Effect of Stimulant Medications for Attention-Deficit/Hyperactivity Disorder on Later Substance Use and the Potential for Stimulant Misuse, Abuse, and Diversion

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The objective of this article is to review literature about the effects of stimulant therapy on substance use disorders and the potential for misuse and diversion of stimulants. We reviewed published literature relevant to these objectives, and studies were selected if they were published or accepted for publication in peer-reviewed journals. Prospective longitudinal studies show that attention-deficit/hyperactivity disorder (ADHD) is a risk factor for subsequent substance use disorders. These studies also suggest that ADHD pharmacotherapy in childhood reduces the risk for substance use disorders. Misuse and diversion of prescribed stimulants occur among a minority of ADHD patients, especially those with conduct or substance use disorders. Long-acting stimulants may be less likely to be misused or diverted. *(J Clin Psychiatry 2007;68[suppl 11]:15–22)*

Although there is strong evidence that attention-deficit/hyperactivity disorder (ADHD) is associated with an increased risk for substance use disorders (SUDs),[1] we know relatively little about the causes of the association. In the drug abuse literature, self-medication for symptoms of anxiety, depression, and aggression has been suggested to be an important pathway to SUDs.[2] Notably, each of these symptoms is highly prevalent among ADHD patients. It is also possible that some ADHD patients use medications to control their ADHD symptoms. In support of this, recent work has shown that the majority of both ADHD and non-ADHD youth who continue to use substances of abuse do so to change their mood, to improve sleep, and for other reasons, but not for the substances' euphorigenic effects.[3] Although drug-abusing ADHD patients do not selectively abuse stimulants, they are heavy users of nicotine, which is known to have modest therapeutic effects on ADHD symptoms.[4] The symptoms of ADHD may directly increase the risk for SUD. For example, impulsivity could lead ADHD youth to try drugs they would not otherwise have tried. Also, chronic ADHD and its associated social and school failure could create demoralization, which in turn might fuel substance use.[5]

This article reviews literature on the effects of stimulant therapy on substance use disorders and the potential for misuse and diversion of stimulants. Studies were selected if they were published or accepted for publication in peer-reviewed journals.

IS ADHD A RISK FACTOR FOR SUBSTANCE USE DISORDERS?

Because the onset of ADHD is typically prior to the onset of SUDs, it is reasonable to suggest that ADHD is a risk factor for SUDs rather than that SUDs are a risk factor for ADHD. Fortunately, we do not need to rely on logic to assess the validity of this statement. Longitudinal studies of children with ADHD and children who develop SUD have addressed this issue from an empirical perspective.

Prospective studies of children with ADHD show that the groups with comorbid conduct or bipolar disorders are most likely to develop SUD.[6–8] For example, in 5- to

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8-year follow-up studies, more alcohol use was shown among hyperactive and largely conduct disordered adolescents with ADHD compared to non-ADHD controls.[9] Katusic et al.[10] followed 363 youth with ADHD and 726 matched controls from age 5 to mid-adolescence. ADHD predicted a 3-fold risk for SUD and an earlier onset of SUD. Molina and Pelham,[8] in a longitudinal study of 142 adolescents and 100 controls, also found that ADHD was associated with an increased risk for SUD.

If ADHD is a risk factor for SUD, then ADHD should be common among adolescents and young adults who later develop an SUD. This idea has been confirmed by longitudinal studies of children and adolescents with SUD.[11,12] For example, Kellam et al.[13] found that aggression, inattention, and impulsivity in the first grade predicted an increased risk for substance use in adolescence and young adulthood.

Although, as shown above, there is substantial evidence that patients with ADHD are at high risk for subsequent SUDs, comparatively little is known about the effects of ADHD on the developmental pathway from drug abuse to drug dependence and on pathways from use of licit substances (e.g., nicotine and alcohol) to illicit substances. Glantz and Pickens[14] suggested that there are specific developmental pathways that prime youth for a worsening course of substance use, abuse, and dependence.

Biederman et al.[15] evaluated the developmental pathways of SUD in adults with ADHD from 2 perspectives. Consistent with prior reports, adults with ADHD exhibited a 2-fold increased risk for SUDs. Among adult ADHD patients with alcohol use disorders, ADHD increased the risk for subsequent drug abuse or dependence. Also, compared with non-ADHD controls, ADHD patients were at increased risk for a chronic course of SUD. The effect of ADHD on these developmental pathways could not be accounted for by psychiatric comorbidity. Thus, in addition to predicting SUD, ADHD also predicts developmental sequences among different types of SUD. This work is particularly important because the discovery of developmental SUD pathways associated with ADHD might lead to improved primary prevention, which could reduce the risk for SUD in ADHD subjects. Such data could also be used to justify secondary prevention efforts to stop or mitigate transitions from milder to more severe SUDs.

DO STIMULANT MEDICATIONS CAUSE SUBSTANCE USE DISORDERS?

For decades, the stimulant medications methylphenidate, dextroamphetamine, and mixed amphetamine salts have been the most common drugs used in the treatment of ADHD. The stimulants increase the availability of synaptic dopamine[16,17]; reduce the overactivity, impulsivity, and inattention characteristic of patients with ADHD; and improve associated behaviors, including on-task behavior, academic performance, and social functioning.[18] Studies demonstrate robust effects in both children and adults,[19] and long-acting formulations extend the action of these medications over 8 to 12 hours to allow once-daily dosing.[20–22]

Although stimulants have been the mainstay of ADHD pharmacotherapy, several nonstimulant medications have also shown evidence of efficacy. These include tricyclic antidepressants,[23–25] bupropion,[26–28] modafinil,[29,30] monoamine oxidase inhibitors,[31,32] and atomoxetine.[33–35]

A recent meta-analysis of ADHD efficacy outcomes found that efficacy effect sizes for stimulants were significantly greater than those for other medications, even after correcting for study design features that might have confounded the results.[36–38] Although head-to-head trials are needed to make definitive statements about efficacy differences, these results were compatible with the efficacy differences between atomoxetine and mixed amphetamine salts reported by Wigal et al.[39,40] and the conclusions of another review limited to a smaller subset of studies that excluded short-acting stimulants.[41]

Although stimulants are highly efficacious for ADHD, their use in young children with ADHD and ADHD patients with SUDs raises concerns about their effects on increasing de novo SUD risk and exacerbating SUD and about the inherent risk of abuse of the medications themselves. In addressing the concern about stimulant treatment of ADHD increasing the risk for SUDs, prospective, naturalistic follow-up studies have provided useful information by tracking the development of SUD in ADHD patients who had and had not been treated with stimulants. These studies have produced what appear to be contradictory results. Some suggest that the stimulant treatment of ADHD is a risk factor for SUDs, others suggest it has no effect, and some find it protects youth with ADHD against subsequent substance use. To make sense of these contradictory findings, Wilens et al.[42,43] conducted a meta-analysis, which identified 2 studies that followed youth with ADHD into adolescence and 4 that followed youth with ADHD into adulthood. The analysis showed that stimulant-treated youth with ADHD were half as likely to develop SUD as those that had not been treated with pharmacotherapy. The magnitude of risk reduction was such that the ultimate risk of SUD in the stimulant-treated group was similar to the risk in individuals without ADHD. These data clearly show that, rather than causing SUD, stimulant treatment of ADHD protects youth with ADHD from developing SUD.

An intriguing finding from the Wilens et al.[42,43] meta-analysis of longitudinal studies of ADHD is that the effects of stimulant therapy on subsequent SUDs differed in adolescence and adulthood. Studies reporting follow-up into adolescence showed a strong protective effect on the development of SUD: stimulant-treated subjects were 5.8 times less likely to develop SUDs than untreated subjects. In contrast, for studies that followed children into adult-

hood, stimulant-treated subjects were only 1.4 times less likely to develop SUDs than untreated subjects. Evidence for lack of a protective effect in adulthood was also reported by Faraone et al.[44] They used a retrospective strategy to assess the impact that prior pharmacotherapy for ADHD had on substance use disorders in adulthood in 206 adults with ADHD. Their results showed a high degree of consistency across substances of abuse in finding no link between prior pharmacotherapy for ADHD and subsequent substance use, abuse, or dependence. They could not, however, show a protective effect of stimulants on subsequent SUDs. In addition to the nearly complete lack of statistically significant difference among treatment groups, the nonsignificant differences were very small and not suggestive of deleterious effects of prior treatment.

We can only speculate as to why the protective effect of stimulants is not evident in adulthood. One possibility is that, due to parental monitoring, treatment compliance and hence efficacy is greater for youth than adults. Moreover, the exposure to stimulants was more recent for adolescents compared to adults.[44] Another possibility is that, because adolescents have not fully passed through the age of risk to develop SUD, the protective effect of stimulants may be to delay rather than stop subsequent SUDs. More research is needed to understand this developmental effect of stimulants on substance use and to further clarify protective mechanisms.

Why does stimulant therapy protect against SUDs? One possibility is that the effect is indirect. Some ADHD symptoms may increase the risk for using substances. If so, reduction of those symptoms would protect youth from SUD. For example, impulsivity could lead ADHD youth to try drugs they would not otherwise have tried. Also, chronic ADHD and its associated social and school failure could create demoralization, which in turn might fuel substance use. Another possibility is that, compared with other ADHD youth, ADHD youth who are treated with stimulants have parents who are more concerned and provide more supervision. Another possibility is that stimulant treatment directly affects the reward circuits of the brain to reduce the risk for SUD. This idea is intriguing but must remain speculative in the absence of studies addressing that issue.

We have suggested that stimulant therapy reduces classic symptoms associated with ADHD such as poor self-esteem, demoralization, and school failure and that, accordingly, such treatment reduces the risk of SUD.[42] It is also possible that stimulants act directly on the reward system to reduce the reward value of drugs, which in turn makes them less susceptible to abuse drugs. This latter hypothesis has seen some support in studies of an ADHD animal model known as the spontaneously hypertensive rat. The spontaneously hypertensive rat is both a good behavioral model of ADHD and an accurate neurochemical model of the disorder.[45] Prior work has successfully used the spontaneously hypertensive rat to show that repeated exposure to methylphenidate during the pubertal period diminishes subsequent sensitivity to the incentive properties of cocaine.[46] If this work generalizes to humans, it could be that the timing of stimulant exposure is a critical factor in predicting protective effects on SUDs and how those effects unfold through adolescence and adulthood.

Regardless of the mechanisms involved, the current literature provides additional assurance to clinicians that the use of stimulant therapy will not increase subsequent risks for SUDs. This is especially important considering that high efficacy of stimulant medications compared with alternatives.[36,38]

ARE STIMULANT MEDICATIONS MISUSED, ABUSED, OR DIVERTED BY ADHD PATIENTS?

Over the last decade, reports of illicit use of stimulant medications have emerged. A survey study completed in Wisconsin[47] evaluated whether children had been approached to give or sell their prescribed medication. While the actual rates of diversion were not reported, the authors reported that 16% of children had been approached to sell or give away their medication.[47] Marsh et al.,[48] in a retrospective review of adolescents' medical charts, reported an increase in methylphenidate misuse, but only among the Caucasian sample. Along the same lines, another larger survey study completed by Poulin[49] in New Brunswick, Nova Scotia, Canada, in 13,549 students (grades 7–12) indicated that 8.5% of the sample had used nonprescribed stimulants in the year prior to the survey. Of those students who were receiving prescribed stimulants, 15% had given their medications to others while 7% had sold their medication to other students. Compared to those receiving prescribed stimulants, students using nonprescribed stimulants had much higher rates of use of cigarettes, marijuana, and alcohol[49]—similar to data indicating that adults abusing stimulants typically did so in the context of a myriad of other SUDs.[50]

Low and Gendaszek[51] recently showed in a survey study of 150 undergraduate students at Bates College that 4% had misused amphetamine compounds, 7% methylphenidate, and 24% both (total of 36%). In contrast, 34% of those undergraduates surveyed reported using nonprescribed stimulants including either 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy; 15%) or cocaine (3%) or both (17%). Of interest, the majority of undergraduates using nonprescribed stimulants noted using them primarily to enhance academic functioning.[51] Systematic data are lacking on the diversion and misuse of stimulant agents in adults with ADHD.

Teter et al.[52] studied the prevalence of methylphenidate misuse among 2250 undergraduates using an Internet survey. Of these students, 3% reported past-year methylphenidate misuse. Compared with prescription stimulant

users who did not misuse their medication, those who misused methylphenidate were more likely to use other substances and to report adverse consequences from substance use. There were no gender differences.

McCabe et al.[53] studied the misuse and diversion of prescribed stimulant medication among 1536 middle and high school students. Misuse or diversion was reported by 4.5% of the overall sample. Among students reporting prescription stimulant use, 23% had been asked by peers to sell, give, or trade their prescribed stimulant medication. Misuse and diversion were lower among African American students and among students planning to attend college.

The same research group completed 2 studies of the misuse and diversion of stimulants among undergraduate college students.[54,55] The first study[54] selected a nationally representative sample of 10,904 randomly selected college students from 4-year colleges in the United States. The lifetime prevalence of nonmedical stimulant use was 6.9%. The prevalence during the prior year was 4.1%, and the prevalence during the prior month was 2.1%. Stimulant misuse was higher among subjects who were male, were white, were members of fraternities and sororities, and had lower grades. Misuse was more common at colleges located in the Northeast and among colleges with highly competitive admissions standards. Students who misused stimulants were also at greater risk for using alcohol, cigarettes, marijuana, Ecstasy, and cocaine. They were also more likely to engage in risky behaviors.

The second college study[55] by this group was based on a self-administered Internet survey completed by a random sample of 9161 undergraduate students attending a large public midwestern university. The lifetime prevalence of stimulant misuse was 8.1%; the 1-year prevalence was 5.4%. Subjects who misused stimulants reported acquiring them from friends and peers. As the researchers found in their prior survey, stimulant misuse was more common among subjects who were male, were white, were a member of a social fraternity or sorority, and had lower grades. Subjects who had been prescribed stimulants for ADHD in elementary school were not at higher risk for stimulant misuse or other drug use during college compared with subjects who were never prescribed stimulant medication.

Using the same study sample, Teter et al.[56] surveyed motives for stimulant misuse. The most common reasons given were to (1) help with concentration, (2) increase alertness, and (3) provide a high. Men were more likely than women to report stimulant misuse, but there were no gender differences in motives. Stimulant misuse and the number of reasons for misuse were associated with elevated rates of substance use.

Teter et al.[57] reported data from a random sample of 4580 college students who had completed an Internet survey. They found an 8.3% lifetime prevalence of stimulant misuse and a 5.9% past-year prevalence of stimulant misuse. Among those that misused stimulants in the past year, three fourths misused an amphetamine agent and one fourth misused methylphenidate. Past-year misuse of stimulants was more common among Caucasians and Hispanics compared with African Americans and Asians. The most common reasons for misuse were to help with concentration, to help with studying, and to increase alertness. Other reasons were getting high and experimentation (29.9%). Nearly all subjects who misused stimulants did so orally, and 38% also reported intranasal use.

White et al.[58] surveyed 1025 college students. Of these, 16% had misused stimulant medication. Nearly all cases of misuse involved methylphenidate and did not differ by gender. Most subjects who misused stimulant medication did so orally; 40% reported intranasal use. Similar to Teter et al.,[56] the main reasons for misuse were improving attention, partying, reducing hyperactivity, and improving grades.

Wilens et al.[59] studied the misuse and diversion of stimulants in a 10-year longitudinal study of boys with ADHD. Of 98 subjects receiving psychotropic medications, 56% were ADHD subjects, and 44% were controls receiving medications for other purposes. Eleven percent of the ADHD group reported selling their medications compared with no subjects in the control group. Twenty-two percent of the ADHD group misused their medications compared with 5% of the control group. All of the misuse could be attributed to subjects having conduct or substance use disorders and was with immediate-release and not extended-release stimulants. The authors concluded that the majority of ADHD patients, particularly those without conduct or substance use disorders, used their medications appropriately. They further emphasized the need to monitor medication use in ADHD individuals with conduct and/or substance use disorders and to carefully select agents with a low likelihood of diversion or misuse in this group.

Kroutil et al.[60] examined misuse of stimulants using data from the National Survey on Drug Use and Health. The majority of past-year misuse involved drugs other than methamphetamine. Past-year misuse was more prevalent among persons aged 12 to 25 compared with older adults. It was also greater among Caucasians compared with other ethnicities. Prevalence did not differ between large metropolitan areas and less-populated areas. About 13% of past-year stimulant misusers met the survey criteria for dependence or abuse.

One group in which the bulk of studies indicate concern for misuse and diversion is those with SUD.[52–57,59] However, open and controlled studies of adolescents and adults with ADHD and SUD do not indicate any evidence of (1) abuse of the stimulant or nonstimulant medication, (2) diversion of the stimulants, (3) worsening of the underlying SUD, or (4) drug interaction between ADHD medications and substances of abuse.[61] It remains to be seen if higher rates of stimulant abuse occur in clinical practice of the treatment of ADHD in adolescents and adults with SUD.

Table 1. Risk Factors for Stimulant Misuse and Diversion

Conduct disorder
Substance use disorder
Use of immediate-release stimulant
Male gender
Caucasian race
Member of fraternity or sorority

Although all of the studies reviewed show evidence for the misuse and diversion of stimulants, clinicians should be aware that not all stimulant-treated ADHD patients divert or misuse their medications. Table 1 summarizes risk factors for misuse and diversion. When working with high-risk patients, clinicians should discuss the potential for misuse and diversion of stimulants either with parents or, for adolescents and adults, with the patients themselves. Clinicians need to be particularly vigilant in discussing and monitoring adolescents and young adults with ADHD and conduct or substance use disorders for the appropriate use of medications. Such monitoring may include questioning, specifically about appropriate use or misuse of the medication, as well as potential diversion of the medicine, and observing that pill counts are accurate. For patients who have many risk factors, particularly conduct disorder and SUDs, use of a nonstimulant alternative should be considered.

ARE LONG-ACTING STIMULANTS LESS LIKELY TO BE MISUSED OR DIVERTED COMPARED WITH IMMEDIATE-RELEASE STIMULANTS?

There are both empirical and theoretical reasons to suggest that long-acting stimulants are less likely to be misused or diverted compared with immediate release stimulants. In Wilens and colleagues'[59] work, all of the medications misused or diverted were the immediate-release preparations of stimulants. Similarly, Jaffe[62] observed that extended-release psychostimulants were unsuccessfully misused in a group of adolescents with ADHD and SUD. Kollins et al.[63] compared the acute behavioral effects of orally administered sustained-release methylphenidate, immediate-release methylphenidate, and placebo in 10 healthy volunteers. The immediate-release formulation produced stimulant-like drug effects, such as increased ratings of "good effects," that were dose dependent. In contrast, the sustained-release formulation produced only transient effects on these measures. The authors concluded that the abuse potential of immediate-release methylphenidate may be greater than that of sustained-release methylphenidate.

That immediate-release compared to extended-release stimulants may have more liability for misuse or diversion in naturalistic samples parallels basic research highlighting the vital importance on route of administration on the brain (striatal) kinetics and euphorigenic properties of the agent.[64] For example, differences in the pharmacokinetics and euphorigenic properties of methylphenidate exist for intranasal,[65] oral,[64,66] and intravenous[64,66] administration. Additionally, recent research indicates important differences in brain imaging/dopamine transporter occupancies when comparing extended- and immediate-release methylphenidate.[67,68] Compared to 40 mg of immediate-release methylphenidate, 90 mg of osmotic release oral system (OROS) methylphenidate had a less steep dopamine transporter occupancy curve, lower saturation of the dopamine transporter, and a prolonged time of dopamine transporter occupancy. Similarly, in these blinded, non–drug-abusing subjects without ADHD, lower "feeling the effect" and "liking the effect" of the drug was noted with OROS methylphenidate compared to immediate-release methylphenidate. Given the difficulties in extracting methylphenidate or amphetamine from beaded or osmotic extended-release preparations, these stimulant formulations may be less frequently misused and abused than immediate-release forms. Not only do the osmotic/beaded systems prevent the immediate extraction of the active compound, but the mechanisms of release may translate into different effects at the dopamine transporter,[67,68] the major receptor affected by this class of agents.[69–71]

To better understand how the time course of methylphenidate administration affects clinical outcomes, several groups have examined the possibility that methylphenidate leads to tachyphylaxis or acute tolerance. Due to tachyphylaxis, methylphenidate concentrations measured soon after an initial dose cause a greater pharmacodynamic effect than concentrations present at a later time. This manifests itself in a clockwise hysteresis in the plasma concentration-effect relationship. This acute tolerance shows no carryover to the next day.

In vivo neuroimaging studies by Volkow et al.[70] showed that methylphenidate exerts its pharmacodynamic effects by binding to dopamine transporters, most of which are located in striatum. This increases dopamine levels[64] and is believed to counteract the excess of dopamine transporter activity observed in some neuroimaging studies of ADHD patients.[72,73]

In 2 studies, Aoyama et al.[74,75] studied the effects of methylphenidate on dopamine concentrations in rat striatum following intravenous administration of methylphenidate. Both studies reported clockwise hysteresis for the effects of methylphenidate on dopamine release in striatum. At early time points, increasing methylphenidate in striatum led to higher dopamine levels, but at later time points the same methylphenidate concentrations led to lower dopamine levels.

Volkow et al.[76] used positron emission tomography to study the pharmacokinetics and pharmacodynamics of intravenous methylphenidate in the human brain. This work tracked the distribution of radioactively labeled methylphenidate ([11C]methylphenidate) in the brain over time. The uptake of [11C]methylphenidate in striatum was very

fast, with peak concentrations occurring within 10 minutes. Clearance was relatively slow (T1/2 = 90 minutes). While they were being imaged, subjects rated the degree to which they felt "high," a "rush," or "restlessness." These ratings were positively correlated with the initial uptake in striatum, but, consistent with tachyphylaxis, the ratings subsequently returned to baseline even though striatum showed the presence of substantial concentrations of methylphenidate.[76] The authors concluded that there was rapid tolerance to the behavioral effects of intravenous methylphenidate. Hence, a picture is emerging in which the method of administration and the mechanism of release of the stimulants are related to the abuse liability of the stimulants. While intravenous and intranasal stimulant administration pose the highest risk for abuse, oral administration of extended-release stimulants appears to be associated with the lowest abuse liability.

A new long-acting stimulant approved in February of 2007 by the U.S. Food and Drug Administration is lisdexamfetamine dimesylate. Lisdexamfetamine is a prodrug in which *d*-amphetamine is covalently bonded to L-lysine, an essential amino acid. Following rate-limiting hydrolysis of the bond, the pharmacologically active *d*-amphetamine molecule is released. This technology leads to several advantages as regards abusability. When intranasally or intravenously administered to rats,[77] lisdexamfetamine leads to minimal blood levels of *d*-amphetamine. When lisdexamfetamine is given orally to humans, the rise in blood level is less steep than the rise for immediate-release *d*-amphetamine,[78,79] which may explain why lisdexamfetamine leads to lower likeability scores than *d*-amphetamine at equivalent base *d*-amphetamine doses.[76]

WHAT CAUSES THE ASSOCIATION BETWEEN ADHD AND SUBSTANCE USE DISORDERS?

Our review has shown that ADHD appears to be a risk factor for SUDs and that this link cannot be accounted for by prior use of stimulant medication. What, then, explains the link between ADHD and SUD? As noted above, one simple explanation is that ADHD symptoms, particularly impulsivity, lead to greater SUD exposure and use, which would increase the risk for SUDs. Self-medication remains a major consideration. Wilens et al.[3] examined if ADHD individuals were "self-medicating" with cigarettes, alcohol, or other substances of abuse. As part of a 5- and 10-year longitudinal controlled study in 90 subjects with ADHD and 96 controls (mean ± SD age; 19.7 ± 2.7 and 19.2 ± 2.7 years; 58% male and 52% male; respectively, p values NS), they examined responses on the Drug Use Severity Index for evidence of self-medication. Across all groups, 36% of subjects reported using for self-medication to aid sleep (3%) or change mood (33%), 25% to get high, and 39% had other or unknown motivation for use. There were no differences between ADHD and controls in their motivation to use the various substances. Interestingly, ADHD symptoms did not differ between ADHD individuals who self-medicated and those who used medications to get high. Hence, evidence of self-medication clearly exists, although such evidence did not differ by ADHD status.

It is also possible that ADHD and SUDs share biological risk factors. We know from family studies that there is a strong familial association between ADHD and SUD,[80,81] which suggests that the 2 disorders may share genetic or other familial risk factors. The offspring of substance-abusing parents are at increased risk not only for SUDs, but also for inattention, impulsivity, aggressiveness, hyperactivity, and ADHD.[82] Wilens et al.[83] studied the children of opioid-dependent parents. These children had Child Behavior Checklist scores consistent with the diagnoses of ADHD and conduct disorder. Earls et al.[84] found an elevated risk for ADHD in the children of alcoholics but not a matched control group. Roizen et al.[85] compared children with developmental disabilities to those with ADHD. The ADHD youth were significantly more likely to have a parent with alcoholism or other drug abuse, ADHD, learning disabilities, depression, and delinquency. Two community-based epidemiologic studies are consistent with these findings. Zucker and Noll[86] and Rubio-Stipec et al.[87] found more evidence of ADHD symptoms in children of parents with an SUD compared to parents without an SUD. A high-risk study found that the risk for ADHD in children of parents with SUD was elevated relative to controls.[88]

Family studies of ADHD also document a familial association between ADHD and SUDs, especially in the family members of children with ADHD. Both Morrison and Stewart[89] and Cantwell[90] reported elevated rates of substance use in parents and second-degree relatives of children with ADHD. These findings were consistent with a subsequent report in which higher rates of alcoholism were found in the adult siblings of adult ADHD probands compared to the siblings of psychiatric controls.[91] Similar findings have been seen in 2 large double-blind family-genetic studies of ADHD including female and male probands[81,92] in which we reported higher rates of SUD in the relatives of ADHD probands. Taken together, these findings suggest that ADHD and SUDs may share familial causes. This idea is consistent with our preliminary work showing a risk for SUDs that was similar among the relatives of ADHD probands with and without SUDs and that was significantly higher than the risk to relatives of normal control children.[93]

In summary, ADHD is a risk factor for SUD, and that risk is higher in those with comorbid mood and conduct disorders. Self-medication, family history, and environmental mediators appear to influence that risk in youth with ADHD. Treatment of ADHD appears to reduce the risk for SUD. While most patients with ADHD use their medication appropriately, a growing literature indicates substantial misuse, abuse, and diversion of the medication

to non-ADHD subjects, particularly older adolescents and young adults. Recent findings derived from basic and clinical work suggest that extended-release preparations of stimulants may result in less abuse and diversion.

Drug names: atomoxetine (Strattera), bupropion (Wellbutrin and others), lisdexamfetamine (Vyvanse), methylphenidate (Daytrana and others), modafinil (Provigil).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, bupropion and modafinil are not approved by the U.S. Food and Drug Administration for the treatment of attention-deficit/hyperactivity disorder.

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