



Substance use disorders in adolescents with psychiatric comorbidity: When to screen and how to treat

Consider pharmacotherapy, psychotherapy when treating substance use disorders

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Substance use during adolescence is common in the United States. Data from the 2014 Monitoring the Future Survey estimated that among 12th graders, 60.2% used alcohol, 35.1% used marijuana, and 13.9% used a prescription drug for nonmedical use within the previous year.¹ An estimated 11.4% of adolescents meet DSM-IV threshold criteria for a substance use disorder (SUD).² Substance use in adolescents often co-occurs with psychological distress and psychiatric illness. Adolescents with a psychiatric disorder are at increased risk for developing a SUD; conversely, high rates of psychiatric illness are seen in adolescents with a SUD.^{3,4} In one study, 82% of adolescents hospitalized for SUD treatment were found to have a co-occurring axis I disorder.⁵ Furthermore, co-occurring psychiatric illness and SUD complicates treatment course and prognosis. Adolescents with co-occurring psychiatric illness and SUD often benefit from an integrated, multimodal treatment approach that includes psychotherapy, pharmacologic interventions, family involvement, and collaboration with community supports.

In this article, we focus on pharmacologic management of non-nicotinic SUDs in adolescents, with an emphasis on those with comorbid psychiatric illness.

Screening and assessment of substance use

It is important to counsel children with a psychiatric illness and their parents about the increased risk for SUD before a patient transitions



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It is important to be curious and nonjudgmental when evaluating substance use patterns in adolescents



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Table 1

Representative screening tools for substance use in adolescents

| Screening tool | Substance assessed | Administration of tool |
|---|---|------------------------|
| National Institute of Alcohol and Alcoholism screening questions ⁶ | Alcohol | 2 questions |
| CRAFFT ⁷ | Alcohol, <i>Cannabis</i> , other substances used to get high | 4 to 9 questions |
| Screening to Brief Intervention (SB2I) ⁸ | Tobacco, alcohol, <i>Cannabis</i> , illegal drugs, prescription drugs not prescribed to patient, over-the-counter drugs, inhalants, herbs, or synthetic drugs | 8 questions |

to adolescence. Discussions about substance abuse should begin during the 5th grade because data suggests that adolescent substance use often starts in middle school (6th to 9th grade). Clinicians should routinely screen adolescent patients for substance use. Nonproprietary screening tools available through the National Institute on Alcohol and Alcoholism and the National Institute on Drug Abuse are listed in *Table 1*.⁶⁻⁸ The Screening to Brief Intervention (S2BI) is a newer tool that has been shown to be highly effective in identifying adolescents at risk for substance abuse and differentiating severity of illness.⁸ The S2BI includes screening questions that assess for use of 8 substances in the past year.

Adolescents with psychiatric illness who are identified to be at risk for problems associated with substance use should be evaluated further for the presence or absence of a SUD. The number of criteria a patient endorses over the past year (*Table 2*) is used to assess SUD severity—mild, moderate, or severe. Additional considerations include substance use patterns such as type, site, quantity, frequency, context, and combinations of substances.

It is important to be curious and nonjudgmental when evaluating substance use patterns with adolescents to obtain a comprehensive assessment. Teenagers often are creative and inventive in their efforts to maximize intoxication, which can put them at risk for complications associated with acute intoxication. Rapidly evolving methods of ingesting highly concentrated forms of tetrahydrocannabinol (“wax,” “dabs”) are

an example of use patterns that are ahead of what is reported in the literature.

Any substance use in an adolescent with a psychiatric illness is of concern and should be monitored closely because of the potential impact of substance use on the co-occurring psychiatric illness and possible interactions between the abused substance and prescribed medication.

Treatment interventions

Although this review will focus on pharmacotherapy, individual, group, and family psychotherapies are a critical part of a treatment plan for adolescents with comorbid psychiatric illness and SUD (*Table 3, page 47*). Collaboration with community supports, including school and legal officials, can help reinforce contingencies and assist with connecting a teen with positive prosocial activities. Involvement with mutual help organizations, such as Alcoholics Anonymous, can facilitate adolescent engagement with a positive sober network.¹⁰

Pharmacologic strategies for treating co-occurring psychiatric illness and SUD include medication to:

- decrease substance use and promote abstinence
- alleviate withdrawal symptoms (medication to treat withdrawal symptoms and agonist treatments)
- block the effect of substance use (antagonist agents)
- decrease likelihood of substance use with aversive agents
- target comorbid psychiatric illness.

Table 2

General criteria for substance use disorders

| | |
|--|---|
| Impaired control over substance use | Substance used in greater quantity or over a longer time than intended Persistent wish or efforts to decrease substance use Significant time is devoted to obtain, use, or recover from the substance |
| Social impairment | Substance use interferes with meeting responsibilities at work, school, or home Continued substance use despite social or interpersonal problems due to substance use Important social, occupational, or recreational activities are decreased because of substance use |
| Risky use | Substance use in situations in which the substance use puts the individual or others at risk of physical harm Continued substance use despite knowledge that a physical or psychological problem is likely to have been caused or made worse by substance use |
| Psychological and physiological dependence | Signs of tolerance to the substance Signs of withdrawal from the substance Cravings to use the substance |
| Source: Reference 9 | |

Medication to decrease substance use and promote abstinence. One strategy is to target cravings and urges to use substances with medication. Naltrexone is an opiate antagonist FDA-approved for treating alcohol and opioid use disorders in adults and is available as a daily oral medication and a monthly injectable depot preparation (extended-release naltrexone). Two small open-label studies showed decreased alcohol use with naltrexone treatment in adolescents with alcohol use disorder.^{11,12} In a randomized double-blind placebo controlled (RCT) crossover study of 22 adolescent problem drinkers, naltrexone, 50 mg/d, reduced the likelihood of drinking and heavy drinking ($P \leq .03$).¹³ Acamprosate, another anti-craving medication FDA-approved for treating alcohol use disorder in adults, has no data on the safety or efficacy for adolescent alcohol use disorder.

There is limited research on agents that decrease use and promote abstinence from non-nicotinic substances other than alcohol. There is one pilot RCT that evaluated N-acetylcysteine (NAC)—an over-the-counter supplement that modulates the glutamate system—for treating adolescent *Cannabis* dependence. Treatment with NAC, 2,400 mg/d, was well tolerated and

had twice the odds of increasing negative urine cannabinoid tests during treatment than placebo.¹⁴ Although NAC treatment was associated with decreased *Cannabis* use, it did not significantly decrease cravings compared with placebo.¹⁵

Medication to alleviate withdrawal symptoms. Some patients may find the physical discomfort and psychological distress associated with substance withdrawal so intolerable that to avoid it they continue to use drugs or alcohol. Medication to treat withdrawal symptoms and agonist treatments can be used to alleviate discomfort and distress associated with withdrawal. Agonist treatments, such as methadone and buprenorphine, bind to the same receptors as the target substance, which allows the patient to shift to controlled use of a prescribed substitute. Agonist treatments are used for short detoxification and over longer periods of time for maintenance treatment. Methadone, which decreases craving and withdrawal symptoms from opiates by binding to the μ -opiate receptor and blocking other substances from binding, is frequently used for detoxification and maintenance treatment in adults. There is limited data on methadone substitution therapy for ado-

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Agonist treatments are used for short detoxification and over longer periods of time for maintenance treatment

Table 3

Psychotherapeutic interventions for substance use disorders in adolescents

Individual interventions

Motivational Enhancement Therapy
Cognitive-Behavioral Therapy
Adolescent Community Reinforcement Approach
Contingency Management

Family-based interventions

Brief Strategic Family Therapy
Family Behavioral Therapy
Functional Family Therapy
Multidimensional Family Therapy
Multisystemic Therapy
Community Reinforcement and Family Training

lescents in the United States.¹⁶ Methadone maintenance for adolescents in the United States is restricted to severe cases of opioid use disorder. Federal guidelines specify that adolescents age <18 can only receive methadone if they have had 2 unsuccessful detoxification attempts or outpatient psychosocial treatments and have met DSM criteria for an opioid use disorder for 1 year.¹⁷

Buprenorphine is a partial μ -opiate receptor agonist that is FDA-approved for use in adolescents age ≥ 16 with opioid dependence. Although a waiver from the U.S. Drug Enforcement Administration is required to prescribe buprenorphine, it generally can be administered in outpatient settings with relative ease compared with methadone.

Marsch et al¹⁸ examined the efficacy of buprenorphine compared with clonidine for detoxification over 1 month in 36 adolescents with opioid dependence. Clonidine is an α -2 adrenergic agonist that often is used during detoxification from opioids.¹⁹ Although both buprenorphine and clonidine relieved withdrawal symptoms, a significantly higher percentage of patients receiving buprenorphine completed treatment (72%) compared with those taking clonidine (39%) ($P < .05$).¹⁸ Detoxification with buprenorphine also was associated with a higher percentage of negative urine drug screens (64% vs 32%, $P = .01$), and those receiving buprenorphine were more likely to continue on naltrexone maintenance for continued medication-assisted treatment after detoxification compared with those randomized to clonidine.

Woody et al²⁰ compared use of buprenorphine/naloxone for opioid detoxification vs short-term maintenance. Patients age 16 to 21 were randomized to detoxification over 2 weeks vs stabilization and maintenance for 9 weeks and taper over 3 weeks. Maintenance treatment with buprenorphine/naloxone was associated with less opioid use, less injection drug use, and less need for addiction treatment outside of that received through the study compared with detoxification treatment. When buprenorphine/naloxone was discontinued both the detoxification and maintenance groups had high rates of positive urine toxicology screens at 1-year follow up (mean 48% to 72%). These data suggests maintenance with buprenorphine/naloxone for adolescents and young adults is more effective than short-term detoxification for stabilizing opioid use disorders, although optimal treatment duration is unclear. Clinically, it is important to continue buprenorphine/naloxone maintenance until the patient has stabilized in recovery and has acquired coping skills to manage urges, cravings, and psychological distress (eg, anger, stress) that often arise during a slow taper of agonist treatment.

Antagonist treatment to block the effect of substance use

As an opioid receptor antagonist, naltrexone is effective for treating opioid use disorder because it blocks the action of opioids. Fishman et al²¹ published a descriptive series of 16 adolescents and young adults followed over 4 months who received the injectable depot preparation (extended-release) nal-

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Methadone maintenance for adolescents in the United States is restricted to severe cases of opioid use disorders



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Often adolescents are not willing to adhere to disulfiram because they are concerned about the aversive reaction with alcohol

trexone while in residential treatment, and then discharged to outpatient care. Most patients who received extended-release naltrexone remained in outpatient treatment (63%) and reduced their opioid use or were abstinent at 4 months (56%). One barrier to naltrexone treatment is the need to be abstinent from opioids for 7 to 10 days to prevent precipitated opioid withdrawal. Therefore, naltrexone is a good option for adolescents who present for treatment early and are not physiologically dependent on opioids or are receiving treatment in a structured environment after detoxification, such as residential treatment or sober living.

Aversive agents to diminish substance use. Aversive agents produce an unpleasant reaction when a target substance is consumed. Disulfiram is prototypic aversive agent that prevents the breakdown of acetaldehyde, a toxic metabolite of alcohol. Patients who drink alcohol while taking disulfiram may experience adverse effects, including tachycardia, shortness of breath, nausea, dizziness, and confusion. There have been 2 studies examining the efficacy of disulfiram in adolescents with alcohol use disorder. Niederhofer et al²² found that disulfiram treatment significantly increased cumulative abstinence in a small RCT ($P = .012$). In another small randomized, open-label, 3-month study of adolescents who received disulfiram or naltrexone in addition to weekly psychotherapy, disulfiram was superior to naltrexone in mean days abstinent from alcohol, 84 days vs 51 days, respectively ($P = .0001$).²³ Often adolescents are not willing to adhere to disulfiram because they are concerned about the aversive reaction when combined with alcohol use. Consider prescribing disulfiram for adolescents who are about to go “on pass” from a therapeutic school or residential SUD treatment center and will be returning to an environment where they may be tempted to use alcohol.

Pharmacotherapy to treat co-occurring psychiatric illness

Continued treatment of a psychiatric illness that co-occurs with SUD is important. As

we recommended, consider psychosocial treatments for both the SUD and comorbid psychopathology. Several single-site RCTs have evaluated the efficacy of the selective serotonin reuptake inhibitors (SSRIs) fluoxetine and sertraline for depressive disorders in adolescents with a co-occurring SUD.²⁴⁻²⁸ Most studies have shown improvement in depressive symptoms and substance use in medication and placebo groups.^{24,25,27,28} However, treatment with fluoxetine, 20 mg/d, or sertraline, 100 mg/d, when compared with placebo was associated with improved depressive symptoms in 1 of 3 studies and had no significant difference in SUD outcome. The authors of these studies believe that the general improvement in depression and the SUD was related to use of cognitive-behavioral therapy (CBT) and/or motivational enhancement therapy.^{24,25,27,28}

Research on the use of mood stabilizers for adolescents with mood dysregulation and a SUD is limited but has suggested benefit associated with pharmacotherapy (*Table 4*).²⁹⁻³² Two RCTs and 1 open-label study demonstrated reductions in substance use with mood stabilizer treatment in adolescents with co-occurring SUD and mood dysregulation.²⁹⁻³² The effect of pharmacotherapy on mood dysregulation ratings are less clear because there was no change in severity of affective symptoms observed in a small RCT of lithium (average blood level 0.9 mEq/L)²⁹; and improvement in affective symptoms was noted in topiramate (300 mg/d) and placebo groups when both groups were treated with concurrent quetiapine.³² Because of the high risk of SUD and severe morbidity in juvenile bipolar disorder and severe mood dysregulation,³³ larger RCTs are warranted.

Several studies have evaluated the impact of stimulant and nonstimulant treatments for attention-deficit/hyperactivity disorder (ADHD) in adolescents with a co-occurring SUD.³⁴⁻³⁹ The largest and only multisite study evaluated the efficacy of osmotic (extended) release methylphenidate (OROS-MPH) vs placebo for adolescents who also were receiving CBT for SUD.³⁶ In this 16-week RCT, the OROS-MPH and placebo groups showed improvement

Table 4

Pharmacotherapy trials for treating mood dysregulation and SUD in adolescents

| Study | Psychiatric disorder | SUD | Study design | Intervention | Outcome |
|---|--|------------------------------|---|--|---|
| Geller et al, 1998 ²⁹ | Bipolar spectrum disorder | All SUDs | 6-week RCT, N = 25 in outpatient treatment | Lithium (average blood level 0.9 mEq/L) | Decreased positive urine drug tests ($P = .028$), improved functioning, no change in affective symptoms |
| Donovan et al, 1996, ³⁰ 1997 ³¹ | Oppositional defiant disorder and/or conduct disorder and significant mood dysregulation | <i>Cannabis</i> use disorder | 5-week, open-label, N = 8 in outpatient treatment | Valproic acid (mean blood level 75 μ g/mL) | Decreased <i>Cannabis</i> use ($P < .007$), improvement in affective symptoms ($P < .001$) |
| DelBello et al, 2011 ³² | Bipolar disorder | Frequent <i>Cannabis</i> use | 16 week RCT, N = 75 treated with quetiapine ≤ 800 mg/d | Topiramate, 300 mg/d | Decreased <i>Cannabis</i> use, no difference in the improvement in affective symptoms between topiramate and placebo groups |

RCT: randomized placebo controlled trial; SUD: substance use disorder

in self-reported ADHD symptoms with no difference between groups. Parent report of ADHD symptoms did indicate a greater reduction in symptoms in the OROS-MPH group compared with placebo. Both groups had a decrease in self-reported days of substance use over the past month with no differences between groups. Pharmacotherapy trials for ADHD that have included psychotherapy highlight the effectiveness of CBT for SUD and co-occurring psychiatric illness.^{36,39,40}

Although conduct disorder and anxiety disorders commonly co-occur with SUD, there has been less research evaluating the impact of pharmacotherapy on treating these disorders. Riggs et al^{25,34,35,41} evaluated the impact of pharmacotherapy targeted to co-occurring ADHD and major depressive disorder in the context of conduct disorder and SUD. When evaluated in an outpatient setting, the presence of a treatment intervention to address the co-occurring SUD was an important component that led to a reduction in conduct symptoms.^{25,35} There have been no comprehensive studies on the impact of pharmacotherapy for treating anxiety and SUD in adolescents.

Recommendations for clinical management

Although more research is needed to evaluate the role of pharmacotherapy for adolescents with co-occurring psychiatric illness and a SUD, recommended practice is to continue pharmacotherapy and closely monitor response to treatment when at-risk substance use begins in patients with co-occurring psychiatric illness. In adolescents with a threshold SUD, continue pharmacotherapy for unstable mood disorders with first-line choices of SSRIs for unipolar depression and second-generation antipsychotics for bipolar spectrum illness. Suggested conservative pharmacological interventions for anxiety disorders include SSRIs and buspirone, which have been shown to be effective for treating anxiety in children and adolescents.^{42,43} For patients with comorbid ADHD and SUD, if possible, it is recommended to first stabilize substance use (low-level use or abstinence) and consider treating ADHD immediately thereafter with a nonstimulant such as atomoxetine, which has data on efficacy and safety in context to substance use; and/or an α -agonist or an extended-release stimu-

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For patients with comorbid ADHD and SUD, first stabilize substance use and consider treating ADHD immediately thereafter



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One strategy is to make continued prescription of any medication contingent on engaging in SUD treatment

lant. Because of the potential for misuse and toxicity associated with concurrent substance use, benzodiazepines should be considered a last treatment of choice for adolescents with anxiety disorders and a SUD. Similarly, the use of immediate-release stimulants should be avoided in patients with ADHD and a SUD. When prescribing medications that could be misused or toxic when combined with a substance, it is important to evaluate the risk and benefit of continued use of a particular medication and consider prescribing lower quantities to decrease risk for misuse (1- to 2-week supply). Adolescents often are reluctant to engage in SUD treatment and one strategy to consider is to make continued prescription of any medication contingent on engaging in SUD treatment. Enlist parents in helping to monitor, store, and administer their child's medication to improve adherence and decrease the potential for misuse, diversion, and complications associated with substance intoxication.

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Related Resources

- National Institute on Drug Abuse. www.drugabuse.gov.
- National Institute on Alcohol Abuse and Alcoholism. www.niaaa.nih.gov.
- Substance Abuse and Mental Health Services Administration. www.samhsa.gov.

Drug Brand Names

| | |
|---------------------------------------|--|
| Acamprosate • Campral | Lithium • Lithobid, Eskalith |
| Atomoxetine • Strattera | Methadone • Dolophine |
| Buprenorphine • Subutex | Naltrexone • ReVia, Vivitrol |
| Buprenorphine/ naloxone • Suboxone | Osmotic (extended) release methylphenidate • Concerta |
| Buspirone • Buspar | Sertraline • Zoloft |
| Clonidine • Catapres | Topiramate • Topamax |
| Disulfiram • Antabuse | Quetiapine • Seroquel |
| Fluoxetine • Prozac | Valproic acid • Depakote |

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Enlist parents in helping to monitor and administer their child's medication to improve adherence and decrease potential for misuse

Bottom Line

It is important to screen for substance use in adolescents with co-occurring psychiatric illness and vice versa. When at-risk or hazardous substance use is detected there are effective psychosocial and pharmacologic interventions that can be used to treat adolescent substance use disorders alone and in combination with certain psychiatric disorders.