

Impact of ADHD and Its Treatment on Substance Abuse in Adults

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Attention-deficit/hyperactivity disorder (ADHD) is a risk factor for substance abuse in adults. Additional psychiatric comorbidity increases this risk. ADHD is associated with different characteristics of substance abuse: substance abuse transitions more rapidly to dependence, and lasts longer in adults with ADHD than those without ADHD. Self-medication may be a factor in the high rate of substance abuse in adults with ADHD. While previous concerns arose whether stimulant therapy would increase the ultimate risk for substance abuse, recent studies have indicated that pharmacologic treatment appears to reduce the risk of substance abuse in individuals with ADHD. When treating adults with ADHD and substance abuse, clinicians should assess the relative severity of the substance abuse, the symptoms of ADHD, and any other comorbid disorders. Generally, stabilizing or addressing the substance abuse should be the first priority when treating an adult with substance abuse and ADHD. Treatment for adults with ADHD and substance abuse should include a combination of addiction treatment/psychotherapy and pharmacotherapy. The clinician should begin pharmacotherapy with medications that have little likelihood of diversion or low liability, such as bupropion and atomoxetine, and, if necessary, progress to the stimulants. Careful monitoring of patients during treatment is necessary to ensure compliance with the treatment plan.

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PREVALENCE

The prevalence of attention-deficit/hyperactivity disorder (ADHD) in school-aged children is approximately 6% to 9%.¹ Data on prevalence in adults are limited, but ADHD may affect up to 5% of adults.² Substance use disorders (SUD; denoting drug or alcohol abuse or dependence) affect up to 27% of the adult population.³ There is a bidirectional overlap between ADHD and substance abuse. The study of comorbidity between SUD and ADHD is relevant to both research and clinical practice in developmental pediatrics, psychology, and psychiatry, with implications for diagnosis, prognosis, treatment, and health care delivery. The identification of specific risk factors of SUD within ADHD may permit more targeted treatments for both disorders at earlier stages of their expression, po-

tentially dampening the morbidity, disability, and poor long-term prognosis in adolescents and adults with this comorbidity.^{4,5} In the following sections, we will review data relevant to understanding the overlap between ADHD and SUD with an emphasis on ADHD as a risk factor for substance abuse.

Although not the topic of this report, higher rates of ADHD have been reported in adolescents and adults with SUD relative to controls.^{6,7} It is estimated that between 15% to 25% of adults with a lifetime history of a SUD may have ADHD.⁷ In adolescents, there have been 3 studies assessing ADHD and other disorders in substance abusing groups,^{8,9} including juvenile offenders,¹⁰ demonstrating an overrepresentation of ADHD (along with both mood and conduct disorders) in adolescents with conduct disorder. Studies in adults with SUD are similar to those in adolescents. When both alcohol and drug addiction are included, from 15% to 25% of adult addicts and alcoholics currently have ADHD.^{11–13}

For example, Schubiner et al.¹¹ found that 24% of 201 inpatients in a substance abuse treatment facility had ADHD, and that two thirds also had conduct disorder. The importance of careful diagnosis, however, has been demonstrated by Levin et al.,¹² who found that while 10% of cocaine-dependent adults met strict criteria for ADHD (clear childhood and adult ADHD), another 11% were found to have ADHD symptoms only as adults.

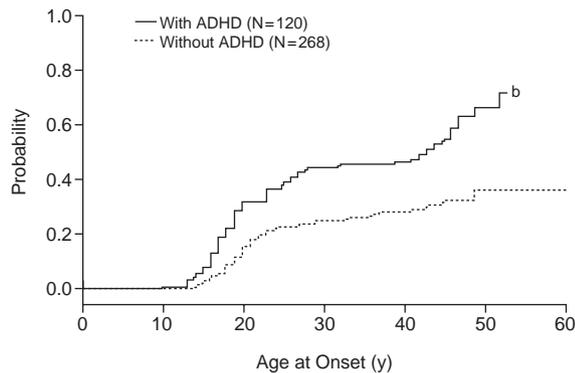
Conversely, ADHD is a risk factor for later SUD. Biederman et al.² compared 120 adults with ADHD to 268

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Figure 1. Age at Onset of Substance Abuse in Individuals With Attention-Deficit/Hyperactivity Disorder^a



^aReprinted with permission from Wilens et al.¹⁶

^b $p \leq .05$ vs. adults without ADHD by Cox proportional hazards model.

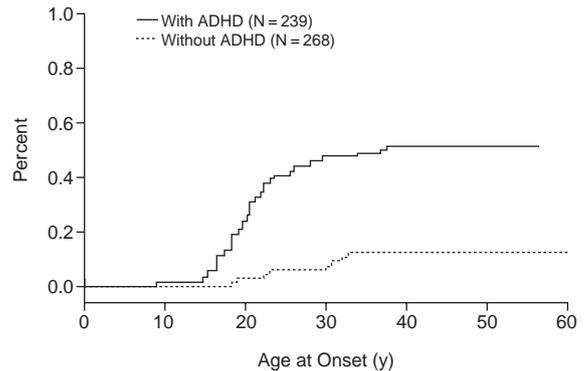
adults without ADHD (mean age of 40 years) and found a lifetime rate of a SUD of 52% in adults with ADHD and 27% in adults without ADHD. Similar findings were reported earlier by Shekim and colleagues.¹⁴

COURSE OF SUBSTANCE USE DISORDERS IN ADULTS WITH ADHD

There appear to be important differences in the characteristics of SUD in adults with ADHD relative to adults without ADHD. Adults with ADHD begin to abuse substances at an earlier age and abuse substances more often than their peers without ADHD. Their substance abuse continues longer, and they move from alcohol abuse to substance abuse more rapidly than those without ADHD.

While adolescents with and without ADHD have the same rate of substance abuse, such is not the case for adults with ADHD. In a prospective study, Biederman et al.¹⁵ found the rate of substance abuse in adolescents both with ADHD (N = 140) and without ADHD (N = 120) to be 15%. However, between adolescence and adulthood the rate of substance abuse increases substantially for individuals with ADHD. My colleagues and I¹⁶ studied the onset of SUD in adults with ADHD. We examined retrospectively derived data from 120 consecutively referred adults with SUD and ADHD and 268 adults with substance use disorder but no ADHD. The mean age at onset of substance abuse was 19 years in adults with ADHD, compared with 22 years in adults without ADHD (Figure 1). We found that substance abuse increased in adulthood for approximately 48% of individuals with ADHD, compared with approximately 30% of individuals without ADHD. Studies^{16,17} have found that adults with ADHD and co-occurring conduct or bipolar disorder are at a higher risk for substance abuse and have an earlier onset of substance abuse when compared with adults with ADHD alone.

Figure 2. Risk of Abuse Following Dependence in Substance Abusers With and Without ADHD^{a,b}



^aReprinted with permission from Biederman et al.¹⁹

^bHazard ratio = 4.9 (95% confidence interval = 1.7 to 14.3; $p = .003$) for ADHD adults vs. adults without ADHD estimated using Cox regression correcting for age, sex, socioeconomic status, and other psychiatric comorbidity.

My colleagues and I¹⁸ also found that the duration of the substance abuse was longer in adults with ADHD than in those without. In stratifying our data to examine substance-abusing adults with and without ADHD, we found that although the rate of remission from substance abuse was 80% in both groups, the mean duration of substance abuse in adults with ADHD was 133.1 months, compared with 95.9 months in adults without ADHD.

Biederman et al.¹⁹ investigated the effect of ADHD on transitions from substance use to abuse to dependence and from one class of abusive agents to another. The researchers found that adults with ADHD (N = 239) were significantly more likely to progress from an alcohol use disorder to a drug use disorder than adults without ADHD (N = 268). Also, adults with ADHD were significantly more likely to go back to the less severe substance abuse from dependence than adults without ADHD, who generally fully remit from substance dependence (Figure 2).

Connections Between Substance Use and ADHD

The high rate of substance abuse in adults with ADHD is well-known, but researchers are still trying to learn the cause. The core symptoms of hyperactivity, impulsivity, and inattention, as well as the role of functioning, comorbidity, and overall competency, are currently being studied as potential causal candidates in the link between ADHD and SUD.

Researchers have undertaken studies on the role of self-medication in symptom control in adults with ADHD. Individuals with ADHD may use specific drugs, such as cocaine, that act in a manner similar to prescribed ADHD medications to lessen symptoms. However, Biederman et al.² reported that individuals with ADHD did not choose their drugs as selectively as originally hypoth-

esized. Substance-abusing adults with ADHD (N = 44) and adults without ADHD (N = 29) used the same drugs in similar ratios, with marijuana being the most frequently abused agent, followed distantly by cocaine, stimulants, and hallucinogens. Although individuals with ADHD may not choose their drugs selectively, self-medication could still be operant. For example, Horner and Scheibe²⁰ asked 15 substance-abusing adolescents with ADHD and 15 substance-abusing adolescents without ADHD questions about substance abuse. When asked why they began to abuse substances, both the adolescents with ADHD and those without ADHD answered “to get high.” When they were asked why they continued to abuse substances, most of the adolescents with ADHD cited the mood-altering properties of the substances, while those without ADHD cited the euphoric properties of the substances.

Inattention has also been found to play a role in substance abuse. Tercyak et al.²¹ recently demonstrated an important link between the presence of attentional dysfunction and the initiation and maintenance of cigarette smoking. Tapert et al.²² followed 66 youths without ADHD at a high risk for substance abuse for 8 years to learn if attentional symptoms at baseline predicted later substance abuse. Poor attention and executive functioning at baseline predicted substance abuse at follow-up, even when results were controlled for socioeconomic status, conduct disorder, family history of substance abuse, and learning disabilities. The youths who had low scores on neuropsychological tests of attention at baseline had greater substance use frequency than those with higher baseline scores on attention tests.

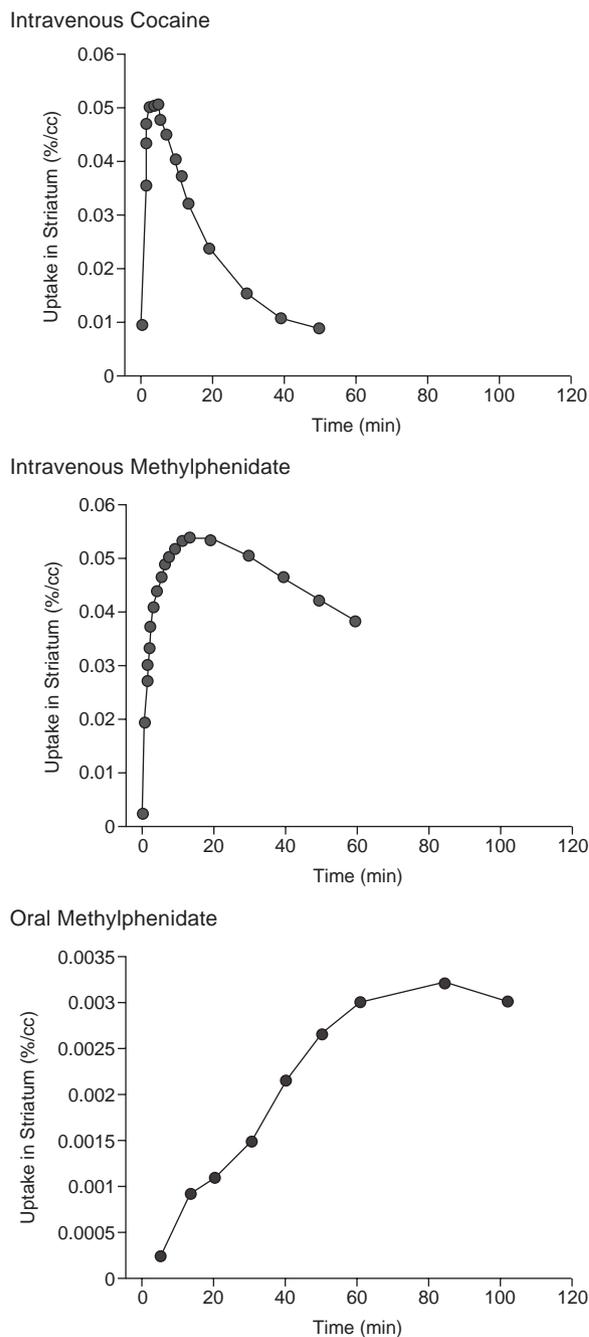
Stimulants and Substance Abuse

Stimulant medications have been cited as a possible cause of the high rate of substance abuse in adults with ADHD. Research on the subject has so far been inconclusive, with discordant findings²³⁻²⁵ in the literature.

Methylphenidate is one of the most commonly prescribed stimulant medications for ADHD, but has been scrutinized for its pharmacologic properties, which resemble those of cocaine. Kollins et al.,²⁶ in their review of the literature, found that 48 (80%) of the 60 studies reviewed concluded that methylphenidate acts in a manner similar to cocaine or produces effects indicative of abuse potential. Grabowski et al.²⁷ conducted a study on methylphenidate as a replacement medication for cocaine. Twenty-five individuals were given 45 mg/day of methylphenidate and 24 individuals were given a placebo. The two groups had no significant differences in trial retention or cocaine use, and neither group reported an increase in craving.

Methylphenidate and cocaine may have similar psychoactive properties, but the route of administration controls their behavioral effects. Volkow et al.²⁸ studied whether intravenous (IV) cocaine, IV methylphenidate,

Figure 3. Rate of Drug Uptake Into the Brain



^aReprinted with permission from Volkow et al.²⁸

and oral methylphenidate had similar pharmacokinetic properties. They found that both IV cocaine and IV methylphenidate had a rapid brain (striatal) uptake but oral methylphenidate had a slow brain uptake (Figure 3). The participants who were given the IV cocaine and the IV methylphenidate reported feeling a euphoria, but those who were given oral methylphenidate did not. This lack of a high limits the abuse potential of oral methylphenidate.

My colleagues and I²⁵ concluded recently that the literature does not support the claim that stimulant treatments add to the risk of substance abuse in individuals with ADHD. Our group reviewed 6 studies that evaluated a total of 674 medicated subjects and 360 unmedicated subjects. We found that the pooled odds ratio for the studies revealed a 1.9-fold reduction in risk of substance abuse for youths who were treated with stimulants compared with youths who were not treated for ADHD. Only 1 study showed an increase in substance abuse in individuals treated with stimulants, 1 study showed no difference, and 4 out of the 6 studies showed a decrease in substance abuse. This review suggests that not only is there a lack of aggregate data supporting the idea that stimulants increase the risk of substance abuse, but stimulant pharmacotherapy appears to decrease SUD by as much as one half (compared with the general population risk for SUD).

TREATMENT OF ADULTS WITH ADHD AND SUBSTANCE ABUSE

All adults with ADHD should be systematically queried for SUD. Evaluation and treatment of comorbid ADHD and SUD should be part of a plan in which consideration is given to all aspects of the adult's life. Any intervention in this group should follow a careful evaluation of the patient, including psychiatric, addiction, social, cognitive, educational, and family evaluations. A thorough history of substance use should be obtained including past and current usage and treatments. Careful attention should be paid to the differential diagnoses, including medical and neurologic conditions whose symptoms may overlap with ADHD (e.g., hyperthyroidism) or be a result of SUD (e.g., protracted withdrawal, intoxication, and hyperactivity). Current psychosocial factors contributing to the clinical presentation need to be explored thoroughly. Although no specific guidelines exist for evaluating the patient with active SUD, in our experience at least one month of abstinence is useful in accurately and reliably assessing for ADHD symptoms. Semistructured psychiatric interviews or validated rating scales of ADHD^{29,30} are invaluable aids for the systematic diagnostic assessments of this group.

Adults with ADHD and SUD have special treatment considerations. If possible, the first priority in treatment should be to address the SUD, i.e., to stabilize the SUD either to abstinence or to a stable low-use pattern.¹³ By treating the SUD first, treatment retention is improved and the effectiveness of treatments for ADHD is increased. After the addiction has been addressed, the clinician should reevaluate the patient and establish a treatment hierarchy based on the relative impairment from the patient's disorders. For example, if a patient has ADHD and major depressive disorder, then the depression should be treated first if it has a greater negative effect on the patient's life than the ADHD.

Treatment of patients with ADHD and SUD necessitates multimodal involvement including empirically based SUD treatments/psychotherapy and pharmacotherapy. Psychotherapy is helpful in reducing substance abuse and can aid in treatment of the ADHD. Group and individual therapy both have been reported to be useful in treating substance abuse.³¹ Reliance on 12-step programs alone may not be adequate, as it has been the author's experience that adults with ADHD often have difficulty following these programs. Researchers have demonstrated the effectiveness of individual cognitive therapies, such as the empirically based strategies of A. T. Beck, in the treatment of ADHD.³² Cognitive-behavioral therapy may also be a particularly effective therapy in adults with ADHD plus SUD, as special cognitive therapy interventions, integrating relapse prevention, exist for adults with SUD. The latency to initiate pharmacotherapy for ADHD in adults with ADHD plus SUD remains under study. SUD should be addressed prior to initiating pharmacotherapy. Once there is evidence of stabilization or solid motivation for SUD treatment, ADHD pharmacotherapy can be initiated. Medication serves an important role in reducing the symptoms of ADHD and other concurrent psychiatric disorders. Effective agents for adults with ADHD include the psychostimulants, noradrenergic agents, and catecholaminergic antidepressants.³³ Findings from open and controlled trials suggest that medications used in adults with ADHD plus SUD effectively treat the ADHD but have little effect on substance use or cravings, and the trials are plagued by high attrition. A total of 5 studies have been presented or reported in the adult literature: 4 open³⁴⁻³⁷ and 1 controlled³⁸ (Table 1).

The first line of pharmacologic treatment for adults with ADHD and SUD, based on the risk for medication diversion and misuse, should be the nonstimulants, such as bupropion, tricyclic antidepressants, and atomoxetine. Second-line agents for ADHD in adults with comorbid SUD include the stimulants: pemoline, methylphenidate, and amphetamines (Table 2). Because of its high likelihood for abuse, methamphetamine should be avoided.

Antidepressants

Tricyclic antidepressants, such as desipramine and imipramine, have been tested for effectiveness in adults with ADHD. A randomized, placebo-controlled study³⁹ of desipramine in adults with ADHD found significant reduction in symptoms of ADHD from baseline to endpoint. Forty-one adults were given 200 mg/day of desipramine for 6 weeks. Sixty-eight percent of participants treated with desipramine responded positively to treatment, while none of the participants given the placebo showed a positive response. The literature is limited, however, in studies of tricyclic antidepressants and current substance abuse in patients with ADHD.

Studies that have evaluated the newer antidepressant bupropion in the treatment of ADHD with comorbid sub-

Table 1. Medication Studies of Adults With ADHD Plus Substance Use Disorders (SUD)

Study	N	Design	SUD Sample	Medication	Duration	Retention	Outcome	Concurrent Treatment
Levin et al, 1998 ³⁴	12	Open	Cocaine dependence	MPH	12 wk	67%	Improvements in ADHD symptoms, decrease in cocaine use (self-reported and urine test)	Individual weekly relapse-prevention therapy
Upadhyaya et al, 2001 ³⁵	10	Open	Alcohol and/or cocaine abuse/dependence	Venlafaxine	12 wk	40%	Significant improvements in ADHD and in alcohol craving and frequency	Weekly and then monthly psychotherapy
Levin et al, 2002 ³⁶	11	Open	Cocaine dependence	Bupropion	12 wk	91%	Reductions in ADHD and cocaine cravings (p < .01)	Individual weekly relapse-prevention therapy, weekly meetings
Wilens et al, 2001 ³⁷	32	Open	Mixed SUD	Bupropion SR	6 wk	59%	Improvements in ADHD symptoms (46% decrease), substance use severity (22% decrease, p < .01)	No additional therapy
Schubiner et al, 2002 ³⁸	48	Double-blind, placebo-controlled	Cocaine abuse	MPH	13 wk	58% placebo, 45% MPH	Trend to improved hyperactive-impulsive symptoms, no difference in cocaine use (self-reported or urine test)	Twice weekly group CBT for SUD; weekly individual CBT for ADHD
Total	113	Double-blind = 1, open = 4	ADHD and mixed SUD	Bupropion = 2, MPH = 2, Venlafaxine = 1	6-13 wk	58%	Significant reduction in ADHD symptoms in 4/5 studies; mild reduction in SUD	The majority of subjects received concurrent therapy

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CBT = cognitive-behavioral therapy, MPH = methylphenidate, SR = sustained release.

Table 2. Medications Available for the Treatment of ADHD Plus Substance Abuse Disorders

First-line treatments
Antidepressants
Bupropion, desipramine
Norepinephrine reuptake inhibitor (promising)
Atomoxetine
Second-line treatments
Stimulants ^a
Pemoline
Methylphenidate
Dextroamphetamine

^aIn order of increasing abuse potential.

stance abuse have generally found bupropion to be effective. Riggs et al.⁴⁰ examined the use of bupropion in treating ADHD in adolescents with substance abuse and conduct disorder. The open, 5-week trial in 13 adolescents (all completed) in residential treatment resulted in moderate reductions in ADHD symptoms and mild reduction in substance abuse and craving. The mean score on the Conners Hyperactivity Index declined by 13%, mean score on the Daydream Attention score declined by 10%, and mean score on the Clinical Global Impressions-Severity of Illness scale declined by 39%.

Solkhkah et al.⁴¹ conducted an open, 6-month study of the effectiveness of bupropion sustained release, up to a maximum of 400 mg/day, in 14 adolescents with ADHD, substance abuse, and mood disorders. The researchers found moderate reductions in ADHD symptoms, substance abuse, and cravings in the 13 completers. Participants' scores on the Drug Use Screening Inventory-Revised declined 39% from baseline to endpoint, and scores on the ADHD Symptom Checklist declined 43% from baseline to endpoint. There were no serious adverse events in the group.

A 12-week study by Levin et al.⁴² on the effectiveness of bupropion in 11 adults with ADHD seeking treatment for cocaine abuse found similarly positive results. Of the 11 patients, 10 completed the study. Study participants were given 250 to 400 mg/day of bupropion and concurrent psychotherapy. ADHD and cocaine use decreased considerably over the course of the trial. The mean scores on the ADHD Rating Scale declined by half from baseline to the close of the trial. Cocaine craving, as measured by a visual analog scale, decreased by a mean of 46%, and the number of days of cocaine use, as measured by the Addiction Severity Index, declined by 91% from baseline to endpoint.

Prince et al.⁴³ studied bupropion sustained release, in doses up to 200 mg/day, to investigate whether it successfully treated ADHD in adults with substance abuse while reducing the substance abuse. They conducted an open, 6-week trial comprising 32 adults diagnosed with ADHD and substance abuse. Subjects were referred for SUD treatment. Only 19 individuals completed the study, a 41%

dropout rate. However, the study showed significant reductions in ADHD symptoms and only minor reduction in substance abuse in adults treated with bupropion. The study participants whose ADHD responded to treatment showed the most improvement in substance abuse; conversely, 60% of participants whose substance abuse diminished also showed a decline in symptoms of ADHD. No reports of drug interactions with substances of abuse emerged.

Atomoxetine

Another medication that has been found effective in the treatment of ADHD in adults is atomoxetine. Atomoxetine, a nonstimulant, is a highly specific noradrenergic reuptake inhibitor that is not associated with substance abuse pathophysiology or neural networks. Michelson et al.⁴⁴ recently reported on two 10-week, double-blind, controlled studies on atomoxetine in adults with ADHD (N = 536) showing significant reductions in symptoms on both the self-rated and investigator-rated versions of the Conners Adult ADHD Rating Scale. Atomoxetine is unscheduled and has so far shown no signs of abuse potential. For example, one study by Heil et al.⁴⁵ systematically evaluated the abuse liability of atomoxetine and demonstrated that no abuse liability in adults exists at therapeutic dosing. Very recent data on atomoxetine in adults with ADHD and SUD show an absence of acute liability in this group (data on file, Eli Lilly and Co., Indianapolis, Ind.). Atomoxetine is clearly promising as a first-line agent given its lack of abuse liability and relative freedom from drug interactions with substances of abuse. Moreover, atomoxetine may also be useful in addressing any additional psychiatric comorbidities, such as anxiety and mood disorders, reported in adults in ADHD.²

Stimulants

Stimulants, such as methylphenidate and amphetamines, are considered second-line agents for adolescents and adults with ADHD and SUD. When prescribing stimulants, the clinician should begin with a medication with a low abuse liability, such as pemoline or methylphenidate. A study²⁷ has suggested that methylphenidate does not encourage preexisting substance addictions, but diversion and abuse of the medication itself is still a concern, especially in the ADHD and comorbid SUD population. The use of extended-release stimulant preparations is recommended because they may reduce the risk of medication abuse.⁴⁶

In the largest study to date, Schubiner et al.³⁸ conducted a 12-week controlled trial of methylphenidate in 48 adults with ADHD and cocaine abuse. Despite the high attrition rate, they found a significant reduction in symptoms of ADHD with no change in cocaine craving or use. An open trial of methylphenidate in 12 adults with ADHD and cocaine abuse⁴⁷ found a reduction in symptoms of ADHD and cocaine craving and use from baseline to endpoint.

Of interest, no evidence exists to suggest that treating ADHD pharmacologically during an active SUD exacerbates the SUD. In particular, studies of bupropion⁴⁰⁻⁴³ show no increased substance use or craving in general, or cocaine use in particular. Moreover, methylphenidate treatment did not increase cocaine use or cocaine craving according to subjective and objective data. These findings are consistent with those of Grabowski et al.,²⁷ who systematically evaluated methylphenidate as a potential cocaine-blocking agent by studying cocaine addicts without ADHD and administering methylphenidate or placebo. While methylphenidate was not effective in reducing cocaine use or craving compared with placebo, there was no evidence that methylphenidate exacerbated any aspect of the cocaine addiction. Similar findings have been reported in a pilot study using dextroamphetamine in adult amphetamine abusers⁴⁸ in which no exacerbation of the stimulant abuse or craving emerged during the 12-week randomized and controlled trial.

CONCERNS AND MONITORING

Concerns still exist about the safety of pharmacotherapy in adults with ADHD and SUD. Medications with known drug interactions with substances of abuse (e.g., marijuana and tricyclic antidepressants⁴⁹) should be avoided. Patients should be monitored for compliance with the treatment plan, misuse or abuse of medication, and reselling of medication. Also, patients may believe that pharmacologic treatment conflicts with the drug-free ideology they are being taught, but they should be reminded that they are taking prescribed medication, not illegal or commonly abused drugs.

Monitoring of adults in treatment for ADHD and substance abuse requires frequent follow-up questionnaires, objective toxicology screens, and contingency plans. Clinicians need to know what they plan to do if the individual they are treating continues to abuse substances. Gradual steps must be taken with patients who cannot control their substance abuse. For example, a patient whose urine tests positive for substances might be referred to a self-help group such as Alcoholics Anonymous or Narcotics Anonymous. If the patient continues to use substances, the clinician might insist that he or she seek outpatient substance abuse treatment. If the outpatient treatment is not effective, the clinician could ask the patient to consider inpatient treatment.

CONCLUSION

Adults with ADHD are at a higher risk for substance abuse than adults without ADHD, especially when comorbid conditions are present. ADHD also changes the course of substance abuse in adults. Self-medication has been examined as a possible cause of the high rate of substance

abuse in adults with ADHD, as has treatment with stimulants. Research on these subjects is inconclusive, but recent studies have indicated that pharmacotherapy reduces, not increases, the risk of substance abuse in adults with ADHD.

Treatment for adults with ADHD and substance abuse should begin by addressing substance abuse initially and throughout the treatment for the ADHD. Psychotherapy and pharmacotherapy are both important in the treatment of adults with ADHD and substance abuse. Several medications are effective in reducing symptoms of ADHD, including the antidepressant bupropion, the nonstimulant atomoxetine, and the stimulants. Stimulants with abuse potential should be sequenced after nonstimulant trials.

Drug names: atomoxetine (Strattera), bupropion (Wellbutrin), desipramine (Norpramin), dextroamphetamine (Dexedrine, Dextrostat, and others), imipramine (Tofranil, Surmontil, and others), methamphetamine (Desoxyn), methylphenidate (Ritalin, Concerta, and others), pemoline (Cylert).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, bupropion and desipramine are not approved by the U.S. Food and Drug Administration for the treatment of attention-deficit/hyperactivity disorder (ADHD) and substance use disorders; dextroamphetamine, methylphenidate, and pemoline are not approved for the treatment of ADHD in adults; and imipramine is not approved for the treatment of ADHD in adults and adolescents.

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