Pharmacological Treatment of Youth Substance Use Disorders

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Abstract

While the majority of youth who experiment with alcohol and drugs do not develop problematic levels of use, 5% of adolescents and 15% of young adults meet criteria for a substance use disorder (SUD). Pharmacotherapy, in combination with behavioral interventions, has the potential to increase the likelihood of successful treatment for youth struggling with SUD; however, the literature in this area is limited. To date, there are no Food and Drug Administration (FDA)-approved medications for adolescent SUD, other than buprenorphine, which has been approved down to 16 years of age for opioid use disorder. Despite alcohol and cannabis being the most commonly used substances during adolescence, only three medications have been tested among this demographic, and only two have warranted further study (i.e., naltrexone for alcohol and N-acetylcysteine for cannabis use disorder). Although less common in adolescents and young adults, the most promising pharmacological findings for this age group are for opioid (buprenorphine) and tobacco (bupropion and varenicline) use disorders. In addition, despite the recent marked increases in electronic nicotine delivery systems (i.e., vaping) among youth, treatment strategies are still in their infancy and no recommendation exists for how to promote cessation for youth vaping. Current findings are limited by: small, demographically homogeneous samples; few trials, including a substantial number of youth younger than 18; low retention; medication adherence rates; and minimal information on effective dosing levels and long-term outcomes. Overall, pharmacotherapy may be a potentially effective strategy to increase treatment effects; however, more rigorous research trials are warranted before FDA approval would be granted for any of the potential adjunctive medications in this age group.

Keywords: adolescent, alcohol, cannabis, opioid, tobacco, pharmacotherapy

Introduction

SUBSTANCE USE IS COMMON during adolescence and confers risk for long-term problems. Over 90% of adults with substance use disorders (SUD) started using alcohol or drugs during adolescence (Adolescent Substance Use: America's #1 Public Health Problem 2011), with earlier initiation of substance use corresponding to a greater lifetime risk of SUD (Anthony and Petronis 1995; Grant and Dawson 1997; Dawson et al. 2008). Furthermore, substance use during adolescence is related to numerous negative outcomes, including comorbid psychopathology (Deas and Thomas 2002; Rowe et al. 2004), poor academic achievement (Kristjansson et al. 2013; Heradstveit et al. 2017), neurocognitive impairments (Squeglia and Gray 2016; Gray and Squeglia 2018), and interpersonal issues (World Health Organization 2018). Concerningly, substance-related consequences have risen steeply from 3,300 deaths in 1980 to 33,100 deaths in 2014, indicating the increasing morbidity and mortality of substance use (Dwyer-Lindgren et al. 2018).

While the majority of youth who engage in substance use do not reach problematic levels of use, 5% of adolescents (ages 12–17) and 15% of young adults (ages 18–25) meet criteria for SUD (Substance Abuse and Mental Health Services Administration and Center for Behavioral Health Statistics and Quality 2016). Despite the pervasiveness of SUD, access to treatment is limited: for all age ranges, only 11% of those who meet criteria for SUD receive treatment (Substance Abuse and Mental Health Services Administration and Center for Behavioral Health Statistics and Quality 2016). Among youth, substance use treatment rates are considerably low, as only 6% of adolescents and 8% of young adults who meet criteria for SUD receive treatment.

Evidence-based treatments for youth substance use are almost exclusively psychosocial (e.g., motivational interviewing, cognitive

behavioral treatment, and family-based therapy; see Substance Abuse and Mental Health Services Administration website for a list of treatments, and treatment effect sizes are small to modest in promoting abstinence (Silvers et al. 2019; Tanner-Smith and Lipsey 2015). Decreasing or eliminating substance use at this early stage could have significant long-term implications; however, efforts have only been modestly effective, with up to 86% of youth returning to use within 12 months following treatment (Waldron and Turner 2008; Tripodi et al. 2010; Jensen et al. 2011; Tanner-Smith et al. 2013; Hogue et al. 2014; Winters et al. 2014; Miranda and Treloar 2016).

Considering the widespread prevalence of SUD among adolescents, one strategy to improve outcomes is to identify ways to increase the efficacy of existing treatments, particularly since only modest effects have been observed in existing psychosocial treatments. While medication should not be considered a standalone treatment for adolescent SUD, pharmacological interventions have the potential to complement existing psychosocial interventions and enhance outcomes, similar to the improvements seen in adult literature (Mann et al. 2014). Several medications have been approved by the Food and Drug Administration (FDA) as efficacious in treating adult SUD; however, minimal pharmacotherapy research has focused on adolescents, and there are no FDA-approved medications for adolescent SUDs, other than buprenorphine, which has been indicated down to 16 years of age for opioid use disorder. This limits treatment options for this especially vulnerable age group, as safety and efficacy of medications for adolescents cannot be inferred from adult studies (Bridge et al. 2007).

Recent studies have suggested that pharmacological interventions may increase the effectiveness of psychosocial interventions for adolescent SUD (Tables 1 and 2). This review will synthesize the current literature on pharmacological treatments of youth SUD, starting with the most commonly used substance during adolescence (alcohol) to the least common (methamphetamines). The brain undergoes substantial neuromaturation until the mid-20s (Giedd 2008); therefore, studies of youth up to 25 years of age were included. Studies where adolescent substance use or SUD was not the sole condition of focus were excluded and are reviewed elsewhere (Miranda and Treloar 2016). Limitations for each pharmacotherapy option and individual study limitations will be discussed to provide a balanced review and recommendations.

Alcohol Use Disorder

Alcohol is the most prevalent substance used by adolescents, with 30% of 18-year olds reporting alcohol use in the past month (Johnston et al. 2019), and 3% of 12–17 year olds meeting criteria for an alcohol use disorder (Substance Abuse and Mental Health Services Administration and Center for Behavioral Health Statistics and Quality 2016, tables 5.2a and 5.2b). Earlier use of alcohol leads to greater risk of alcohol use in the long term; adolescents who initiate alcohol use before age 15 are six times more likely to abuse alcohol as adults than those who begin drinking after age 21 (Dawson et al. 2008). Alcohol use is associated with a number of adverse social and cognitive outcomes (Squeglia and Gray 2016), and is responsible for over 4,000 deaths among underage youth in the United States per year (Centers for Disease Control and Prevention 2016).

Alcohol is involved in altering the neural transmission of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, and glutamate, an excitatory neurotransmitter (Vengeliene et al.

2008). Pharmacotherapy for adults with alcohol use disorder has focused on decreasing craving and withdrawal symptoms to decrease likelihood of relapse. Currently, three medications are FDA-approved for adult (18+ years of age) alcohol use disorder: disulfiram, acamprosate, and naltrexone. None are indicated for youth.

Naltrexone

Naltrexone is an opioid receptor antagonist that has been shown to reduce alcohol consumption and relapse rates in adults with alcohol use disorder when combined with psychosocial interventions (Roozen et al. 2006). It is thought that alcohol's addictive properties are mediated by opioids found naturally in the human body, which activate the dopaminergic reward system. Naltrexone blocks endogenous opioids, decreasing the release of dopamine and dampening the reward pathway for alcohol use (Center for Substance Abuse Treatment 2009).

Naltrexone is currently FDA- approved for use in those 18 years of age and older for both alcohol use disorder and opioid use disorder. Naltrexone may be administered both orally and intramuscularly. The recommended dosing for alcohol use disorder is 50 mg per day orally or 380 mg intramuscularly given every 4 weeks (Naltrexone: Drug information uptodate 2018). Common side effects of oral naltrexone include nausea, headache, dizziness, and elevations in liver enzymes. Side effects of long-acting injectable naltrexone are similar, but also include injection-site reactions such as swelling, bruising, or redness. Naltrexone must be used with caution in patients with severe hepatic or renal impairment. Hepatocellular injury is possible, and it is recommended that use be discontinued if signs or symptoms of hepatitis occur. However, more specific guidelines have not been studied.

The limited literature suggests that naltrexone is safe and may be a potentially promising medication for adolescent alcohol use disorder. A small open-label pilot study found that 25–50 mg of naltrexone daily was well tolerated and associated with minimal side effects in treatment-seeking adolescents ($N=5$) who met criteria for alcohol use disorder (Deas et al. 2005). Two clinical trials have examined the effect of naltrexone on adolescent alcohol use. Adolescents 15–19 years of age ($N=22$), who had reported any alcohol use at least twice in 30 days before their initial screening visit, were enrolled in a within-subject, randomized, double-blind, placebo-controlled crossover trial of naltrexone. In a counterbalanced order, all youth received 8–10 days of placebo and 8–10 days of 50 mg daily of naltrexone, separated by a 4–11 day washout period. Compared to placebo, naltrexone reduced the likelihood of drinking and heavy drinking, blunted alcohol craving in both the laboratory and natural environment, and altered subjective responses to alcohol consumption (Miranda et al. 2014). Naltrexone was generally well tolerated by participants, with only two participants withdrawing from the naltrexone arm due to mild nausea.

The largest youth naltrexone study to date was completed on 128 nontreatment-seeking youth (18–25 years of age), who reported at least four binge drinking episodes (i.e., ≥4 drinks for women and ≥5 for men) in the past month. Participants were randomized to naltrexone (25 mg targeted +25 mg daily) or placebo (placebo targeted + placebo daily) for 8 weeks (O'Malley et al. 2015). Naltrexone did not reduce the frequency of drinking or number of heavy drinking days; however, naltrexone did reduce drinking intensity. Participants randomized to the naltrexone group significantly reduced drinks per drinking day (naltrexone = 4.9 drinks per drinking day vs. placebo 5.9 drinks) and percentage of drinking days with estimated blood alcohol content ≥0.08 g/dL (naltrexone = 35%

TABLE 1. RANDOMIZED CONTROLLED TRIALS OF PHARMACOTHERAPY FOR ADOLESCENT SUBSTANCE USE DISORDERS

Medication	Clinical trial	Sample characteristics	Design	Intervention and comparator dosing (mg/day)	Results	Limitations
Alcohol use disorder						
Naltrexone	Miranda et al. (2014)	$N = 22$ nontreatment-seeking adolescents who consumed alcohol two or more times in 30 days before recruitment. Mean age = 18.36 ± 0.95 (range 15–19) Gender: 45% male Race: 72% white 18% Asian/Pacific Islander	Randomized, double-blind crossover study. Participants randomized to each condition for 8–10 days (mean 9.93 ± 0.34) in counterbalanced order, with a 4- to 11-day washout period.	Intervention: 50 mg naltrexone daily Control: placebo Platform intervention: none	Naltrexone (relative to placebo): ↓ Drinking and heavy drinking ($ps < 0.003$) ↓ Craving in the laboratory and natural environment ($ps < 0.04$) ↓ Subjective responses to alcohol consumption ($ps < 0.01$)	Brief treatment period (8–10 days). Small sample size. Excluded treatment-seeking adolescents and co-occurring substance use or disorders.
	O'Malley et al. (2015)	$N = 128$ nontreatment-seeking youth who reported ≥4 heavy drinking days (≥4 drinks women and ≥5 drinks men) in the 4 weeks before study enrollment. Mean age = 21.5 ± 2.15 (range 18–25) Gender: 68.8% male Race: 77% white, 8% African American	Randomized (1:1), double-blind, two-group, parallel placebo-controlled study, 8-week treatment period.	Intervention: 25 mg +25 mg targeted naltrexone daily Control: placebo Platform intervention: all participants received psychosocial intervention	Naltrexone (relative to placebo): No group differences between heavy drinking days and percent days abstinent. ↓ Number of drinks per drinking day and percentage of drinking days with estimated BAC ≥0.08.	Adult/transitional age (18–25). Relatively brief treatment duration. Nontreatment-seeking youth compensated for appointments and adherence, limits generalizability. Measures of estimated BAC among participants likely much more variable than variability in individuals.
Cannabis use disorder						
N-Acetylcysteine	Gray et al. (2012a)	$N = 116$ treatment-seeking youth who met criteria for DSM-IV (American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. 1994) cannabis dependence Mean age = 18.9 ± 1.5 (range 13–21) Gender: 72.4% male Race: 83% white	Randomized (1:1), double-blind, two-group, parallel, placebo-controlled study, 8-week treatment period.	Intervention: N-acetylcysteine (1200 mg) twice daily Control: placebo twice daily Platform intervention: all participants received contingency management and individual weekly cessation counseling	N-acetylcysteine (relative to placebo): Twice the odds of submitting negative urine cannabinoid tests during treatment (OR 2.4, 1.1–5.2, $p = 0.029$), with detectable differences within the first week of treatment. Time to first negative urine cannabinoid test and end-of-treatment abstinence favored N-acetylcysteine, but nonsignificant.	Single university-based research clinic. Relatively small sample size. Older adolescent patient population. Minimal racial diversity in sample. Study not powered to detect end-of-treatment abstinence or sustained posttreatment effects.

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TABLE 1. (CONTINUED)

Medication	Clinical trial	Sample characteristics	Design	Intervention and comparator dosing (mg/day)	Results	Limitations
Topiramate	Miranda et al. (2017)	N=66 treatment-seeking youth using cannabis at least twice weekly in 30 days before study participation and experienced ≥1 symptoms of cannabis abuse or dependence (DSM-IV). Mean Age=18.81±2.08 (range 15–24) Gender: 46% male Race: 50% white	Randomized (2:1), double-blind, two-group, parallel, placebo-controlled study, 6-week treatment period.	Intervention: 25 mg topiramate a day, then titrated by 25–50 mg over 4 weeks to 200 mg/day for the final 2 weeks of study. Control: placebo Platform intervention: all participants received biweekly motivational enhancement therapy for treating cannabis use among adolescents	Topiramate (relative to placebo): No improvement in abstinence rates. ↓ the number of grams of marijuana smoked per use day.	Significant side effects. Topiramate group had cognitive side effects: ↓ retrieval fluency and ↓ memory during treatment, in addition to difficulty with concentration, attention, dizziness, depression, anxiety, balance/coordination, and reaction time. High attrition (only 48% of topiramate group completed trial, compared to 77% of placebo). Small sample size, relatively short treatment period.
Tobacco use disorder Nicotine replacement therapy (NRT)	Hanson et al. (2003)	N=100 treatment-seeking youth who smoked ≥10 cigarettes per day for ≥6 months and motivated to quit (≥7 on a scale of 1–10 assessing motivation to quit). Mean age=16.8±1.5 (range 13–19) Gender: 43% male Race: 87% white	Randomized (1:1), double-blind, two-group, parallel, placebo-controlled study, 13-week treatment period.	Intervention: nicotine patch Control: placebo patch Platform intervention: individual cognitive-behavioral therapy and contingency management	NRT (relative to placebo): ↓ craving scores and overall withdrawal symptoms	Small sample size, minimal racial diversity. High attrition (53%). Compliance with NRT not objectively confirmed and often participants failed to return unused patches to help confirm compliance. Large incentives from contingency program, unclear if participants were motivated for contingencies or smoking cessation.
	Moolchan et al. (2005)	N=120 treatment-seeking adolescents who smoked ≥10 cigarettes per day for ≥6 months, and were motivated to quit smoking. Mean age=15.2±1.33 (range 13–17) Gender: 30% male Race: 73% white	Randomized, double-blind, double-dummy, three-arm trial, 12-week treatment period.	Intervention: (1) active patch and placebo gum or (2) active gum and placebo patch Control: placebo gum and placebo patch Platform intervention: All participants received group cognitive-behavioral therapy at each visit	Carbon monoxide-confirmed prolonged abstinence rates of active-patch group (18%) vs. placebo (2.5%). Abstinence rates for the active gum condition (6.5%) did not differ from either condition.	Participants deterred from gum use due to aversive taste, and participants had limited instruction in proper use of nicotine gum.
	Roddy et al. (2006)	N=98 treatment-seeking youth in an open-access youth project in a socioeconomically disadvantaged region. Mean age=14.0 (range 11–21) Gender: 42% male Race: not reported	Randomized (1:1), double-blind, two-group, parallel, placebo-controlled study, 6-week treatment period.	Intervention: nicotine patch Control: placebo patch Platform intervention: weekly individual or small group counseling	NRT (relative to placebo): At 4 weeks, 5% patch group was abstinent vs. 2% placebo At 13 weeks, 0% patch and placebo were abstinent	Small sample size; too small to detect an effect of NRT on smoking. Younger smokers with lighter smoking levels and lower CO levels compared to other studies examining NRT effectiveness in adolescents and young adults.

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TABLE 1. (Continued)

Medication	Clinical trial	Sample characteristics	Design	Intervention and comparator dosing (mg/day)	Results	Limitations
	Rubinstein et al. (2008)	N=40 adolescent smokers who smoked ≥5 cigarettes daily for ≥6 months. Mean age=16.7±0.99 (range 15–18) Gender: 46% male Race: not reported other than "less than half being white"	Randomized, open-label, 12-week trial, adolescent smokers were assigned on a 1:1.5 ratio to receive either weekly counseling alone (control) for 8 weeks, or 8 weeks of counseling along with 6 weeks of nicotine nasal spray.	Intervention: Nicotrol nasal spray (1 mg total) for 6 weeks Control: none Platform intervention: 8 sessions of American Lung Association's Not On Tobacco curriculum	No group difference in cessation rates (p=0.16), number of cigarettes smoked per day (p=0.22), or cotinine levels at 12 weeks (p=0.16).	57% participants stopped using nicotine nasal spray after only one week, with 39% of participants stating that the nasal sprayer had "lots of side effects." Lack of placebo spray arm. Lack of association between self-reported smoking and cotinine levels suggests potential measurement bias.
	Scherphof et al. (2014)	N=257 treatment-seeking Dutch adolescents who smoked ≥7 cigarettes a day. Mean age=16.7±1.13 (range 12–18) Gender: 47% male Race: not reported	Randomized (1:1), double-blind, two-group, parallel, placebo-controlled study, 6- or 9-week treatment period.	Intervention: 21, 14, or 7 mg nicotine patch based on number of cigarettes smoked per day at time of enrollment Control: placebo patch Platform intervention: none	NRT (relative to placebo): Doubled abstinence rates after 2 weeks (OR=2.02, 95% CI=1.11–3.69), but no differences at end of treatment. End-of-treatment abstinence rates significantly ↑ in high-compliant (OR=1.09, 95% CI=1.01–1.17) and not in low compliant participants.	NRT compliance was assessed using online self-report measures, which may have elicited socially desirable answers.
Bupropion	Killen et al. (2004)	N=211 treatment-seeking adolescents (1) who reported smoking ≥10 cigarettes daily, (2) had smoked for ≥6 months, and (3) had one or more failed attempts to quit smoking. Mean age=17.3±0.8 (range 15–18) Gender: 69% male Race/ethnicity: 50% white, 12% Hispanic, 7% Asian	Randomized, double-blind, placebo-controlled, 10-week study	Intervention: nicotine patch plus bupropion SR (sustained release; 150 mg per day) Control: nicotine patch plus placebo group Platform intervention: weekly group skills training sessions	No difference between abstinence rates at weeks 10 and 26: (1) patch plus bupropion 23% and 8%, (2) patch plus placebo 28% and 7%.	Low dosing of bupropion: 150 mg per day (recommended dose for adult smokers is 300 mg per day). Limited patch and medication compliance.

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TABLE 1. (CONTINUED)

Medication	Clinical trial	Sample characteristics	Design	Intervention and comparator dosing (mg/day)	Results	Limitations
	Niederhofer and Huber (2004)	N=22 adolescents who met DSM-IV criteria for nicotine dependence. Mean age=17.3±0.7 (range 16–19) Gender: 50% male Race: not reported	Randomized (1:1), double-blind, two-group, parallel, placebo-controlled study, 90-day treatment period.	Intervention: bupropion 150 mg daily Control: placebo Platform intervention: psychosocial or behavioral intervention (no details provided on type or duration)	Bupropion (relative to placebo): Higher abstinence (55%, 6/11) compared to placebo group (18%, 2/11) throughout the 90 days of treatment. Mean cumulative abstinence duration was significantly ↑ in bupropion group than in the placebo group (78.4±39.6 vs. 30.2±19.2, p=0.004).	Small study size. Study used a lower bupropion dose (150 mg) than now suggested. Some subjectivity as investigators determined judgments of whether self-reported tobacco use was likely to be true.
	Muramoto et al. (2007)	N=312 treatment-seeking adolescents who smoke ≥6 cigarettes per day, had an exhaled carbon monoxide level of ≥10ppm, and had at least two previous quit attempts. Median age: 16 (range 14–17) Gender: 54% male Race/ethnicity: 74% white, 15% Hispanic	Randomized, double-blind, placebo-controlled, parallel-group, dose-ranging trial, 6-week treatment period.	Intervention: (1) Bupropion SR 150 mg per day or (2) 300 mg per day Control: placebo Platform intervention: all participants received weekly brief interventional counseling	6 weeks: Cotinine-confirmed 7-day point prevalence abstinence rates: placebo, 5.6%; 150 mg, 10.7%; and 300 mg, 14.5% (p=0.03, 300 mg vs placebo). 26 weeks: Confirmed point prevalence abstinence rates: placebo, 10.3%; 150 mg, 3.1%; and 300 mg, 13.9% (p=0.049).	Study shortened the follow-up from 52 weeks to 26 weeks due to recruitment difficulties. Compensation for study participation may have influenced motivation for enrollment and continued participation more so than overall motivation to quit.
	Gray et al. (2011)	N=134 treatment-seeking youth who smoke ≥5 cigarettes per day with baseline urine cotinine >100 ng/mL. Mean age=(range 12–21) Gender: 58% male Race: 89% Caucasian	Randomized, double-blind, four-group, parallel, placebo-controlled study, 6-week treatment period.	Intervention: (1) bupropion SR + with contingency management (2) bupropion SR without contingency management Control: (3) placebo with contingency management or (4) placebo without contingency management	Combined bupropion SR + contingency management yielded significantly superior abstinence rates during active treatment when compared with placebo and no contingency management treatment: bupropion SR and contingency management 27%, bupropion SR without contingency management 8%, placebo and contingency management 10%, and placebo and noncontingency management 9%.	Reported abstinences may be underestimated, as those who missed appointments were considered to be nonabstinent at all missed visits. Low treatment completion rate (30%) was lower than other larger scale studies. Minimal racial diversity in sample.
Varenicline	Gray et al. (2012b)	N=29 treatment-seeking youth who smoke ≥5 cigarettes per day, with one previous unsuccessful quit attempt. Mean age=18.9±1.0 (range 15–20) Gender: 58% male Race: not reported	Randomized, double-blind, 8-week treatment period.	Interventions: Varenicline (≤2mg) vs. bupropion sustained release (150–300 mg) Control: none Platform intervention: none	Varenicline (relative to bupropion): ↓ cigarettes smoked per day from 14.1±6.3 to 0.9±2.1 and those receiving bupropion XL reduced from 15.8±4.4 to 3.1±4.0.	No placebo control group. Poor participant retention.

TABLE 1. (CONTINUED)

Medication	Clinical trial	Sample characteristics	Design	Intervention and comparator dosing (mg/day)	Results	Limitations
Opioid use disorder Buprenorphine	Marsch et al. (2005)	$N=36$ self-referred treatment-seeking adolescents who met DSM-IV criteria for opioid dependence. Mean age: 17.4 ± 0.7 (range 13–18) Gender: 39% male Race: 97% white	Randomized, double-blind, double-dummy, parallel groups, 28-day trial.	Interventions: Outpatient detox with buprenorphine ($\leq$8 mg) + placebo patch vs. clonidine ($\leq$3 mg) patch + placebo tablets Control: none Platform intervention: behavioral counseling thrice weekly	↑ Retention in buprenorphine group (72%) vs. clonidine (39%) ($p<0.05$). ↑ Percentage of opioid negative urine tests (64% vs. 32%, $p=0.01$).	Study focused primarily on treatment outcomes during treatment, without any posttreatment follow-up. Minimal racial diversity in sample. Medication doses were in the low-moderate range relative to adult doses.
Buprenorphine/ Naloxone	Woody et al. (2008)	$N=152$ treatment-seeking adolescents who met DSM-IV criteria for opioid dependence. Multisite, national sample from community programs that used methadone or buprenorphine/naloxone. Mean age: 19.4 ± 1.5 (range 15–21) Gender: 59% male Race/ethnicity: 74% white, 25% Hispanic	Randomized, nonblinded 12-week trial.	Interventions: 14-day outpatient detoxification ($\leq$14 mg of buprenorphine) vs. 12-week buprenorphine/naloxone ($\leq$24 mg) Control: none Platform intervention: all participants received weekly individual and group counseling	Compared to the detoxification group, participants in the 12-week buprenorphine/naloxone group showed the following: → Opioid-positive urine tests at week 4 (26% vs. 61%) and 8 (23% vs. 54%), but not at week 12 (43% vs. 51%). → reported opioid use before week 6 ($p<0.001$). → reported injections before week 6 ($p=0.01$). → cocaine and marijuana use	Small proportion of patients younger than 18 was not sufficient to meaningfully analyze outcomes. Lack of blinding by evaluators. Buprenorphine dosing was typically observed, which strengthens internal validity, but may not parallel real-world conditions. Low follow-up rate.
	Marsch et al. (2016)	$N=53$ youth who met DSM-IV opioid dependence criteria Mean age: 20.5 ± 2.6 (Range 16–24) Gender: 58% male Race: 70% white	Randomized, double-blind, placebo-controlled, multicenter randomized controlled trial, 63 days in length.	Intervention: 28-day or 56-day buprenorphine/naloxone detoxification and followed over a 63-day study period.	Participants who received a 56-day buprenorphine taper were retained in treatment 11 days longer on average than participants who received a 28-day buprenorphine taper. Participants who received a 56-day buprenorphine taper had a significantly ↑ percentage of opioid-negative scheduled urine tests compared with participants who received a 28-day buprenorphine taper (35 vs. 17%).	Small sample size. Less than half of participants enrolled in both conditions completed the entire 63 days of study.
Methamphetamine use disorder Bupropion	Heinzerling et al. (2013)	$N=19$ youth with DSM-IV methamphetamine abuse or dependence and low frequency of methamphetamine use (use on $\leq$18/30 days). Mean age: 17.6 ± 1.4 (Range 14–21) Gender: 47% male Race: 70% white	Randomized, double-blind, placebo-controlled, 2:1 ratio to bupropion or placebo during outpatient treatment (substance use counseling) for 8 weeks.	Intervention: Bupropion SR 150 mg twice daily Control: placebo Platform intervention: group drug counseling	Adolescents receiving bupropion and females provided significantly fewer methamphetamine-free urine tests compared to participants receiving placebo ($p=0.043$) and males ($p=0.005$) respectively, compared to placebo.	Small sample size. Difficulties recruiting and retaining participants.

OD, odds ratio; CI, confidence interval; BAC, blood alcohol content.

TABLE 2. SUMMARY TABLE OF MEDICATIONS FOR ADOLESCENT SUBSTANCE USE DISORDERS

SUD indication	Medication	Number of studies and participants	Safety/tolerability	SUD outcomes
Alcohol use disorder	Naltrexone	3 (N = 155)	Positive	Mixed/mostly positive
Cannabis use disorder	N-acetylcysteine	1 (N = 116)	Positive	Positive
Tobacco use disorder	Nicotine replacement therapy	9 (N = 1118)	Positive (negative for nasal sprayer)	Mixed for patch, mostly negative for nasal sprayer
	Bupropion SR	3 (N = 657)	Positive	Positive at 300 mg
	Varenicline	3 (N = 258) + 1 pending publication (N = 307)	Positive	Preliminary/encouraging
Opioid use disorder	Buprenorphine (Buprenorphine/Naloxone)	3 (N = 241)	Positive	Positive
Methamphetamine use disorder	Bupropion SR	1 (N = 19)	Positive	Negative

SUD, substance use disorder.

drinking days vs. placebo 46%). No serious adverse side effects from the naltrexone were reported.

These studies suggest that naltrexone is tolerable in this population and could potentially decrease the quantity of alcohol use in youth who use alcohol or have an alcohol use disorder; however, further research is needed. Inclusion criteria for both studies were based on frequency of drinking in the past month, with relatively low thresholds, such as drinking twice in the past month (Miranda et al. 2014) or binge drinking four times in the past month (O'Malley et al. 2015). Neither study required a diagnosis of alcohol use disorder, which would be required for FDA-approval medication trials. Furthermore, effects appear to be small (i.e., on average, one less drink per drinking occasion) and time limited: 1 year after naltrexone treatment, differences among groups were not sustained at subsequent follow-ups (DeMartini et al. 2016).

N-acetylcysteine

Glutamate has emerged as a therapeutic target in the treatment of addictions (Kalivas and Volkow 2011). Repeated use of an addictive substance results in glutamate dysregulation in various brain regions involved in motivation and learning (McFarland et al. 2003; LaLumiere and Kalivas 2008). N-acetylcysteine (NAC) is an over-the-counter medication most commonly prescribed for acetaminophen overdose or as a mucolytic. It has been FDA-approved for pediatric and adult populations since 1963 and has a long-established safety record (Bailey and McGuigan 1998; Grandjean et al. 2000). NAC can be administered in several forms: oral, intravenous, or inhaled. NAC administration restores glutamate homeostasis by upregulation of the glutamate GLT1 transporter, clearing excess glutamate from the nucleus accumbens, resulting in reductions in substance-seeking and self-administration of substances (McClure et al. 2014; Roberts-Wolfe and Kalivas 2015). A recent meta-analysis of seven clinical trials found that NAC was superior to placebo for reducing drug cravings (Duailibi et al. 2017), and clinical findings indicate that NAC reduces substance use across a range of substances, including cannabis, alcohol, tobacco, and cocaine (Tomko et al. 2018), and is an appropriate medication to use for pediatric disorders (Naveed et al. 2017).

Secondary analyses were performed on data from an adolescent cannabis cessation trial (Gray et al. 2012a) to examine the effect of NAC on co-occurring alcohol use in youth who met criteria for cannabis dependence (Squeglia et al. 2016). Participants were randomized to either NAC or placebo over the 8-week treatment course. Decreased cannabis use (based on urine cannabinoid tests and creatinine-adjusted cannabinoid levels) was associated with a concurrent reduction in alcohol use in the NAC-treated group, but not in the placebo-treated group. Considering this sample was not attempting to reduce alcohol use and was not receiving a combined behavioral treatment for alcohol use, these findings support the assertion that NAC may be exerting effects across substances, including alcohol. Findings are also consistent with the growing preclinical literature supporting NAC for reducing alcohol use (Quintanilla et al. 2016; Lebourgeois et al. 2018), as well as clinical findings from adult studies (Squeglia et al. 2018). However, to date, no clinical trial has been completed that examines the effect of NAC on youth who are seeking treatment for alcohol use disorder, although one is currently beginning recruitment this year for adolescents (13–19 years of age) who meet criteria for an alcohol use disorder (R01 AA027399; ClinicalTrials.gov Identifier: NCT03707951).

Ondansetron

One open-label pilot study of ondansetron was completed on 12 treatment-seeking adolescents (14–20 years of age), who met criteria for alcohol use disorder and had consumed ≥12 alcoholic drinks in the past month (Dawes et al. 2005). All participants in the study received 4 μg/kg twice per day of ondansetron over the 8-week trial. Preliminary findings suggested that ondansetron was safe and well tolerated. Participants decreased drinking; however, given the lack of control group, information about efficacy of this medication cannot be inferred.

Limitations

In general, the literature on pharmacotherapy for adolescent alcohol use disorder is lacking. The majority of this research has been performed with naltrexone, and most youth in those studies were between age 18 and 25, limiting interpretability and applicability for younger teens. Furthermore, the clinical relevance and long-term effects of these medications are unknown. Effective interventions during adolescence could have substantial long-term implications by reducing both the acute and enduring consequences of heavy adolescent drinking. Earlier treatment during this

vulnerable period is warranted, as it could help prevent more severe, treatment-resistant alcohol use disorder in adulthood.

Cannabis Use Disorder

Cannabis is the second most commonly used substance (Johnston et al. 2019) and the most common reason for substance treatment referrals among youth 12–17 years of age (Substance Abuse and Mental Health Services Administration and Center for Behavioral Health Statistics and Quality 2018). With the legalization of cannabis in several states, the perception of the risks associated with cannabis use is at their lowest ever (Johnston et al. 2019). Currently, there are no FDA-approved pharmacotherapies for adult or youth cannabis use disorder. Two trials examining pharmacotherapy for adolescent cannabis use disorder have been completed.

N-acetylcysteine

The strongest clinical findings to date for NAC in relation to SUD are adolescent and cannabis specific (Tomko et al. 2018). A four-week open-label trial of NAC (1200 mg twice daily) found that it was safe and tolerable for youth with cannabis use disorder (Gray et al. 2010). A follow-up 8-week double-blind randomized controlled trial of NAC was completed on 116 treatment-seeking youth with cannabis use disorder (15–21 years of age) (Gray et al. 2012a). All participants received contingency management for negative urine cannabinoid tests and brief weekly cessation counseling, and half were randomized to NAC or placebo. Participants who received NAC had more than twice the odds of submitting negative urine cannabinoid tests during treatment, with detectable differences within the first week of treatment (Gray et al. 2012a). Secondary measures of time to first negative urine cannabinoid test and end-of-treatment abstinence favored NAC. Overall treatment effect lost statistical significance at posttreatment follow-up, although the study was not powered to detect long-term effects. There were no significant differences between treatment groups related to adverse events or tolerability. A secondary analysis of this study revealed that low impulsivity in participants and medication adherence to NAC were associated with increased abstinence rates (Bentzley et al. 2016).

A follow-up 12-week, multisite, double-blind randomized, placebo-controlled trial was completed with 302 treatment-seeking adults 18–50 years of age, with cannabis use disorder. While the overall findings were negative for the effect of NAC on cannabis abstinence, authors performed subgroup analyses on participants who were 18–21 years of age ($n = 58$), as this age range overlapped with the previous adolescent NAC cannabis trial (Gray et al. 2012a). While not powered for these analyses, interestingly, effect sizes were similar to the original trial (i.e., 18–21 year olds were twice as likely to have negative drug screens in the NAC vs. placebo group). These findings suggest the potential of NAC for treating adolescent cannabis use disorder specifically. A replication follow-up study on youth with cannabis use disorder 14–21years of age is currently underway (R01 DA042114; ClinicalTrials.gov Identifier: NCT03055377).

Topiramate

Topiramate is a medication most often used to treat epilepsy. Topiramate is a sodium channel antagonist and glutamate antagonist and exerts an increase in GABA activity as well (Sneider et al. 2018). Topiramate may have many side effects, including impair-

ments in cognition and expressive language, weight loss, and symptoms of depression and anxiety. In addition, topiramate may cause significant metabolic acidosis and interacts with many other medications.

A randomized controlled trial of topiramate was completed on treatment-seeking youth ($N = 66$; 15–24 years of age), who had used cannabis at least twice weekly in the past month and had experienced ≥1 symptom of cannabis use disorder (Miranda et al. 2017). All participants completed motivational enhancement therapy and were randomized in a 2:1 ratio to receive topiramate or placebo for six weeks. Topiramate reduced the number of grams of cannabis smoked per day, but did not improve abstinence rates over the course of the trial. Only 48% of youth randomized to topiramate completed the 6-week trial compared to 77% of those in the placebo condition, with adverse effects being the most commonly reported reason for withdrawal in the topiramate group. A follow-up analysis found that memory difficulties were an overwhelming predictor of dropout in the topiramate condition: 42% of participants who dropped out experienced memory difficulties, whereas none of those who remained in the study experienced these effects (Gray et al. 2018). Due to the lack of significant efficacy and extensive side effect profile of topiramate, it is currently not recommended to treat adolescent cannabis use disorder.

Limitations

Despite cannabis being the second most commonly used substance during adolescence, as well as the most common reason for treatment referral, only two clinical trials have been completed on pharmacotherapy for youth cannabis use disorder and only one has had promising findings. Further research is warranted with more diverse and larger samples. NAC is an appealing medication, given that it is an over-the-counter supplement that is safe, inexpensive, and tolerable for this age group. However, this medication may not be efficacious for all individuals, so other pharmacological interventions should be explored.

Tobacco Use Disorder

Over 90% of adults who use tobacco products began using during adolescence (US Department of Health and Human Services 2014). While adolescent use of combustible tobacco products (i.e., cigarettes) has declined over the last several years, vaping (or electronic cigarette use) is rapidly on the rise. In 2018, 21% of U.S. high school seniors reported vaping in the past month, a 10%-point increase from 2017, which was the largest one-year increase in any substance used over the 44 years that Monitoring the Future has been tracking adolescent substance use (Johnston et al. 2019). Tobacco is the leading preventable cause of death in the United States, and it is estimated that over 5 million adolescents today will die prematurely as a result of smoking-related causes (US Department of Health and Human Services 2014).

Currently, the FDA has approved three types of medications for tobacco use disorder in adults (seven in total): nicotine replacement therapy (NRT) (=five different delivery methods, including patch, gum, lozenge, inhaler, and nasal spray), bupropion, and varenicline. Given poor youth tobacco cessation rates and several efficacious pharmacotherapy options for adult smokers (Cahill et al. 2013; Hartmann-Boyce et al. 2013), randomized trials have evaluated tobacco cessation pharmacotherapies in youth smokers, most in combination with psychosocial treatments to bolster abstinence rates. A recent meta-analysis reviewed nine randomized controlled trials of pharmacotherapy evaluation for youth smokers (12–20 years

of age; $N = 1,118$) and found that pharmacotherapy resulted in increased abstinence rates in the short term, but showed no benefit for longer-term abstinence (Myung and Park 2018). The most promising findings in the adolescent studies have been with bupropion, particularly when combined with psychosocial interventions.

Nicotine replacement therapy

Nicotine is an agonist to nicotinic acetylcholine receptors in the brain. NRT works by stimulating these receptors without the carcinogenic effects of combustible tobacco. NRT increases abstinence by reducing the physiological and psychomotor withdrawal symptoms often experienced during an attempt to stop smoking (Flowers 2016; Hartmann-Boyce et al. 2018). Nicotine replacement comes in several forms of administration, and is currently FDA approved for those 18 years of age and older. The patch, lozenge, and gum are the most commonly used therapies and are available over the counter, while nicotine nasal spray and oral inhaler require a prescription. In addition, a prescription is required for adolescents younger than 18 to purchase a NRT. The dose of NRT is titrated to minimize symptoms of withdrawal, with the goal to wean the dose as tolerated. Side effects of NRT are similar to those observed in the use of tobacco products, including nausea, abdominal pain, and headache.

Several trials have examined NRT as a treatment for youth tobacco cessation (Hanson et al. 2003; Moolchan et al. 2005; Roddy et al. 2006; Rubinstein et al. 2008; Scherphof et al. 2014). A recent meta-analysis showed that a combination of nicotine patch therapy and cognitive-behavioral therapy was associated with significantly higher abstinence rates at six months (Bailey et al. 2013). Overall, current guidelines recommend using behavioral support to initially address tobacco use disorder in adolescents. This may include referral to a smoking cessation program. However, if an adolescent shows signs of dependence, the nicotine patch may be prescribed, in addition to a behavioral intervention (Management of smoking cessation in adolescents uptodate 2018).

Bupropion

Bupropion is FDA- approved for adults with tobacco use disorder. It is most commonly used as an antidepressant due to its mechanism as a norepinephrine and dopamine reuptake inhibitor; however, it also acts as a nicotinic receptor antagonist. Through its unique mechanism of action, bupropion can mitigate withdrawal symptoms by increasing dopamine and norepinephrine in the brain, while also blocking the effects of nicotine (Slemmer et al. 2000). Bupropion is contraindicated in anyone with a medical history of seizures or eating disorders. Its limited use among those with a history of seizure disorders extends to those with a history of complicated alcohol withdrawal, excluding its use in a large population with comorbid alcohol use disorder and tobacco use disorder.

Three clinical trials have examined the efficacy of bupropion as a treatment for youth tobacco cessation. The first study enrolled 211 youth (15–18 years of age) (Killen et al. 2004). All received the nicotine patch and half were randomized to bupropion (150 mg a day) and half to placebo. Abstinence rates were not significantly different at the end of treatment (23% bupropion vs. 28% placebo); however, compliance was low in both groups (e.g., 44% reported they used all their pills on two treatment weeks or less). Despite the lack of treatment effect, a large majority of adolescents in both treatment groups reduced their consumption to a few cigarettes per day and maintained this reduction over time, with many participants avoiding a return to daily smoking.

A follow-up study of 312 treatment-seeking youth (13–17 years of age) examined the effect of higher doses of bupropion and found that bupropion SR 150 mg per day did not result in quit rates significantly higher than those with placebo; however, bupropion SR 300 mg per day resulted in significantly higher quit rates than placebo at the end of treatment (Muramoto et al. 2007). Findings suggest that the prior study by Killen et al. (2004) may have used too low a dose to reduce or promote abstinence from smoking.

The third study assessed the combined effect of bupropion SR and contingency management for smoking cessation among 134 treatment-seeking adolescent smokers (12–21 years of age) (Gray et al. 2011). Abstinence rates for combined bupropion SR and contingency management were 27%, while rates were 8% for bupropion SR without contingency management, 10% for placebo and contingency management, and 9% for placebo and non-contingency management. Combined bupropion SR + contingency management yielded significantly superior abstinence rates during active treatment when compared with placebo and no contingency management treatment. Findings suggested that combined behavioral treatment and bupropion may be superior to either bupropion SR or contingency management alone.

Varenicline

Varenicline is currently only FDA-approved for adults with tobacco use disorder. Varenicline is a nicotinic acetylcholine receptor partial agonist. In this way, it both stimulates the receptor to attenuate withdrawal symptoms and blocks the maximum release of acetylcholine by nicotine to decrease smoking satisfaction. Dosing of varenicline for adults is recommended to start at 0.5 mg once per day for the first 3 days, followed by 0.5 mg twice per day for 4 days, and then increased to 1 mg twice per day for the next 12 weeks (12-week course at 2 mg daily recommended) (Management of smoking cessation in adolescents uptodate 2018). Varenicline has been associated with significant adverse effects, including drowsiness and seizures, and must be used with caution while driving. Varenicline was previously thought to potentially increase suicidality and neuropsychiatric side effects in the same way as bupropion and other antidepressants; however, this assertion was recently refuted by a large-scale randomized controlled trial specifically examining these outcomes across an array of at-risk and general populations (Anthenelli et al. 2016).

Recent studies have evaluated varenicline as a pharmacotherapy for youth smokers. This medication was shown previously to have a similar pharmacokinetic profile as in adults, with no serious adverse events ($N = 72$) (Faessel et al. 2009), and a preliminary 2-week adolescent outpatient laboratory study demonstrated safety and feasibility of using varenicline to treat tobacco use disorder in youth smokers ($N = 29$) (Gray et al. 2012b). A recent randomized trial of varenicline with 157 youth smokers (14–21 years of age) found that varenicline promoted abstinence early in the trial, but no difference in biologically confirmed abstinence was found at the end of the 12-week treatment between varenicline and placebo groups (Gray et al. Varenicline for adolescent smoking cessation: A randomized clinical trial. *JAMA Pediatrics*; in review) (ClinicalTrials.gov Identifier: NCT01509547). A 12-week varenicline trial from a Pfizer-sponsored multisite study recently completed recruitment on 307 adolescent smokers (12–19 years of age) who were motivated to quit smoking. While findings are not published, primary results uploaded to ClinicalTrials.gov suggest no difference between high-dose or low-dose varenicline treatment versus placebo (ClinicalTrials.gov Identifier: NCT01312909).

Electronic nicotine delivery systems

Even among adult cigarette smokers who are part of high-risk populations, there is still debate and concern regarding the risks and benefits of electronic nicotine delivery systems (ENDS) use (e.g., e-cigarettes, vaping) (US Department of Health and Human Services 2016). No study has been completed to assess ENDS as a smoking cessation tool in youth. In fact, youth rarely use ENDS as smoking cessation tools, and often times engage in dual use of combustible cigarettes and ENDS (US Department of Health and Human Services 2016). Other types of nicotine cessation medications have low or no abuse liability in youth, whereas ENDS have high abuse liability and their use may lead to combustible product use (Stanton et al. 2019). Furthermore, there is growing concern that more widespread use of any type of nicotine and smoking device may renormalize smoking culture among youth (Barrington-Trimis et al. 2015), subverting decades of antismoking efforts.

Limitations

Although there is interest in quitting among younger smokers, cessation continues to be a challenge. An additional barrier to tobacco cessation is that younger smokers are less likely to utilize smoking cessation treatment strategies (Curry et al. 2007), and several of the studies reviewed here struggled with low treatment adherence rates. There is also limited treatment-focused work in the area of alternative nicotine and tobacco products among youth. Use of electronic cigarettes (vaping) has been increasing steadily in youth (Cullen et al. 2018), and there is little evidence to support interventions, pharmacological or otherwise, to promote abstinence from alternative products. It may be the case that future clinical trials need to consider how nicotine is being administered when developing and testing treatment, or somehow control for these varying administration methods. Exclusive cigarette smokers and ENDS users may respond differently to treatment strategies, which will be important to test over the coming years in both youth and adults. The FDA has made treatment strategies for youth vaping a priority and has recently held public hearings addressing inadequate treatment for cessation from these products in youth.

Opioid Use Disorder

Use of prescription opioids among youth has been declining. In 2018, 3% of 12th graders reported misuse of prescription opioids, which is almost two-thirds lower than the peak of 10% in 2004 (Johnston et al. 2019). Heroin use among youth remains consistently low (Johnston et al. 2019), suggesting that the opioid epidemic is more specifically affecting adult populations in the United States. Nonetheless, treatment for youth affected by opioid use is important, given the high morbidity and mortality associated with opioid use disorder.

Buprenorphine

Buprenorphine is the only FDA-approved medication for any adolescent SUD, and is indicated down to 16 years of age for opioid use disorder. Three randomized controlled trials have examined buprenorphine for treatment of youth opioid use disorder (Borodovsky et al. 2018). The first clinical trial randomized youth (ages 16–18) with opioid use disorder ($N = 36$) to either a 28-day buprenorphine or clonidine detoxification, and found that buprenorphine significantly increased adherence to treatment (i.e., 72% remained in treatment in the buprenorphine group relative to 39% of those who received clonidine) and biologically confirmed abstinence from opioids (64% vs. 32%) (Marsch et al. 2005). The second trial included 152 youth participants (15–21 years of age) with opioid use disorder, recruited across six sites, randomized to either a two-week buprenorphine/naloxone detoxification (detox group) or an eight-week buprenorphine/naloxone administration period with a four-week taper (Woody et al. 2008). Patients in the buprenorphine/naloxone group were prescribed up to 24 mg per day for nine weeks and then tapered to week 12; patients in the detox group were prescribed up to 14 mg per day and then tapered to day 14. All were offered weekly individual and group counseling. Participants in the detox group were significantly less likely to remain in the assigned treatment than those in the 12-week buprenorphine/naloxone group (21% vs. 70%). Compared to participants in the 12-week buprenorphine/naloxone group, participants in the detoxification group had higher proportions of opioid-positive urine test results at weeks four (61% vs. 26%) and eight (54% vs. 23%), but not at week 12 (51% vs. 43%). Participants in the 12-week buprenorphine/naloxone reported significantly less opioid use, less injecting, and lower use of other drugs.

The third double-blind placebo-controlled trial included 53 youth participants (16–24 years of age) with opioid use disorder randomized to either a 28- or 56-day buprenorphine/naloxone detoxification and followed over a 63-day study period (Marsch et al. 2016). Participants who received a 56-day buprenorphine taper were retained in treatment 11 days longer on average than participants who received a 28-day buprenorphine taper. Participants who received a 56-day buprenorphine taper had a significantly higher percentage of opioid-negative scheduled urine tests compared with participants who received a 28-day buprenorphine taper (35% vs. 17%).

Limitations

Results from the three trials suggest that buprenorphine is more effective than clonidine for youth with opioid use disorder, and longer detoxification schedules result in higher treatment engagement and improved rates of opioid abstinence (Borodovsky et al. 2018). Buprenorphine is the only FDA-approved medication for adolescent opioid use disorder; however, it is not approved for youth younger than 16. Limitations from these studies include the limited sample sizes, lack of diversity in samples, poor treatment retention, and high opioid relapse rate postmedication administration (Fiellin 2008).

Methamphetamine Use Disorder

Methamphetamine use is fairly uncommon in youth, with only 0.5% of 18-year olds reporting past year use of methamphetamines (Johnston et al. 2019). There are currently no FDA-approved medications for adult or adolescent methamphetamine use disorder. One small pilot trial randomized 19 adolescents who met criteria for methamphetamine abuse or dependence to bupropion SR 150 mg for eight weeks (Heinzerling et al. 2013). All participants received weekly counseling. Adolescents in the placebo group provided significantly more methamphetamine-free urine tests compared to participants receiving bupropion. Results did not support the feasibility or utility of additional trials of bupropion for adolescent methamphetamine use disorder.

Conclusion

While behavioral interventions, therapy, and support groups are important parts of treating youth SUD, more research is urgently needed to evaluate the safety and efficacy of pharmacotherapy

options in this vulnerable age group. Pharmacotherapy, in combination with behavioral interventions, has the potential to increase the likelihood of successful treatment for youth struggling with SUD, and disrupting the trajectory to a more severe SUD and/or polysubstance use.

Clinical Significance

The literature on pharmacotherapy for adolescent alcohol, cannabis, tobacco, opioid, and methamphetamine use disorders is limited. To date, there are still no FDA-approved medications for adolescent SUD, other than buprenorphine, which has been approved down to 16 years of age for opioid use disorder. Despite alcohol and cannabis being the most commonly used substances during adolescence, there have been limited pharmacological investigations for youth alcohol or cannabis use disorders. In addition, treatment strategies for youth vaping are still in their infancy and no recommendations exist for how to promote cessation from ENDS. There is evidence that some of the medications approved for adults are beneficial for adolescents, the most promising findings being buprenorphine for opioid use disorder and bupropion and varenicline for tobacco use disorders. NAC appears to be a promising treatment for cannabis use disorder, and potentially alcohol use disorder, but more research is needed. Overall, pharmacotherapy could be a potentially effective way to support psychosocial interventions and increase treatment effects; however, more rigorous research trials are warranted before FDA approval would be granted for any of the potential adjunctive medications.

Disclosures

K.M.G. has consulted for Pfizer, Inc. None of the other authors have disclosures.

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