# Substance Use Disorders in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder: Implications for Treatment and the Role of the Primary Care Physician

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***Objectives:*** Review the association between attention-deficit/hyperactivity disorder (ADHD) and substance use disorder (SUD) in children and adolescents. Discuss treatment implications and the role of the primary care physician in the management of this comorbidity.

***Data Sources:*** Articles published from 1991 to 2007 were identified through a MEDLINE search using the search terms *attention-deficit/hyperactivity disorder* and *substance use disorder*.

***Study Selection:*** Publications cited include reviews of substance use disorders in children and adolescents with ADHD, manuals of diagnostic tests, and 69 studies of substance use disorders in children and adolescents with ADHD. No non–English-language publications were identified.

***Data Synthesis:*** Recent reports identify SUD in a high proportion of respondents with ADHD and ADHD in a high proportion of respondents with many types of SUD. Factors that appear to increase the risk for SUD include comorbid psychiatric disorders, particularly conduct disorder. Pharmacotherapy for ADHD appears not to increase the risk for subsequent SUD. Guidelines for the evaluation and treatment of patients with comorbid ADHD and SUD are outlined. Psychostimulants carry the risk for misuse by both patients and family members through diversion. Although nonstimulants such as atomoxetine have low abuse potential, they appear to be less efficacious than stimulants. Formulations that have the potential to lower the abuse liability of stimulants are being developed. These include a transdermal form of methylphenidate that has been shown to be efficacious in the treatment of ADHD and a prodrug stimulant, lisdexamfetamine, recently approved for the treatment of ADHD. Clinical data indicate that lisdexamfetamine is efficacious, and significantly lower likability scores were seen with lisdexamfetamine than with equivalent oral doses of *d*-amphetamine sulfate.

***Conclusions:*** Pharmacotherapy may reduce the risk for SUD in patients with ADHD. Psychostimulants remain the first-line therapy for the core symptoms of ADHD. New formulations of pharmacologic agents with a reduced potential for abuse are being developed.

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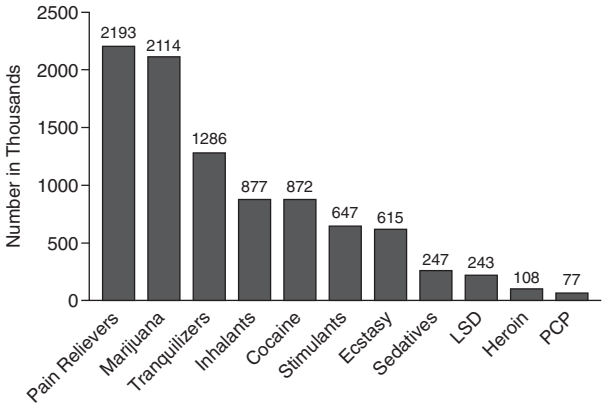
Attention-deficit/hyperactivity disorder (ADHD) is one of the most common behavioral disorders among school-aged children, with a prevalence of 3% to 7% in the United States.[1] This chronic disorder severely impairs function both at home and at school, and its symptoms persist into adolescence in as many as 85% of patients.[2] In addition, ADHD is frequently comorbid with substance use disorder (SUD) associated with alcohol, tobacco, and other drugs.[3] Most drug use and SUD originate in adolescence or even in childhood.[4] Substance use disorder is thus being increasingly conceptualized as a developmental disorder, as is ADHD, indicating that the earlier in the course of these disorders that treatment is initiated, the more successful the outcome.[5]

Since behavioral disorders and SUD are frequently comorbid[6,7] and inadequate treatment of either may potentially lead to poor outcome for the comorbid condition, many clinicians have suggested that treatment of behavioral disorders and SUD should ideally be provided in an integrated fashion.[8,9] Experience indicates that in most instances, treatment for behavioral disorders (such as ADHD) and SUD are typically provided in an independent and disjointed manner. While there is not much evidence at this point that integrated treatment of ADHD and SUD will lead to better outcomes for either ADHD or SUD, clinicians are frequently faced with this comorbidity that presents a unique dilemma in that some of the most effective treatments for ADHD (stimulants) have abuse liability themselves.[10]

Of concern is that nonmedical use of certain prescription medications, particularly opioid analgesics and

**Figure 1. Numbers of Persons Aged ≥ 12 Years Who Used an Illicit Drug for the First Time in 2005[a]**




[a]From the Substance Abuse and Mental Health Services Administration.[12]
Abbreviations: LSD = lysergic acid diethylamide, PCP = phencyclidine.

stimulants, has increased recently in the United States.[11] According to the 2005 National Survey on Drug Use and Health,[12] prescription-type psychotropic drugs taken nonmedically were used by 6.4 million persons (2.6%) aged greater than or equal to 12 years: these included pain relievers by 4.7 million, tranquilizers by 1.8 million, stimulants by 1.1 million, and sedatives by 272,000. The incidence of first-time use of an illicit drug in 2005 is shown in Figure 1. Among youths aged 12 to 17 years, 3.3% were users of prescription-type psychotropic drugs taken nonmedically (Figure 2). Users of all illicit drugs included 3.8% of respondents aged 12 to 13 years, 8.9% of those aged 14 to 15 years, 17.0% of those aged 16 to 17 years, and 22.3% of those aged 18 to 20 years.[12]

Increasingly, primary care physicians have to assess and manage behavioral/mental health disorders since mental health disorders are seen in 14% to 20% of children and adolescents in the United States, but few of these patients are seen by mental health experts.[13] The reasons for this include the shortage of mental health workers, the stigma associated with receiving mental health services, chronic underfunding of the public mental health system, reduced reimbursement to mental health providers, and disparate insurance benefits.[13] As a result, about 75% of all children with psychiatric disabilities are seen in primary care settings, and half of all pediatric office visits involve behavioral, psychosocial, or educational concerns.[13–15]

Clinical challenges in the treatment of persons with comorbid ADHD and SUD include making the diagnoses of ADHD and SUD, selecting appropriate treatments, and preventing misuse and the diversion of pharmacologic agents used in the treatment of ADHD. As Wilens has noted,[3] the identification of specific risk factors for SUD in patients with ADHD may permit more targeted treatments for both disorders at earlier stages of their expression. Most primary care physicians, however, are not trained in the assessment and management of SUD. A "practice parameter" for the assessment and treatment of children and adolescents with SUD was recently published.[16] In addition, useful guidelines on the diagnosis, evaluation, and treatment of ADHD have been published by the American Academy of Pediatrics,[17,18] the American Academy of Child and Adolescent Psychiatry,[19] and the Texas Consensus Conference Panel on Pharmacotherapy of Childhood Attention-Deficit/Hyperactivity Disorder.[20]

The purpose of this article is to review the relevant published literature on the association between ADHD and SUD in order to create awareness about SUD in children and adolescents and the important role that primary care physicians can play in addressing this comorbidity in their clinical practice.

## METHOD

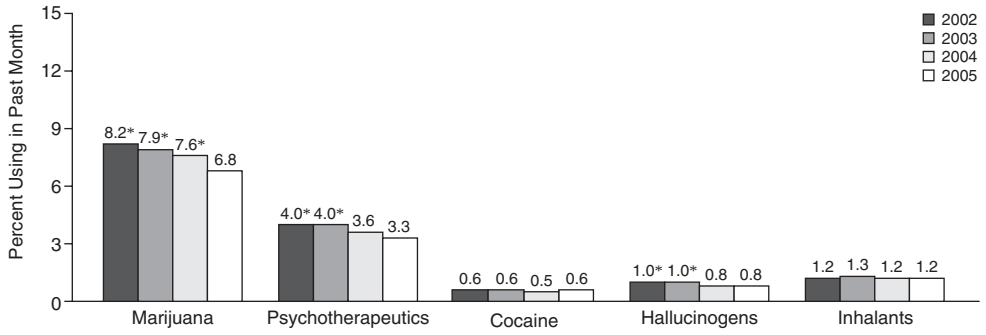
Articles published from 1991 to 2007 were identified through a MEDLINE search using the search terms *attention-deficit/hyperactivity disorder* and *substance use disorder*. Publications cited include reviews of substance use disorders in children and adolescents with ADHD, manuals of diagnostic tests, and 69 studies of substance use disorders in children and adolescents with ADHD. No non–English-language publications were identified.

Factors associated with SUD in ADHD patients are identified, and data on the nonmedical use of ADHD medications are presented. Clinician guidelines for the evaluation and treatment of patients with comorbid ADHD and SUD are provided. Supporting data on how patients with untreated ADHD carry a potentially higher risk for developing SUD are reviewed. Finally, the clinical implications of managing the ADHD and SUD comorbidity and selecting the appropriate agents to treat ADHD are discussed. Current, new, and prospective approaches being used to lower the abuse potential of ADHD medication while maintaining adequate treatment and symptom control are identified.

## SUBSTANCE-RELATED DISORDERS

The DSM-IV-TR divides substance-related disorders into 2 groups: the substance use disorders (substance dependence and substance abuse) and the substance-induced disorders (substance intoxication and substance withdrawal).[1] Substance abuse is defined as a maladaptive pattern of substance use manifest by recurrent and significant consequences related to the repeated use of substances over the past 12 months. The essential feature

**Figure 2. Use of Illicit Drugs by Youths Aged 12 to 17 Years During Previous Month in 2005 and Comparison With Previous 3 Years[a]**




[a]From the Substance Abuse and Mental Health Services Administration.[12]
*Difference between estimate and the 2005 estimate is statistically significant at the .05 level.

of substance dependence is a cluster of cognitive, behavioral, and physiologic symptoms indicating loss of control as the individual continues use of the substance despite significant substance-related problems.[1]

## THE LINK BETWEEN ADHD AND SUD

The concurrence of ADHD and SUD has been consistently observed for many years: a high proportion of adolescents and adults with ADHD are shown to have SUD, and many persons with SUD are found to have ADHD.[21] For example, in a study of 538 adolescents (mean age of 16.6 years) at a hospital-based adolescent clinic in Boston, Mass., SUD was reported in 63% of the 165 girls and 56% of the 79 boys with ADHD symptoms.[22] Another example involves 946 adolescents aged 15 years in New Zealand: alcohol-related problems were reported in 23% and illicit drug use in 21% of the 82 subjects who had been diagnosed with severe attention-deficit behaviors at age 8 years.[23] Similarly, in a study of 142 adolescents (mean age of 15.2 years) with childhood ADHD and 100 matched controls, use of alcohol, cigarettes, and marijuana was similar in the 2 groups; however, 3 times as many subjects with ADHD as controls reported use of nonmarijuana illicit drugs.[24] Inhalants, hallucinogens, cocaine, and nonprescribed stimulants were responsible for the group differences. Among adults, alcohol abuse or dependence is seen in 17% to 45% of patients with ADHD, and drug abuse or dependence is seen in 9% to 30%.[25] The association between ADHD and SUD is also found among college students. In a group of 334 college students (mean age of 21 years), the incidence of tobacco and marijuana use was significantly higher in the 76 students (23%) who reported a history of ADHD than in students without a history of ADHD.[26]

Interestingly, a high proportion of persons with SUD are found to have symptoms of ADHD. For example, in a recent study of 162 adolescents (mean age of 17 years) admitted to a residential addiction treatment program in Pennsylvania,[27] 34% had a lifetime ADHD diagnosis; these included 36% of the 104 males and 32% of the 57 females. The primary drugs of dependence in these 162 patients were marijuana in 44%, cocaine in 18%, heroin in 14%, and alcohol in 12%.[27] In a study of 600 adolescents with "cannabis-use disorders" admitted to 4 treatment centers (70% were aged 13 to 16 years; 83% were boys),[28] the authors reported that 38% had a diagnosis of ADHD. Studies have also found a strong association between SUD and ADHD in adults. Schubiner et al.[29] reported that 24% of 201 adult inpatients in 2 chemical-dependency treatment centers had ADHD (28% of the 106 men and 19% of the 95 women). Conduct disorder was identified in 79 (39%) of the 201 patients, of whom 34 (43%) also had ADHD.[29] Of 281 patients seeking treatment for cocaine abuse in New York, N.Y., (mean age of 34 years; 82% were men), ADHD symptoms were reported in 72 patients (26%); 30 of these patients did not have childhood symptoms but reported ADHD symptoms after a period of regular drug use.[30] Comorbid diagnoses in the patients with ADHD symptoms included conduct disorder in 63% and antisocial personality disorder in 52%.[30] Many reports suggest that conduct disorder is a mediator for substance use in persons with ADHD. At the same time, ADHD is a risk factor for conduct disorder and thus at the very least ADHD can be construed as an indirect risk factor for SUD.[31] Hence, the association between ADHD and SUD is even more robust in the presence of conduct disorder.

According to the self-medication hypothesis of SUD,[32] the user's choice of drug is the result of an interaction between the psychopharmacologic action of the drug and the dominant painful feelings with which he or she struggles. Wilens and Biederman[5] note that the self-medication hypothesis is plausible in ADHD, considering that ADHD "is chronic and often associated with self-regulatory deficits, comorbid affective symptoms, de-

moralization, and failure, factors frequently associated with SUD in adolescence."[p582]

### Tobacco Use

Attention-deficit/hyperactivity disorder has been shown to be a significant predictor for starting to smoke cigarettes before age 15 years and is associated with a higher risk of smoking into adulthood and a lower likelihood of quitting compared with age-matched subjects without ADHD.[3,26,33,34] In a nationally representative sample of young adults, Kollins and colleagues[35] reported a significant relationship between regular cigarette smoking and self-reported inattentive and hyperactive/impulsive symptoms. Nicotine has been shown to ameliorate ADHD symptoms,[36–40] and it has been proposed that nicotine dependence may develop as an attempt to self-medicate symptoms of ADHD.[26]

In a recent study by Biederman et al.,[41] the subjects were 97 youths with ADHD (mean age of 14.6 years). The 15 youths who smoked cigarettes were significantly more likely to subsequently use alcohol and illicit drugs and develop abuse and dependence on alcohol, drugs, and marijuana than the 76 youths who did not smoke. When these outcomes were adjusted for conduct disorder, subsequent alcohol use was no longer significantly associated with smoking.[41]

## FACTORS ASSOCIATED WITH THE RISK FOR SUD IN PATIENTS WITH ADHD

Several factors have been identified that appear to increase the risk for SUD among persons with ADHD. These factors include a substantial genetic predisposition to both SUD and ADHD.[42,43] Attention-deficit/hyperactivity disorder is associated with neuropsychological impairment and high levels of psychiatric comorbidity that have been independently linked with SUD.[5] Adolescents with ADHD and conduct disorder start smoking earlier and smoke more frequently than those with ADHD without conduct disorder or those without ADHD.[44] Dierker et al.[45] proposed a dual-pathway hypothesis in which substance use arises from deviant behavior (such as conduct disorder) or through internalizing disorders such as anxiety and depression. Biederman et al.[46] reported that early onset bipolar disorder in patients with ADHD is a risk factor for SUD independent of ADHD. The onset of ADHD often precedes that of SUD in children and adolescents, suggesting that the psychopathology is not merely secondary to SUD in most of these patients.[46] In a recent longitudinal study of 428 children aged 12 years in China, the most significant predictive factors for adolescent SUD were male gender, ADHD, conduct disorder, and sibling use of tobacco.[47]

Adolescent girls with ADHD have been reported to be at a higher risk for smoking and substance use than boys with ADHD. For example, in the study of 626 twin pairs by Disney et al.,[48] at age 17 years current use of tobacco, alcohol, or marijuana was reported in 73% of the 24 girls with ADHD and in 44% of the 28 boys with ADHD. Any SUD was reported in 29% and 14%, respectively.[48]

Conduct disorder has been reported in 30% to 50% of ADHD cases,[49] and, as noted, the concurrence of conduct disorder with ADHD, and not the ADHD alone, may place children at higher risk for development of SUD.[31] The authors of the New Zealand study[23] concluded that the presence of early conduct problems, rather than the presence of early attention-deficit behaviors, was prognostic of future substance abuse. Wilens[3] reported that results of several prospective studies of children with ADHD indicate that those with concurrent conduct or bipolar disorders have the poorest outcome with respect to developing SUD and major morbidity. Wilson and Levin[50] have commented that ADHD is associated with a variety of problems that may contribute to antisocial behavior and substance abuse later in development. These characteristics are summarized in Table 1.

**Table 1. Psychopathologic Characteristics of Patients With ADHD That May Contribute to the Development of Substance Use Disorder[a]**

| |
|---|
| Children with ADHD are more likely to |
| Have oppositional-defiant disorder and anxiety, mood, or learning disorders |
| Receive special education |
| Be held back a grade |
| Be suspended or expelled |
| Children with ADHD followed into adolescence are more likely to |
| Have conduct disorders |
| Be arrested |
| Have earlier age at onset of alcohol dependence |
| Children with ADHD followed into adulthood are more likely to |
| Have antisocial personality disorder |
| Abuse cocaine, stimulants, hallucinogens, and/or cannabis |
| Have more substance abuse treatment episodes |

[a]Based on Wilson and Levin.[50]
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

## ABUSE OF PHARMACOLOGIC AGENTS USED IN THE TREATMENT OF ADHD

A small proportion of adolescents and young adults are reportedly using ADHD medications for nonmedical purposes.[51] For example, in a national survey of high-school students, the proportion of seniors who reported nonmedical use of methylphenidate in the past year was 5.1% in 2004 and 4.4% in 2005.[52] Among adolescents being treated for SUD, diversion or nonmedical use of these medications is substantially greater: of 162 adolescent patients admitted to a residential addiction treatment center in Pennsylvania, 31% reported a history of schedule 2 psychostimulant abuse.[27] Of the 55 patients with a lifetime diagnosis of ADHD, 10 reported illicit diversion of

psychostimulant medications by sale, barter, or gift to others.[27] Among 450 adolescents referred for SUD treatment in Alberta, Canada, 23% reported lifetime nonmedical use of methylphenidate or dextroamphetamine and 6% reported current abuse of these medications.[53] According to a survey of sources of prescription drugs for illicit use among 458 undergraduates at the University of Michigan in 2003,[54] the students' peers were the primary source of prescription stimulants. In a study of 334 college students in South Carolina,[26] 76 had received medications for ADHD; of these, 25% reported ever using their medication to get "high," and 29% had given or sold their medication to others.

## EFFECTS OF ADHD TREATMENT ON SUD

Data from 4 studies concerning the risk for SUD in treated and untreated patients with ADHD are summarized in Table 2.[10,55–57] The results of these studies indicate that pharmacotherapy for ADHD did not predict an increased risk for SUD. This was also the conclusion of the meta-analysis of data from 7 studies (N = 1195) by Faraone and Wilens[58]: pharmacotherapy for ADHD did not increase the risk for subsequent SUDs. These results were confirmed in a study of 147 hyperactive children who were followed for 13 years: stimulant treatment in either childhood or high school was not associated with any greater risk for SUD by adulthood.[56] Instead, the data analyzed by Faraone and Wilens seem to suggest that stimulant medications may have a protective effect on later developing SUD.[58] In a recent study of 379 patients with ADHD followed up for a mean of 17.2 years, Katusic et al.[57] reported a lower rate of later substance abuse in the total group of 295 children who had received psychostimulants (20%) than in the 84 children who had not received such treatment (27%). The incidence of substance abuse was significantly lower in treated boys than in untreated boys (22% vs. 36%, p = .016); among the smaller group of girls, however, no statistically significant difference in substance abuse was seen in treated versus untreated girls (15% vs. 10%, p = .67).[57] Whalen et al.[59] used a biomarker (salivary cotinine) to verify self-reports of smoking in 27 adolescents with ADHD. The studies were conducted over 4 days every 6 months during 2 years at high school. A reduction in smoking was recorded in the 11 patients receiving ADHD medications but not in the unmedicated patients.[59]

In a placebo-controlled, 12-week study of the psychostimulant pemoline in 69 adolescents with diagnoses of both ADHD and SUD,[60] ADHD symptoms were "much" or "very much" improved (Clinical Global Impressions-Improvement scale scores of 1 or 2) in significantly more subjects receiving pemoline than placebo, but neither substance use nor symptoms of conduct disorder were reduced. It is important to note that partici-

**Table 2. Studies Assessing the Risk for Substance Use Disorder (SUD) in Treated and Untreated Children and Adolescents With ADHD**

| Study | Method | Population | Results | Conclusions |
|---|---|---|---|---|
| Biederman et al,[55] 1999 | 4-year follow-up throughout adolescence | Medicated, N = 56; nonmedicated, N = 19; controls, N = 137 | Medicated patients at significantly reduced risk for SUD at follow-up; adjusted OR = 0.15 (95% CI = 0.04 to 0.6) | Untreated ADHD is a significant risk factor for SUD; pharmacotherapy was associated with an 85% reduction in risk for SUD |
| Wilens et al,[10] 2003 | Meta-analysis of 6 studies; follow-up into adolescence in 2 studies and into adulthood in 3 studies | Medicated, N = 674 (97% stimulants); nonmedicated, N = 360 | Almost 2-fold reduction in risk for SUD in medicated subjects; pooled estimate of the OR = 1.9 (95% CI = 1.1 to 3.6) | Stimulant therapy in childhood was associated with a significant reduction in risk for drug and alcohol use disorders |
| Barkley et al,[56] 2003 | > 13-year follow-up into adulthood | Medicated with stimulants, N = 98; nonmedicated, N = 21 | Association between stimulant use and drug use frequency in adulthood, p > .05 | No association between stimulant treatment and lifetime substance use, except for ever using cocaine |
| Katusic et al,[57] 2005 | Mean 17.2-year follow-up into adulthood | Medicated with stimulants, N = 295; nonmedicated, N = 84 | Substance abuse in 20% of medicated and 27% of nonmedicated subjects; adjusted OR = 0.6 (95% CI = 0.3 to 1.0) | Stimulant treatment was associated with a reduced risk for later substance abuse |

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, OR = odds ratio.

**Table 3. Validated Screening Instruments for Substance Use Disorders in Adolescents**

| Instrument | Comments |
|---|---|
| CRAFFT[62] | Brief, verbally administered test for primary care professionals that screens for abuse of alcohol and other drugs in teenagers |
| Drug Use Screening Inventory-Adolescent Version[63] | Self-report instrument (149 items) that screens for severity of involvement with drugs and alcohol and associated problems in 10 areas |
| Problem Oriented Screening Instrument for Teenagers[64] | Self-report instrument (139 items) that screens for potential problems in 10 functional domains including substance use and abuse |
| Personal Experience Inventory[65] | Five "basic problem severity" self-report scales (66 items) that assess adolescent alcohol and other drug use |

Abbreviation: CRAFFT = Car, Relax, Alone, Forget, Friends, Trouble (the first key words in the 6 items of the test).

**Table 4. Commonly Used Rating Scales for the Evaluation of ADHD in Children and Adolescents[a]**

| Scale | Patient Age, y | Items | Versions | Time to Administer | Other |
|---|---|---|---|---|---|
| ADHD Rating Scale-IV[66] | 5–18 | 18 | Home and school | 5–10 min | Spanish version |
| Conners Rating Scales-Revised[67] | 3–17 | 80 | Parent | 20–30 min | Short and long versions |
| | | 59 | Teacher | | |
| | | 87 | Adolescent | | |
| SKAMP Rating Scale[68] (standard classroom version) | 7–12 | 10 | Teacher | 5 min | Attention and deportment subscales |

[a]Adult rating scales include those by Conners and Jett[69] and Brown.[70]
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, SKAMP = Swanson, Kotkin, Agler, M-Flynn, and Pelham.

pants in the pemoline study did not receive specific treatment for their SUD, which may explain the lack of improvement in substance use.[60] There is still concern about the nonmedical use of stimulants, since currently marketed stimulants can be used nonmedically (misuse or diversion).[61]

## EVALUATION AND TREATMENT OF ADHD PATIENTS WITH SUD

The primary concerns in the treatment of patients with comorbid ADHD and SUD include making the diagnosis of ADHD in patients with SUD, selecting appropriate medications to normalize the core symptoms of ADHD, and preventing abuse or diversion of ADHD medications. Gordon et al.[27] noted that clinicians who are not trained in SUD can mistake SUD symptoms for ADHD symptoms or overlook SUD in patients with ADHD. Four validated instruments that can be used to identify SUD in adolescents are listed in Table 3.[62–65]

Wilens[3] has provided guidelines for the evaluation and treatment of patients with comorbid ADHD and SUD as follows:

(1) Intervention should follow a careful evaluation of the patient, including psychiatric, addiction, social, cognitive, educational, and family characteristics.
(2) A thorough history of substance use, including current use and treatments, should be obtained.
(3) Careful attention should be given to the differential diagnoses, including medical and neurologic conditions whose symptoms may overlap with ADHD (e.g., hyperthyroidism) or be a result of SUD.
(4) Current psychosocial factors contributing to the clinical presentation should be explored.
(5) In a patient with active SUD, accurate and reliable assessment of ADHD symptoms requires at least 1 month of abstinence.
(6) For systematic diagnostic assessment of these patients, use semistructured psychiatric interviews or validated rating scales of ADHD (Table 4).[66–68]
(7) In patients with both ADHD and SUD, the SUD needs to be addressed initially.
(8) If the SUD is active, stabilize the addiction(s) immediately. This may require inpatient treatment. Self-help groups can be helpful for many patients.
(9) For adults with ADHD, behavioral and cognitive therapies have been efficacious.
(10) Pharmacotherapies reduce the symptoms of ADHD and concurrent psychiatric disorders but may have little effect on substance use or craving.

Primary care physicians should familiarize themselves with available resources within the community and treat SUD and ADHD in an integrated fashion. If it is determined during the screening process that the patient has SUD, he or she should be referred to a specialist trained in addiction psychiatry. Once abstinence is documented for a reasonable period of time, stimulant medications, the most effective class of medications for ADHD, can be resumed.

Abstinence is usually documented by a combination of self-report, collateral information from the family or substance abuse treatment program in which the patient participated (including biological verification of abstinence such as urine toxicology screen), or biological verification by the primary care provider. Bukstein[51] has proposed that ADHD patients with a history of SUD may benefit from relapse-prevention techniques that take the patients' impulsivity into account. Their substance use needs to be monitored, including the use of such techniques as urine toxicology screen. Once some level of stabilization has been reached, assessment and treatment of ADHD should proceed.[51]

Parents should limit their children's access to medications and closely monitor compliance to avoid possible abuse. Clinicians should carefully monitor prescriptions, with high suspicion directed toward early requests for refills or "lost" prescriptions.[51] The patient's family should also be informed of the risk of diversion and misuse, since sources of stimulants for nonmedical purposes include friends and family.[54] Medications should be locked, and the patient should not reveal to friends or acquaintances that he or she is using stimulants to treat ADHD.

Future research on prescription drug abuse should include identification of clinical practices that minimize the risks of addiction, the development of guidelines for early detection and management of addiction, and the development of clinically effective agents that minimize the risks for abuse.[11]

## CLINICAL IMPLICATIONS OF SELECTING APPROPRIATE AGENTS FOR USE

With growing recognition of the validity of ADHD and other childhood psychiatric disorders, the use of stimulant and other psychotropic medications for these conditions has increased.[71] Nevertheless, a systematic analysis of rates of ADHD diagnosis and treatment among children in 4 U.S. communities concluded that undertreatment of ADHD was more likely than overtreatment.[72]

The most commonly used therapeutic agents for ADHD are the psychostimulants methylphenidate and amphetamines, which provide clinical benefit against the 3 core symptoms (inattention, hyperactivity, and impulsivity) in 70% to 80% of patients in all age groups.[61,73] These medications carry a risk of misuse and diversion, both by patients and by family members.[53,54] A commonly expressed concern is that the use of stimulant medications by those with ADHD will increase the risk of SUD in this population. However, as noted, adolescents with untreated ADHD may be at a higher risk of developing SUD than those receiving treatment, suggesting that previous treatment with stimulants may reduce the subsequent risk of abuse of stimulant drugs.[10] Therefore, the question of the relationship between ADHD and SUD, and how this affects the treatment of patients with ADHD, is critical to both health care professionals and the public.[74]

## NONSTIMULANTS

Several nonstimulant medications have been found to be efficacious in the treatment of ADHD, although the degree of response is generally lower than with stimulants.[75] The 3 most promising medications to date appear to be atomoxetine, bupropion, and guanfacine.

Atomoxetine, a selective norepinephrine reuptake inhibitor, has been shown to be effective in several studies in children, adolescents, and adults with ADHD.[76–78] Gibson et al.[79] recently analyzed outcomes of 5 studies that compared atomoxetine and stimulants in the treatment of ADHD in children and adolescents. Duration of treatment in these trials ranged from 18 days to 10 weeks. No significant differences in outcome (ADHD Rating Scale total scores) were found in the 2 studies of immediate-release methylphenidate and atomoxetine.[79] However, significantly greater improvements were seen in patients receiving the 2 extended-release stimulant formulations (extended-release mixed amphetamine salts and osmotic, controlled-release methylphenidate) than in those receiving atomoxetine (measures included the ADHD Rating Scale and SKAMP [Swanson, Kotkin, Agler, M-Flynn, and Pelham] test).[79] The authors concluded that "clinical situations occur in which atomoxetine may be preferred, but psychostimulants should be tried first given the absence of a compelling reason that these medications should not be used in a particular patient."[79(p1140)]

Bupropion, a norepinephrine and dopamine reuptake inhibitor that is indicated for the treatment of depression, was reported to be effective in children and adolescents with ADHD.[75] In a controlled study of 162 adults with ADHD, a treatment response (scores on the ADHD Rating Scale) was seen in significantly more patients receiving extended-release bupropion than placebo (53% vs. 31%, $p = .004$), and treatment was reported to be safe and well tolerated.[80] Bupropion has also been shown to be efficacious for cigarette smoking cessation.[81]

Guanfacine is an $\alpha_2$-adrenergic receptor agonist that has been effective in the treatment of children and adults with ADHD.[82] In a double-blind crossover study of guanfacine, dextroamphetamine, and placebo in 17 adults with ADHD,[83] significantly greater improvements on the ADHD Behavior Checklist were seen with both guanfacine and dextroamphetamine than with placebo ($p < .05$); differences between guanfacine and dextroamphetamine were not significant. An extended-release formulation of guanfacine that is administered once daily has been developed.[84] The efficacy and safety of this extended-release formulation of guanfacine were assessed recently in an 8-week double-blind study.[85] The patients were 345 children

and adolescents with ADHD aged 6 to 17 years (mean of 10.5 years) who received placebo or 2 mg, 3 mg, or 4 mg of extended-release guanfacine once daily. At endpoint, changes in the ADHD Rating Scale (primary endpoint) total scores were –16.7 in patients receiving extended-release guanfacine and –8.9 in the placebo group ($p < .0001$), and treatment was generally well tolerated.[85]

One important advantage of atomoxetine and other nonstimulants in ADHD treatment is that they are far less likely to be associated with abuse and diversion than stimulants.[74] For example, in a placebo-controlled comparative study of atomoxetine and methylphenidate in "light drug users,"[86] atomoxetine was not associated with the subjective effects produced by methylphenidate, leading the authors to conclude that atomoxetine is not likely to have abuse liability.

## NEW FORMULATIONS OF ADHD MEDICATIONS AND THEIR ABUSE POTENTIAL

Several approaches are currently being used to develop formulations of medications with lower abuse potential.[75,82,87,88]

### Transdermal Delivery

A transdermal formulation contains methylphenidate in a multipolymeric adhesive platform from which the medication is released continuously when applied to intact skin.[75,82] The abuse potential of this medication does not appear to have been studied. Its slow-release formulation, however, should minimize the risk for abuse.

The efficacy of the methylphenidate transdermal system (MTS) has been demonstrated in a controlled study by McGough et al.[89] Subjects in the double-blind, placebo-controlled, laboratory-classroom, crossover study were 80 children with ADHD aged 6 to 12 years. The optimal daily dose for each child delivered over the 9-hour patch wear time was determined during a period of 5 weeks. The participants were then randomly assigned to 1 week of MTS or placebo followed by 1 week of the opposite treatment.[89] Measures of efficacy included assessments of deportment and attention and age-adjusted mathematic problems. Children receiving each dose of MTS performed significantly better than when they were receiving placebo. MTS was well tolerated, and there were no reports of serious adverse events at any time. The authors concluded that MTS "represents a successful new strategy in the provision of once-daily administration of stimulant medication for children with ADHD."[89(p483)]

### Prodrugs

Prodrugs are a new class of agents designed to gradually release the active drug and limit the possibility of overdose toxicity. Prodrugs are pharmacologically inactive or minimally active until metabolized by enzymes into an active pharmacologic agent. In theory, if the prodrug is converted into its active metabolite by enzymes in the gastrointestinal tract, its actions when taken by nonoral routes would be minimal, thus reducing the likelihood of abuse by smoking or intranasal or intravenous routes.[82,87]

Lisdexamfetamine is the first prodrug stimulant and is indicated for the treatment of ADHD. Lisdexamfetamine is a therapeutically inactive molecule. After oral ingestion, lisdexamfetamine is converted to L-lysine, an essential amino acid, and active *d*-amphetamine. Lisdexamfetamine was developed with the goal of providing an extended duration of effect that is consistent throughout the day, with a reduced potential for abuse, overdose toxicity, and drug tampering.[90,91]

A pharmacokinetic comparison of *d*-amphetamine sulfate and lisdexamfetamine in rats produced the following results: after intravenous administration, *d*-amphetamine $AUC_{0\text{-inf}}$ was about 50% less after lisdexamfetamine than after *d*-amphetamine sulfate, $C_{max}$ was about 75% less, and $T_{max}$ was about 6 times longer.[92] After oral administration, differences were modest at therapeutic doses but substantial at higher doses. For example, at doses of 1.5 mg/kg of lisdexamfetamine or *d*-amphetamine sulfate, *d*-amphetamine bioavailability was 61% after lisdexamfetamine and 84% after *d*-amphetamine sulfate, while at doses of 60 mg/kg, *d*-amphetamine bioavailability was 52% after lisdexamfetamine and 223% after *d*-amphetamine sulfate.[92]

The abuse potential of oral lisdexamfetamine and *d*-amphetamine sulfate was compared in 36 adults with a history of stimulant abuse in a double-blind crossover study.[93] On the primary measure, scores on the Drug Rating Questionnaire-Subject Liking Scale, the maximum postdose change from baseline was significantly greater in subjects receiving 40 mg of *d*-amphetamine than the comparable dose (100 mg) of lisdexamfetamine ($p = .039$). Mean "liking effects" peaked at 1.5 to 2 hours postdose in subjects receiving *d*-amphetamine and at 3 to 4 hours postdose in subjects receiving lisdexamfetamine. At a higher dose of lisdexamfetamine (150 mg), the maximum drug liking score was higher than that of 40 mg of *d*-amphetamine, but the peak effect for lisdexamfetamine was delayed by about 4 hours compared with *d*-amphetamine.[93]

In a crossover study of 9 adults with a history of stimulant abuse,[94] 50 mg of lisdexamfetamine or 20 mg of *d*-amphetamine was given intravenously over 2 minutes. The behavioral and subjective effects associated with 50 mg of intravenous lisdexamfetamine were not significantly different from those associated with intravenous placebo ($p = .29$). In contrast, 20 mg of intravenous *d*-amphetamine produced significantly greater subjective and behavioral effects than placebo ($p = .01$).[94]

### Tamper Resistance

Abuse potential is reduced by making it more difficult to extract the active pharmaceutical ingredient from the product or by making it more difficult to manipulate the formulation.[88,95] Techniques include making medications "uncrushable," "bioactivated" (formulations that require exposure to specific enteric conditions for release of active agents), or "sequestered" (formulations that release aversive or neutralizing agents when crushed). Prodrugs may also offer some degree of tamper resistance.

## ROLE OF THE PRIMARY CARE PHYSICIAN

Primary care physicians are usually the first health care providers to come in contact with children and adolescents with ADHD. They are faced with a dilemma when ADHD is associated with SUD since some of the most efficacious treatments for ADHD (stimulants) have an abuse liability themselves. Primary care physicians can play a vital role in assessment and management of this comorbidity.

The primary goal should be to assess SUD by maintaining open communication with adolescents and their parents, highlighting confidentiality. Adolescents should be asked about substance use alone, without the presence of a parent or legal guardian, to encourage accurate response. The parent or legal guardian can be interviewed in the presence of the adolescent to promote a trusting relationship with the pediatrician. In addition to asking about alcohol, tobacco, and other drug use during the interview process, it is important to assess and address environmental factors such as family history of SUD by siblings and parents. Deviant behaviors, such as truancy, frequent arguments, and alcohol and tobacco consumption, should also send signals that may warrant further screening. Screening should include obtaining a self-report from the patient, ideally with biological verification (e.g., urine toxicology screen).

Screening for SUD can be conducted quickly by using a screening instrument such as CRAFFT (Car, Relax, Alone, Forget, Friends, Trouble).[62] If an adolescent answers "yes" to 2 of the 6 items on the CRAFFT, he or she needs to be assessed further about substance use. Several quick urine toxicology tests that can be used in the office setting are available on the market. In addition, pediatricians should familiarize themselves with SUD treatment resources available in the community to which they can refer patients with SUD.

Patients considered at risk for substance use/abuse and those currently diagnosed with an active SUD should be treated with nonstimulant medications (e.g., atomoxetine, bupropion, or guanfacine), which have a lower potential for abuse than stimulants,[75] before considering stimulant medication. Extended-release formulations of stimulants can be started after documenting recovery from SUD over an adequate period of time.

To reduce diversion, primary care physicians should also educate patients and families to lock up controlled medications (e.g., stimulants) and to not inform others that they possess controlled medications. The parent or legal guardian of an adolescent with a history of SUD may consider supervising medication administration and maintaining control of the medication container. Primary care physicians should also be wary of frequent "lost" prescriptions of stimulants and requests for refills before the expected date.

## CONCLUSIONS

The prevalence of SUD among adolescents is a significant problem affecting our society. The evidence that untreated ADHD is a risk factor for SUD raises the need for early identification of signs and symptoms and for preventive interventions for SUD. In addition, there is emerging evidence that treatment of ADHD may reduce the risk of SUD. Primary care physicians are usually the first health care providers to come in contact with adolescents with ADHD and are thus in a prime position to treat ADHD and assess and help manage SUD among adolescents.

More longitudinal community-based studies are needed to identify the relationship between pharmacotherapy and SUD. Stimulants remain the first-line therapy for the normalization of core ADHD symptoms owing to their well-established efficacy and safety profiles. Evidence suggests that pharmacotherapy for ADHD may reduce the risk for SUD and may have a protective effect.[58] Studies of integrated treatment with stimulants and treatment for SUD are needed to shed light on *if* and *when* stimulant treatment may be appropriate in patients with comorbid ADHD and SUD.

Since the efficacious treatment of ADHD may also result in the reduction of SUD, the search must continue for new pharmacologic agents. Prodrugs, a new class of agents, may offer a potential means of delivering effective stimulants with a lower substance abuse liability.[90,91]

***Drug names:*** atomoxetine (Strattera), bupropion (Wellbutrin, Zyban, and others), dextroamphetamine (Dexedrine, Dextrostat, and others), guanfacine (Tenex and others), lisdexamfetamine (Vyvanse), methylphenidate (Daytrana, Ritalin, and others).

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