperactivity disorder (ADHD) increase their risk of future substance abuse? Because ADHD is a common pediatric condition with symptoms that often persist into adulthood, and stimulants are an efficacious first-line therapy, this possible association is a concern for psychiatrists whether they treat children or adults.

Some researchers have expressed concerns that stimulant exposure could predispose patients to future substance abuse.<sup>1</sup> Proponents of the biologic model of “kindling” hypothesize early exposure to stimulants could increase the risk of later substance use disorders (SUDs) by modifying or “priming” the brain, which then becomes more receptive to illicit drug exposure. Although there is some evidence that stimulant use does increase SUD risk, other evidence suggests stimulant use does not increase susceptibility to SUDs<sup>2,3</sup> and some studies have suggested stimulant use in ADHD patients may protect against SUDs.<sup>4,5</sup>

This article reviews shared characteristics of ADHD and SUDs and the latest research on the association between the clinical use of stimulants and later development of SUDs. We also offer clinical recommendations for assessing and treating ADHD and comorbid SUD.

### ADHD/SUD overlap

Compared with those without the disorder, patients with ADHD have a 6.2 times higher risk of developing an SUD.<sup>6</sup> Individuals with ADHD experience an earlier age of on-

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set and a longer duration of SUDs.<sup>7</sup> Several retrospective and prospective studies reveal ADHD is a risk factor for SUDs.<sup>8</sup> A longitudinal study that tracked teenage males with or without ADHD into young adulthood found SUDs were 4 times more common among those with ADHD.<sup>9</sup> Up to 45% of adults with ADHD have a history of alcohol abuse or dependence, and up to 30% have a history of illegal drug abuse or dependence.<sup>10</sup>

Conversely, an estimated 35% to 71% of alcohol abusers and 15% to 25% of substance-dependent patients have ADHD.<sup>11</sup> Adults with ADHD and comorbid SUD report earlier onset<sup>12</sup> and greater severity<sup>13</sup> of substance abuse than adults without ADHD. Patients with ADHD experience earlier onset and higher rates of tobacco smoking by mid-adolescence.<sup>14</sup>

### Developmental psychopathology.

Longitudinal studies have suggested certain psychopathologic characteristics of ADHD can predispose an individual to SUDs independent of stimulant exposure. For example, inattention, impulsivity, and hyperactivity predispose an individual to develop an SUD and also are core symptoms of ADHD.<sup>15</sup> Another study found impulsivity, impulsiveness, and difficulty sitting still at age 3 predicted alcohol abuse at age 21.<sup>16</sup> A different longitudinal study found novelty-seeking behavior (restlessness, running/jumping and not keeping still, being squirmy and fidgety) between age 6 to 10 predicted adolescent drug abuse and cigarette smoking.<sup>17</sup> Poor response inhibition is a key characteristic of ADHD and has been linked to adolescent drinking.<sup>18</sup>

ADHD may be an independent risk factor for SUD because a common neurobiologic psychopathology may predispose an individual to develop both conditions. The dopamine system has been implicated in SUD, and dysfunction in the dopaminergic circuits—mostly in basal and frontal cortex with consequent defects in executive function and reward system—also has been found in ADHD.<sup>19</sup> Cognitive dysfunction associated with ADHD may decrease a patient's ability to estimate the negative consequences of substance abuse and to delay immediate gratification from drug or alcohol use.

Table 1

## Risk factors for SUDs in patients with ADHD

Presence of comorbid conditions (ie, oppositional defiant disorder, conduct disorder, bipolar disorder, eating disorder)
White or Hispanic race
Partially treated or residual ADHD symptoms
Attending a competitive college program
College youth who had late onset of stimulant treatment
Member of a college sorority/fraternity
ADHD: attention-deficit/hyperactivity disorder; SUDs: substance use disorders
Source: Reference 26

ADHD patients are more vulnerable to SUDs if they have a comorbid condition, such as oppositional defiant disorder,<sup>13,20</sup> bipolar disorder,<sup>20,21</sup> or conduct disorder (CD).<sup>20,22</sup> Patients with ADHD and comorbid CD are estimated to be 8.8 times more likely to have an SUD before age 18 compared with those with ADHD alone.<sup>23</sup> Comorbid ADHD and CD may increase patients' predisposition to develop dependence on highly addictive drugs, such as cocaine or methamphetamine.<sup>24</sup> Impaired executive function, behavioral dyscontrol, impulsivity, and peer rejection are common in both ADHD and CD and may increase the risk of developing SUDs in individuals who have both conditions.<sup>25</sup> Other risk factors for SUDs in patients with ADHD are listed in *Table 1*.<sup>26</sup>

### Stimulants' affect on SUD risk

**Increased risk.** Limited studies suggest exposure to stimulants is a risk factor for developing SUDs. In a longitudinal study, Lambert et al<sup>27</sup> followed 218 patients with ADHD and 182 without ADHD into adulthood and found a linear trend between duration of stimulant treatment and prevalence of cocaine dependence. ADHD patients exposed to stimulants for >1 year had the highest prevalence of cocaine abuse (27%), compared with untreated subjects (15%), or those treated with stimulants for <1 year (18%). However, the study did not control for comorbid contributing factors, such as CD.

continued

## Clinical Point

A common neurobiologic psychopathology may predispose patients to develop ADHD and substance use disorders



## Stimulants and SUD risk

### Clinical Point

Two meta-analyses found children with ADHD treated with stimulants were less likely to develop SUDs than those not receiving stimulants

Table 2

### Minimizing SUD risk when treating ADHD patients with stimulants

Assess symptom burden and psychosocial impairment
Establish a treatment contract and boundaries at the onset of treatment, including your right to terminate treatment if you suspect stimulant misuse
Assess for comorbidities that may increase your patient's SUD risk (see <b>Table 1, page 21</b> )
Emphasize strict adherence to treatment recommendations
Involve the patient's family as much as possible
Obtain collateral information on the patient's history of ADHD-related symptoms from parents, siblings, significant others, etc.
Distinguish between patients with substance use vs an SUD or a history of an SUD
Obtain urine toxicology screening as appropriate
Carefully document dispensed stimulants—strength of medication, number of capsules, pills, patches, etc. Note date of dispensation and refill dates
Select delayed- or extended-release stimulant formulations
Consider prescribing nonstimulants if appropriate
Use rating scales such as Conners Adult ADHD Rating Scale to monitor ADHD symptom severity and response to treatment
Schedule frequent, face-to-face clinical monitoring visits
ADHD: attention-deficit/hyperactivity disorder; SUD: substance use disorder

**No change.** In a 10-year naturalistic study, Biederman et al<sup>28</sup> followed 109 children with ADHD age 7 to 12 into adulthood. These children had a developmental reading disorder but no other psychiatric comorbidities. When comparing patients who were treated with methylphenidate (n = 43) with those who did not receive stimulants (n = 66), Biederman et al found no significant difference between the 2 groups in the prevalence of SUD for any of the 7 drug categories studied.

**Decreased risk.** Two meta-analyses found children with ADHD who were treated with stimulants and followed until adolescence were 5.8 times less likely to develop

SUDs compared with those who did not receive stimulants.<sup>28,29</sup> This protective effect diminished when patients were followed into adulthood, but individuals treated with stimulants were 1.4 times less likely to develop SUDs than those not treated with stimulants.<sup>30</sup> In a prospective case-control, 5-year follow-up study of 114 patients with ADHD treated with stimulants, Wilens et al<sup>31</sup> found significant protective effects of stimulant treatment on the development of any SUD. They found no effects from time of onset or duration of stimulant therapy on subsequent risk of SUDs or cigarette smoking.

One possible explanation for stimulants' apparently reduced protective effect among adults is for patients with ADHD, stimulant use might delay but not prevent SUDs. It also is likely that by adulthood, loss of parental supervision leads to poor medication adherence and increased susceptibility to SUDs.<sup>30</sup>

Other studies have found exposure to stimulants may protect against SUDs. Katusic et al<sup>23</sup> reviewed medical records for documented SUDs in 295 adults with ADHD treated with stimulants and 84 who did not receive stimulants. They found 20% of patients who received stimulants had a documented SUD compared with 27% of those not treated with stimulants. Barkely et al<sup>32</sup> followed 98 stimulant-treated and 21 untreated ADHD patients with a mean age of 15 and 21, respectively. They found stimulant treatment did not increase the risk for substance use or abuse in either group.

### ADHD and stimulant abuse

The prevalence of stimulant misuse is as high as 9% in patients in grade school and high school and up to 35% in college-age individuals.<sup>33</sup> ADHD patients who misuse stimulants (eg, escalating dose without authorization) or skip stimulant doses to use illicit drugs or alcohol are more likely to sell their medication.<sup>34</sup> Immediate-release stimulant formulations are more liable to be abused than extended-release drugs because they achieve earlier peak drug concentrations and dopamine blockade, indicating rapid drug absorption and central drug activity. Close monitoring and use of extend-

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ed-release formulations are useful deterrents against stimulant abuse.

## Clinical recommendations

Detecting and treating SUDs in patients with ADHD can be challenging. Ideally, the best time to assess for ADHD symptoms is after a prolonged abstinence from any influencing substance. However, in most clinical situations this is not practical. A better approach is a longitudinal assessment for ADHD symptoms. Detecting evidence of early childhood onset of ADHD symptoms before the patient began using substances can be helpful in conducting a proper differential diagnosis. Assessing for symptoms of SUDs in early adolescence, along with serial assessment of ADHD symptoms, also can be helpful. Symptoms secondary to ADHD are likely to show a consistent pattern, whereas symptoms secondary to an SUD may be sporadic.

When assessing SUD risk, consider the patient's clinical condition, history of comorbidities that suggest SUDs, and overall functional status. Collateral information about the patient's behavior and substance abuse from family members is important. A history of CD, bipolar disorder, or antisocial personality disorder should raise concerns about potential future stimulant abuse or diversion. Close monitoring of patients suspected of having an SUD is essential to detect stimulant abuse or diversion, which often manifests as weight loss, requests for higher doses, requests to switch from long-acting or extended-release formulations to immediate-release formulations, and repeated and suspicious "lost prescriptions." Close observation for other subtle signs—such as changes in personality or mood and unexplained accidents or injuries—also may be needed.<sup>35</sup>

Challenges of treating ADHD and co-occurring SUD include poor medication adherence, need for a higher therapeutic stimulant dose, and difficulty in assessing the therapeutic benefit of pharmacotherapy in the presence of an SUD.<sup>36</sup> Treating ADHD comorbid with SUD requires a collaborative approach that involves a psychiatrist, family members, and a behavioral care provider in addition to frequent monitoring.<sup>34</sup>

## Related Resources

- Faraone SV, Wilens T. Does stimulant treatment lead to substance use disorders? *J Clin Psychiatry*. 2003;64(suppl 11):9-13.
- Upadhyaya HP, Rose K, Wang W, et al. Attention deficit hyperactivity disorder medication and substance use patterns among adolescents and young adults. *J Child Adolesc Psychopharmacol*. 2005;15:799-809.
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### Drug Brand Names

Atomoxetine • Strattera	Methylphenidate • Ritalin
Bupropion • Wellbutrin, Zyban	Modafinil • Provigil
Guanfacine • Tenex, Intuniv	Venlafaxine • Effexor

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In the absence of treatment guidelines for treating ADHD with comorbid SUDs, some clinicians prefer to stabilize the SUD before initiating stimulants. Others prefer to use nonstimulants (such as atomoxetine, guanfacine, bupropion, venlafaxine, tricyclic antidepressants, or modafinil) as a first-line treatment. However, nonstimulants have not demonstrated efficacy comparable to that of stimulants for ADHD.<sup>35</sup>

*Table 2* offers clinical recommendations to minimize the risk of SUDs when treating ADHD patients with stimulants. Long-acting stimulant formulations are preferred over short-acting medications because they are less likely to be abused. Psychosocial interventions for treating ADHD and co-occurring SUD disorder include cognitive-behavioral therapy with emphasis on structured skills training and cognitive remediation.

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## Clinical Point

**Nonstimulant medications may be an option for a patient with comorbid ADHD and SUDs**



## Stimulants and SUD risk

### Clinical Point

Extended-release stimulant formulations are less likely to be abused

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## Bottom Line

Evidence suggests when stimulants are initiated in children with attention-deficit/hyperactivity disorder (ADHD), they might protect against substance use disorders (SUDs), although this effect may diminish in adulthood. Treatment for ADHD patients with comorbid SUDs includes stimulant or nonstimulant medications.