

Medication-Assisted Treatment of Substance Use Disorders Among Adolescents

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Substance use disorders (SUDs) are common among adolescents in the United States. Among community-based samples, as many as 1 in 4 adolescents meets criteria for abuse of at least one substance, and 1 in 5 meets criteria for substance use dependence.¹ Early age of first substance use conveys risk of developing SUDs and faster transition time from first use to the development of SUD.^{2,3} Despite the frequency and severity of SUDs among adolescents, only 10% of adolescents with SUDs access mental health care for treatment.⁴ Although there is a paucity of Food and Drug Administration (FDA)-approved medications to treat SUDs among adolescents, medication-assisted treatment (MAT) strategies are well-established as effective for treating certain SUDs in adults.

MAT is a pharmacologic intervention for SUDs that is combined with evidence-based psychosocial approaches and is intended to be part of a comprehensive treatment plan often including psychotherapy, family interventions, and medical management. Therefore, MAT is often limited to specialized addiction clinical programs that can offer the interdisciplinary teams required to implement these comprehensive plans. MAT improves the benefits of behavioral therapy alone for SUDs⁵⁻¹² and improves psychotherapy attendance rates.⁶ Proper implementation of MAT can increase abstinence rates among adolescents with opioid,⁵ alcohol,^{6,8,13-15} cannabis,⁹ and tobacco use disorders.¹⁰⁻¹² As such, understanding available MAT options is important for providers who work with adolescents. With a goal of updating pediatric mental health practitioners, this article briefly reviews medications used for MAT in adolescents with SUDs, focusing on opioid, alcohol, cannabis, and tobacco use disorders. However, it is important to note that nearly all of the following medications are not FDA-approved for used in adolescents, and

that more research is needed to determine their efficacy in adolescents with SUDs.

Alcohol Use Disorder (AUD)

Alcohol is the most commonly abused substance among adolescents: roughly 3.5% of adolescents meet *DSM-IV* criteria for alcohol dependence.⁶ However, there are no FDA-approved medications to treat AUD in adolescent patients. Naltrexone (Vivitrol; Revia), acamprostate (Campral), and disulfiram (Antabuse) are approved for treatment of adults with AUD. All of these treatments have large randomized control trials (RCTs) supporting use in young adults.¹⁵⁻¹⁷ Fewer studies in adolescent populations are available, though some do exist.⁶⁻⁸ Therefore, MAT in adolescents with SUDs involves using off-label medications that have been shown to be effective primarily in adults.

Naltrexone is an opiate antagonist that reduces the euphoria associated with disordered alcohol use. Acamprostate is thought to decrease craving through its antagonism of N-methyl-D-aspartate (NMDA) glutamate receptors. This antagonism equilibrates the excitatory-inhibitory balance disrupted by the increase of glutamate receptor sensitivity occurring in the wake of chronic alcohol consumption. Disulfiram creates an aversion toward alcohol via fostering an “acetaldehyde reaction” when alcohol is consumed: the drug inhibits the conversion of acetaldehyde, a usual byproduct of alcohol, to excretable acetate, so that imbibing alcohol leads to a buildup of acetaldehyde. Acetaldehyde, in turn, causes diffuse vasodilation leading to flushing, hypotension, reflex tachycardia, headache, nausea, and vomiting.¹⁴

Opiate Use Disorder (OUD)

The emerging epidemic of adolescent opiate use disorder in the United States has sparked growing concern.¹⁷

For adults with OUD, the FDA has approved the use of naltrexone, buprenorphine (Buprenex; Butrans; Subutex), and buprenorphine/naloxone dual-therapy (Bunavail; Suboxone). Of these medications, buprenorphine has FDA approval for patients aged 16-18. Given their benefits in adult opiate use management versus the risks of the OUD, these treatment options should be considered for certain adolescent OUD populations.

As described above, naltrexone is an opioid antagonist that reduces the euphoria associated with opiate use. Buprenorphine is a partial opioid agonist that can be prescribed alone or in combination with naloxone for the treatment of OUD. When comparing buprenorphine-naloxone as a detoxification agent versus as a maintenance agent in adolescents, maintenance therapy (over 12 weeks) has shown improved abstinence rates, decreased reported injections, and increased therapy session attendance among patients.⁵ Prior to prescribing buprenorphine, physicians must attend an in-person or online training session and obtain special additional certification from the Drug Enforcement Agency (DEA) prior to treating patients.¹⁷ One reason for this additional requirement is the complicated process surrounding induction of buprenorphine. Methadone (Dolophine; Methadose) is a full opioid agonist used to treat opiate use disorders in adults; research exploring the efficacy of methadone treatment for adolescents with opiate use disorder is notably lacking.

Cannabis Use Disorder (CUD)

According to the 2015 National Survey on Drug Use and Health, 15.7% of 12- to 17-year-old adolescents had tried cannabis in their lifetime.¹⁸ Based on observational data, in a prospective study, Meir et al. showed chronic cannabis use to be associated with a decrease in IQ from childhood to adulthood; however, after adjusting for age at first use, this association only remained in patients who began regular cannabis use before the age of 18.¹⁹

The current recommendation for adolescents with CUD is to refer patients to behavioral or family-oriented therapy, deciding which modality to use on a case-by-case basis.²⁰ However, Brown et al. showed that after 6 weeks of behavioral therapy, 94% of patients who responded to therapy

achieved at least 1 week of abstinence, suggesting that patients who do not achieve a week of abstinence by 6 weeks into therapy would merit either switching therapy modalities or augmenting therapy with MAT.²¹

Currently no FDA-approved MAT is available for CUD in adults or in adolescents. However, a double-blind RCT of adolescents aged 15-21 ($n = 116$) showed an increased percentage of negative urine drug screens over an 8-week period in patients receiving N-acetylcysteine (Acetadote) compared to those in the placebo group.²² These findings were not correlated with differences in reported cravings, suggesting the possibility of an alternative mechanism.²³

Tobacco Use Disorder

In 2015, 17.3% of 12–17-year-olds reported having used tobacco in their lifetime.¹⁸ Three FDA-approved MAT approaches are available for tobacco use disorder—bupropion (Wellbutrin), varenicline (Chantix), and nicotine replacement therapy (NRT), but none of these approaches are currently FDA-approved for use in adolescents (although available data show promising results).¹⁰⁻¹²

In a double-blind RCT ($n = 134$), Gray et al. showed improved abstinence rates for smoking among adolescents receiving bupropion sustained release (SR) and psychotherapy compared to those receiving psychotherapy alone (27% versus 10%).¹⁰ In a small follow-up double-blind RCT, Gray et al. showed no statistically significant difference in abstinence rates between individuals receiving varenicline versus those receiving bupropion.¹¹ Despite black-box warnings on both medications for risk of psychiatric adverse effects including suicidality, both aforementioned studies commented on the lack of any depressive or suicidal symptoms in patients receiving bupropion or varenicline.^{10,11} The results for nicotine replacement therapy (NRT) have been mixed. A double-blind RCT reported by Moolchan et al. showed statistically significant differences in abstinence rates between adolescent smokers receiving patch NRT versus those receiving placebo.¹² However, a meta-analysis of the six published RCTs on NRT in adolescents failed to show significant improvement in abstinence rates among those receiving medical treatment.²⁴

Conclusion

When approaching adolescents with SUDs, specific patient-based treatment options must be individually considered. When reviewing the available evidence, it is important to note differences in study parameters including age ranges, symptom severity, patient motivation for success, comorbidities, required support systems, end-goal measurements, and dosages investigated. Notably, most studies included concurrent psychosocial therapy sessions, integral to MAT. These pharmaceutical treatments are not intended to function as monotherapies but rather as components of a comprehensive approach. Therefore, when providers describe MAT to parents and adolescents, in addition to discussing medication efficacy and possible adverse side effects, they must underscore the importance of comprehensive program adherence.

In the setting of co-occurring SUDs and non-substance mental health diagnoses, the Substance Abuse and Mental Health Services Administration highly recommends referral to dual-diagnosis programs that integrate care of both disorders into the same setting.²⁶ These evidence-based programs focus on incorporating cross-trained practitioners, stage-wise treatments, motivational interventions, cognitive-behavioral approaches, and integrated medication services into the patient's treatment plan.

Given the substantial limitations of existing data for any of the medications mentioned in this article for the treatment of adolescent SUDs, more definitive recommendations for adolescent populations will have to await further double-blind, placebo-controlled randomized controlled studies as well as observational studies with adequate adolescent sample sizes that stratify for varying support systems, severity of disease, motivation, concurrent mental health co-morbidities, and general demographics. Additionally, given the increased prevalence of concurrent opiate and alcohol abuse, specific studies oriented towards treatment of concurrent abuse disorders would be of great benefit.

Take Home Summary

SUDs are common among child and adolescent patients. Although a variety of medications are used to treat alcohol, opioid, cannabis, and tobacco use disorders in adults, due to the lack of available randomized controlled trials for younger children, these pharmacologic interventions are considered off-label when used to treat child and adolescent patients. For providers who lack addiction experience, managing adolescents with substance use disorders should entail presenting patients and families with treatment plans that involve medication-assisted treatment (MAT), including referral to clinical programs with the interdisciplinary teams capable of providing comprehensive care as part of the MAT strategy.

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Disclosure: Drs. Resczenski and Whitmore report no biomedical financial interests or potential conflicts of interest.

The authors would like to thank Dr. Christian Thurstone and Dr. Joel Yager for their comments that greatly improved the manuscript.