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Child and Adolescent Psychiatry (M DelBello, Section Editor)

Pharmacotherapy for Adolescents with Substance Use Disorders

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Opinion statement

Substance use disorders (SUD) are among the most prevalent and serious mental disorders occurring in adolescents. Though significant gains have been made in evidence-based psychosocial therapies for the treatment of adolescent SUD, pharmacotherapy studies are scarce. Psychosocial treatment should most often be considered as the first-line treatment for adolescent substance use disorders. These may include such SUD-specific therapies as motivational enhancement therapy (MET), cognitive-behavioural therapy (CBT) and family-based interventions. We advocate for widespread availability of such treatments. Many patients will continue to struggle with their addictions despite high-quality psychosocial treatment. Comorbid mental disorders are quite common and may limit gains from such treatments. Many adolescents with severe SUD and mental disorders or disorders refractory to psychosocial interventions may benefit from pharmacotherapy in their road to recovery. The evidence for this approach is quite limited, and so any implementation of medication prescription for the treatment of SUD in adolescents needs to be carefully monitored. Potential benefits and risks need to be evaluated in light of the clinical presentation. Patients and families should be made aware of the limited degree of evidence for such an approach and should also be made aware of any off-label use of medications.

Introduction

Substance use most often begins in adolescence. Biological, psychological and social factors render adolescents vulnerable to developing an SUD [1–3]. In a large American sample, the median age of onset of SUD in youth aged 13–18 was found to be 15 years of age with a rapid rise in incidence thereafter. Moreover, drug use disorders (8.9 %) were found to be more common than alcohol use disorders (6.4 %) in this age group [4]. In the general population, the peak age of onset for SUD is in young adulthood (ages 18–20) apart from cannabis use disorder, which typically has its age of onset in older adolescents (ages 16–18) [5, 6]. A "concurrent disorder" refers to the situation where a person has both a mental disorder and an SUD. In adolescents, co-occurring mental disorders and SUDs each have the potential to affect a substantial negative impact on the course and treatment outcome of the other [7].

The scope of this literature review is limited to studies where psychotropic medications were tested in the context of substance use disorders (with or without psychiatric comorbidity), where the mean age of participants was below 18 years old and where the study was published in the period between July 2008 and February 2015. Details of dosing, drug–drug interactions, side effects and contraindications are included only for medications that are approved by the Food and Drug Administration for this age group. Had there been interventions with two randomized controlled trials showing efficacy, but not yet approved by the FDA, we would also discuss prescribing details; however, there were no such interventions found. Studies on adults are discussed with the acknowledgment that extrapolation to adolescent populations has its limitations.

Treatment of alcohol dependence

Published prior to 2008, there are small randomized controlled trials (RCTs) testing acamprosate [8] and disulfuram [9], as well as a case series examining the use of ondansetron [10]. Each of these studies showed preliminary evidence of efficacy for the treatment group in adolescents with alcohol dependence.

More recently, Miranda et al. conducted a cross-over randomized controlled trial of naltrexone versus placebo in 22 adolescents (aged 15–19) with problematic alcohol use [11]. In this trial, alcohol use decreased, craving was blunted and response to alcohol was altered to a statistically significant degree when participants were taking naltrexone relative to placebo. This study was more of a "proof-of-concept" study: only 50 % of the sample met criteria for alcohol dependence and each arm of the trial only lasted 8 to 10 days. Moreover, participants were recruited from the community, not from treatment clinics. The findings support future research for naltrexone as a viable treatment option in adolescents who have alcohol dependence; current use in clinical practice warrants caution until such research is conducted.

Treatment of cannabis dependence

Gray et al. conducted a large controlled treatment trial in youth with cannabis dependence (n=116, aged 15–21) [12•]. Participants were randomized to *N*-acetylcysteine (NAC) or placebo for a period of 8 weeks. Both groups received contingency management and cessation counseling. They found a greater chance of having a negative urine drug screen in the NAC group relative to placebo (OR 2.4 95%CI 1.1–5.2; NNT 7.3). Most secondary outcome measures of reduced cannabis use did not achieve significance. Outcomes at 4 weeks post-treatment numerically favoured the NAC group, but did not reach statistical

significance. While the results are promising, further research is needed to clarify the role of NAC administration in the clinical context.

Treatment of opiate dependence

An RCT published in 2005 examined the use of buprenorphine in adolescent outpatients with opiate dependence [13] and found that buprenorphine administration led to greater treatment retention and fewer positive urine drug screens relative to clonidine. A more recent RCT examined the extended use of buprenorphine in outpatient youth with opiate dependence, suggesting that continuation treatment leads to better outcomes than brief detoxification treatment. Much of the sample in this study was over 18 [14]. Buprenorphine may be a useful option for non-responsive treatment of opioid dependence in adolescents. There are also observational studies examining methadone use in adolescents with heroine dependence [15, 16], suggesting efficacy of methadone treatment.

Fishman et al. published a case series of 16 outpatient adolescents (aged 16–20) with opioid dependence treated with extended-release naltrexone (380 mg IM per month over 4 months). Ten of the 16 participants were retained in treatment after 4 months, and 9 had "good" clinical outcomes as judged by the investigators. We recommend waiting until further research elucidates the potential benefits and risks before taking this approach [17].

Treatment of methamphetamine dependence

Heinzerling et al. conducted a small controlled trial of 19 adolescents (aged 14–21) with methamphetamine dependence randomized to bupropion SR (150 mg po bid) or placebo in a 2:1 ratio [18]. Those in the active treatment group had *fewer* methamphetamine-negative urine drug screens relative to placebo, suggesting that bupropion may actually exacerbate methamphetamine abuse, though small sample size and baseline differences between groups may account for the results. The research group concluded that a larger trial of outpatient adolescents would not be feasible. Given the implication of this trial that bupropion may worsen the course of methamphetamine use disorders, we do not recommend using bupropion for the treatment of methamphetamine dependence at this time.

Treatment of insomnia associated with substance dependence

Insomnia is a common symptom of withdrawal from substances and increases the risk of relapse [19–21]. Insomnia is also a common symptom associated with many mental disorders, including depression and anxiety. It can be difficult to differentiate whether or not insomnia is secondary to substance use, mental disorders or is multifactorial. The following studies include those targeting general withdrawal symptoms (where insomnia was analyzed separately) as well as specifically for insomnia. We have grouped these studies together, given the clinical challenge of elucidating the etiology of insomnia,

Quetiapine

Cooper et al. conducted an adult human laboratory investigation using a within-subject, cross-over design (n=14) to examine the effects of quetiapine on cannabis withdrawal [22]. Quetiapine (up to 200 mg/day in divided doses) significantly improved measures of subjective sleep quality and appetite in the cannabis withdrawal phase relative to placebo; however, it was also associated with increased cravings and requests for cannabis use relative to placebo. Even at low doses, quetiapine can have a negative impact on weight and body mass index [23]. Further study is needed to examine the role of quetiapine in sleep for adolescents with SUD and concurrent disorders. From clinical experience, we have found quetiapine to be very helpful in the treatment of adolescents and young adults in residential or inpatient SUD treatment requiring assistance with withdrawal-related insomnia (particularly as it pertains to cannabis-related withdrawal) at doses from 50 to 100 mg po qhs. Given the preliminary findings of Cooper et al. of increased cravings for cannabis with quetiapine administration, outpatient use may require closer monitoring.

Gabapentin

A small RCT by Brower et al. explored gabapentin as a treatment for insomnia associated with adult alcohol dependence [24]. Gabapentin did not separate from placebo, but the study was likely underpowered as sample size was very small. An observational study in adults suggested that gabapentin is superior to trazodone for the SUD population [25]. Another observational study suggested benefit in children with insomnia (without substance dependence) [26]. Gabapentin has also been studied systematically in over 240 children for the treatment of seizure disorders where it was found to be well tolerated [27]. The junior author (DBC) has found gabapentin (~300–600 mg po qhs) to be helpful in adolescent in-patients with withdrawal-related insomnia.

Trazodone

One adult study found that trazodone administration for insomnia in patients with alcohol dependence led to *more* alcohol consumption post-detoxification relative to placebo [28], suggesting a relative contraindication in this population. Moreover, one observational study would suggest that gabapentin is superior to trazodone for treatment of insomnia associated with alcohol dependence [25]. Trazodone has recently been found to be associated with SSRI non-response and self-harm in adolescents with treatment-resistant depression, particularly in adolescents receiving fluoxetine or paroxetine [29]. The authors tend to limit use of trazodone in adolescents with concurrent disorders to second or third line.

Treatment of major depressive disorder in the context of concurrent substance dependence

Cornelius et al. conducted a survival analysis in 116 outpatient adolescents with alcohol dependence who had achieved abstinence for 7 days [30]. Patients with major depressive disorder (MDD) had a much shorter time to relapse (median=19 days) relative to those without MDD (median=45 days, p<0.05).

In the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) trial (*n*=334), participants who had lower levels of substance-related impairment had better response to treatment for their MDD [31]. In a meta-analysis of adults with comorbid depression and alcohol use disorders, Nunes and Levin (2004) found that antidepressants may improve depression relative to placebo, but have limited benefits on substance use outcomes. Other adult studies have found that antidepressant use in an "early-onset" subtype of alcohol dependence is associated with *increased* alcohol use relative to placebo, whereas the reverse is true in the "late-onset" subtype [32, 33]. These investigators suggest that SSRIs may increase impulsivity in the early-onset subtype. Moreover, recent studies have suggested that this relationship is at least partially mediated by genotype relating to a serotonin transporter gene [34]. These results give reason to pause for use of SSRIs in adolescents with alcohol dependence, as all adolescents with alcohol dependence, by definition, have an early-onset type. That being said, those with early-onset alcohol dependence seeking care in adulthood may be a different population than adolescents with alcohol dependence seeking care while still young—an important distinction as extrapolation from one population to another may not be valid.

Prior to our publication time interval of focus, Riggs et al. had conducted the largest RCT to date on pharmacotherapy for adolescents with concurrent depression and SUDs. Participants were randomized to fluoxetine or placebo. All groups received CBT targeting SUDs. While the primary outcome (Childhood Depression Rating Scale, revised administered by telephone interview) separated from placebo, favoring the use of fluoxetine, many secondary outcomes were not significantly different between groups. Moreover, the proportion of negative urine drug screens was *lower* in the fluoxetine arm relative to placebo, though the clinical implications of this finding are not clear. On self-report measures of substance use, no significant difference between treatment groups was found; however, all groups showed improvement of substance use, depressive symptoms and conduct symptoms, supporting the positive effect of SUD-specific psychotherapy [35].

In the past 5 years, there have been two other randomized trials of fluoxetine versus placebo in the treatment of adolescents with comorbid depression and SUD.

Findling et al. initiated an 8-week RCT in adolescents with major depressive disorder and comorbid alcohol or cannabis dependence with no psychotherapeutic intervention [36]. Participants were allocated to a fluoxetine treatment arm (10 mg/day for 4 weeks, then titrated up) or placebo. The authors report that the trial was terminated early due to futility, noting no statistically significant difference at interim analysis (*n*=34) and little chance of finding significance should the trial go to completion. The extended time at low dose of fluoxetine (10 mg/day) in this trial may account for lack of improvement with fluoxetine; 20 mg per day is typically thought to be the lowest effective dose for this medication. On post hoc analysis, chronicity of depressive symptoms and "no-more-than-moderate" alcohol use predicted response to fluoxetine relative to placebo.

Cornelius et al. studied adolescents (*n*=50) with comorbid MDD and alcohol use disorder [37]. They randomized the participants to fluoxetine (10 mg/day for 2 weeks, then increased to 20 mg/day) and placebo for a 12-week trial. Both groups received CBT with MET. They did not find any between-

group treatment differences with regard to depressive symptoms or alcohol use outcomes, though both groups showed significant improvement. The authors postulated that substance-induced depressive symptoms might have contributed to the lack of distinction between groups.

Zhou et al. have recently conducted a meta-analysis on the use of SSRI antidepressants relative to placebo in adolescents and young adults for comorbid depression and substance use disorders that included a total of five studies [38•]; four of these studies involved providing CBT to both treatment arms. They found that, overall, there was a statistically significant benefit of using antidepressants over placebo for treatment of depressive symptoms; however, the effect size was small and there were no benefits found with regard to substance use outcomes.

In considering all of the above studies, the evidence for use of fluoxetine to treat MDD in the context of active comorbid SUD is not compelling. Future research on pharmacogenetics may further shed light on this treatment issue. Despite the limited evidence, these authors put forward that there are situations in which a trial of fluoxetine or an alternate SSRI may be indicated, namely where depressive symptoms are particularly severe or persistent despite a despite the marked improvement of the substance use disorder.

Fluoxetine

Dose	We recommend starting at 10 mg/day for the first week, then increasing to 20 mg/day if tolerated. The dose can then be titrated up by 20 mg/day increments every 2–4 weeks to a maximum 60 mg/day, depending on response and tolerability.
Contraindications	Fluoxetine is contraindicated in the context of a known bipolar I disorder in the absence of a mood-stabilizing medication. If a first-degree relative has an established diagnosis of bipolar disorder, antidepressants should only be used with caution.
Drug–drug interactions	Fluoxetine is a potent inhibitor of the P450 2D6 enzyme and thus may lead to many different drug–drug interactions. Most notably, it may increase serum levels of risperidone or aripiprazole. Fluoxetine (and sertraline) may inhibit metabolism of buprenorphine [39]. Escitalopram may be a favourable option in patients who are potential candidates for buprenorphine treatment. Serotonin syndrome can result from combining fluoxetine with monoamine oxidase inhibitors. Fluoxetine and its active metabolite have long half-lives and need to be taken into account when switching anti-depressants.
Main side effects	Common side effects with fluoxetine include gastrointestinal upset, headaches, psychomotor activation, sleep disruption and sexual side effects. There appears to be a small, but significant sub-group of adolescents for whom suicidal ideation worsens upon starting fluoxetine [40]. Close monitoring upon initiation is indicated for this reason.
Special points	If fluoxetine is not tolerated or does not lead to adequate response, escitalopram may be tried as RCTs support its use in adolescents [41, 42]. A switch to venlafaxine does not appear to have superior efficacy to another SSRI trial and is less well tolerated relative to the SSRIs in adolescents with depression non-responsive to one SSRI [43, 44]. Moreover, one randomized trial in adults with comorbid MDD and cannabis dependence (n=103) found significantly *lower* rates of abstinence in patients taking venlafaxine relative to placebo

[45]. The authors tend to limit use of venlafaxine in adolescents with concurrent disorders as a result.

Cost Generic forms of fluoxetine are relatively inexpensive.

Treatment of anxiety disorders comorbid with substance dependence

While there is modest evidence that using SSRIs may reduce symptoms of anxiety in the context of concurrent anxiety disorders and alcohol use disorders adults [46, 47], we are not aware of any such trials in adolescents. There is substantial evidence to use SSRIs for the treatment of anxiety disorders in children and adolescents without substance use disorders [48]. Sertraline has been particularly well studied in pediatric populations [49, 50]. In cases refractory to SSRIs, one may consider using gabapentin, given its evidence for use in adult anxiety disorders [51, 52] and adult substance use disorders [53, 54]; however, adolescent data are lacking as are data for adults with concurrent disorders.

Treatment of attention deficit disorder comorbid with substance dependence

Results of an earlier, small cross-over study provided some preliminary support for the use of extended-release methylphenidate in ADHD with concurrent SUD [55]. There are two case series demonstrating within-group improvements in ADHD symptoms when bupropion (sustained-release) is used for concurrent ADHD and SUD in adolescents [56, 57], but no randomized controlled trials examining bupropion that we are aware of.

Riggs et al. conducted a randomized controlled trial of 303 adolescents with ADHD allocated to methylphenidate-OROS or placebo [58]. Both groups received individual CBT for SUD. After 16 weeks of treatment, there was no statistically significant difference between groups on the primary outcome of self-reported ADHD symptoms, though both groups had significant decreases in their symptoms. On secondary outcomes, there was a greater reduction in parent-rated symptoms of ADHD in the MPH-OROS group relative to placebo. On a clinician-rated measure of global impression of improvement, there was no difference between groups. On a patient-rated measure of global impression of improvement, the MPH-OROS group had greater rates of response relative to placebo. There was no difference between groups on self-reported substance use, but more negative urine drug screens in the MPH-OROS group. Given the mix of non-significant outcomes and statistically significant outcomes favoring MPH-OROS, the results of this trial are equivocal. The authors commented on the possibility that self-report of ADHD symptoms in adolescents may not be a valid measure. Clinical experience leads us to agree that some adolescents with ADHD who respond to stimulant medications may not recognize the response effect. Ultimately, the use of extended release stimulants has not been established as effective in the treatment of ADHD in the context of active substance dependence.

As stimulants are a known common class of drugs of abuse, practitioners may be concerned about the use of stimulants in adolescents with co-morbid ADHD and SUD. When long-acting stimulants are taken orally, there is a lower risk of potential for dependence, though we have observed addictive behaviour with the long-acting amphetamines in some of our patients. Methylphenidate-OROS (the trade name version) is particularly quite difficult to use intranasally or intravenously due to the OROS delivery system. Lisdexamfetamine offers the benefit of being prodrug, requiring first-pass metabolism after oral administration to become a psychoactive substance, whereas it is inactive if used intranasally or intravenously. Unfortunately, there are no published randomized controlled trials examining the use of lisdexamfetamine in the context of adolescents ADHD with comorbid substance use. Some long-acting stimulant formulations use encapsulated beads of medication (e.g. Biphentin and Adderall XR); these forms are apparently easier to misuse for euphoric effects than the aforementioned stimulant formulations.

Atomoxetine is a non-stimulant medication approved for the treatment of ADHD in adolescents and may seem an attractive choice for patients with concurrent substance use disorders. Thurstone et al. performed a randomized controlled trial on 70 adolescents with comorbid ADHD and SUD allocated to either atomoxetine or placebo [59]. Both groups received CBT+MI. There was no significant difference in reducing self-reported ADHD symptoms or substance use in this trial. Clinically, we find that stimulants have a much greater impact on ADHD symptoms relative to atomoxetine, and in certain ADHD treatment guidelines, atomoxetine is now considered a second-line choice after extended release stimulants [60].

Given the available evidence, barring other determining factors, we would recommend methylphenidate-OROS as a first-line agent in the context of severe ADHD symptoms or persistent prominent ADHD symptoms despite marked reduction of substance use. Should methylphenidate-OROS not be effective, lisdexamfetamine is a reasonable second option.

Long-acting stimulants

Dose	Methylphenidate-OROS is often started at 18 mg per day and can be increased in 18 mg increments weekly to a target dose of 54–72 mg per day. Some experts have suggested that increasing to 90 mg per day can be tried in older adolescents as may be warranted in young adults in the event that 72 mg only leads to partial response [60]. Lisdexamfetamine is often started at 30 mg per day (often an effective dose) and can be titrated up in 10 mg/day increments weekly to a maximum dose of 70 mg per day and up to 90 mg/day in older adolescents showing partial response [60].
Contraindications	Relative contraindications include a history of stimulant abuse or dependence, a history of an eating disorder, a history of psychosis or a history of any cardiac problems.
Drug–drug interactions	The most concerning drug–drug interactions for stimulants would occur with MAO-Is, potentially triggering a hypertensive crisis. Ongoing recreational amphetamine or cocaine misuse may have additive effects and lead to toxicity.

Main side effects	Common side effects include decreased appetite, insomnia, stomach upset, headaches and mild increases in blood pressure and heart rate may occur. Some patients describe feeling "zoned-out" with stimulants.
Special points	Despite limited ability to abuse long-acting stimulants intranasally or intravenously, risk of diversion is still of concern as many adolescents and young adults will take stimulants they were not prescribed orally for the purposes of academic attainment or to promote wakefulness at parties. Supervised administration by a responsible adult is recommended to help prevent potential misuse of prescribed stimulants. Clinically relevant urine drug screening may be helpful in monitoring treatment response and outcomes.
Cost	Trade name long-acting stimulants can be relatively expensive for the family if not covered by insurance; however, generic forms will have significantly different pharmacokinetics, which may affect abuse liability and effectiveness.

Treatment of borderline personality disorder comorbid with substance dependence

We are not aware of any pharmacology studies on borderline personality disorder in adolescents, likely in part due to controversy with the concept of diagnosing BPD in this age group [61]. In adults, there is evidence that topiramate may be helpful in decreasing some symptoms of BPD (particularly anger) [62–64] and in decreasing alcohol consumption in people with alcohol dependence [65]. The use of topiramate (slowly titrated up to 100 mg twice daily) as an augmentation to psychotherapy to target severe anger in adolescents meeting criteria for BPD with comorbid severe alcohol dependence is worth further investigation. Careful monitoring is needed should severity warrant this approach.

A recent adult RCT suggests that quetiapine extended release (150–300 mg/day with an optimal dosage of 150 mg/day) may reduce symptoms of BPD [66]. Moreover, there is some preliminary evidence that quetiapine may reduce alcohol use in those with a type B profile (earlier onset and greater psychiatric comorbidity) [67], though results are not consistent [68]. This approach warrants further research in adolescents with BPD features and SUD.

Treatment of bipolar disorder comorbid with substance dependence

While there is some very preliminary evidence for the use of lithium in adolescents with bipolar disorder and substance dependence [69], and adult data suggesting that valproic acid may be particularly helpful in this context [70], we recommend treating the bipolar disorder as the

primary target first using standard means [71, 72]. We are not aware of any recent pharmacology trials for treatment of bipolar disorder with comorbid substance dependence in adolescents.

Treatment of schizophrenia comorbid with substance dependence

We are not aware of any studies in adolescents on pharmacological treatment of schizophrenia and co-morbid substance dependence. We are left to extrapolate from young adult first episode psychosis studies and adolescent studies on schizophrenia in general [72]. Compliance with antipsychotics may be particularly problematic in adolescents and young adults with comorbid SUD. Though off-label, we recommend considering depot formulations should oral medication adherence be problematic. In adolescent patients who have had two failed trials of other antipsychotics, we have found that, clinically, clozapine has also been helpful in reducing substance use apart from controlling psychotic symptoms. We recommend a trial of clozapine as the next step in this context. There is some evidence for the use of clozapine in adolescent treatment-resistant schizophrenia [73, 74] and adult data supporting this recommendation in concurrent disorders [75, 76], though RCTs are greatly needed to add further credence to this recommendation.

Conclusion

Psychotropic medications may be a reasonable option for some adolescents with severe SUD refractory to psychosocial treatment or severe comorbid mental disorders in the context of specific SUD treatment. At the same time, the evidence for a pharmacotherapy approach is limited and needs to be evaluated on a case-by-case basis. Careful monitoring of response and adverse events is highly recommended should this approach be used.

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Compliance with Ethics Guidelines

Conflict of Interest
Darren Courtney declares that he has no conflict of interest.
Robert Milin declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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