

Emerging Pharmacologic Treatments for Adolescent Substance Use: Challenges and New Directions

Robert Miranda Jr.¹ · Hayley Treloar¹

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Abstract Adolescence is a key period in the development of substance use and misuse. Substance use typically begins during adolescence, and prevalence rates for many substance use disorders peak before age 21 years. Yet, despite clinical demand, treatments for youth rely almost entirely on psychosocial interventions that yield only modest benefit. One potential way to improve treatment effects is to augment the best available psychosocial interventions with pharmacotherapy. Although pharmacotherapy research has advanced care for adults with substance use disorders, no medication is indicated for adolescents and controlled trials with teenagers are scant. Optimizing treatments for youth will require closing this important gap in medication development research. In this paper, we review the paucity of pharmacotherapy research for adolescent substance misuse, and we discuss how we can leverage human laboratory paradigms and technology to advance our understanding regarding if and how medications may improve treatment options for youths.

Keywords Adolescents · Ecological momentary assessment · Human laboratory · Medication · Pharmacotherapy · Substance use · Review

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✉ Robert Miranda, Jr.
Robert_Miranda_Jr@brown.edu

¹ Center for Alcohol and Addiction Studies, Brown University, Box S121-5, Providence, RI 02912, USA

Introduction

Adolescent substance use patterns are increasingly recognized as key determinants of later substance use and related disorders [1–3]. From early to late adolescence, alcohol use becomes normative, marijuana and illicit drug use markedly increases, and the complex phenomena that comprise substance use disorders (SUDs) reach peak prevalence [2, 4–6]. Although the escalation of substance use behaviors during the adolescent years is normative, it is not benign. High rates of alcohol and drug use during adolescence overlap with a critical period for brain development, which may partially explain the increased vulnerability of young people to SUD [7–9]. Adolescents who initiate alcohol or drug use during adolescence are at increased risk of becoming dependent or having other adverse health consequences in later years [5, 10–14], and risk of developing an SUD is greatest within the first 5 to 10 years of use for alcohol and most illicit drugs [14–16]. Thus, the value of providing interventions for adolescent substance misuse and related disorders is particularly high, and developing or refining interventions for young people can have far-reaching benefits that extend into adulthood.

Although adolescence is a key developmental stage for substance use progression, the current profile of intervention options for adolescents who misuse substances is limited in scope, due to an almost exclusive reliance on psychosocial treatments with limited effectiveness [17]. The state of the science on outpatient psychosocial interventions for adolescent substance misuse, especially at lower levels of use, is trending toward brief, person-centered approaches that provide individually tailored information to youth across a variety of settings [18]. Core elements of these brief interventions include, for example, motivational interviewing and motivational enhancement approaches, personalized feedback on normative substance use, and cognitive behavioral therapy

[19]. Recent meta-analytic reviews of brief interventions suggest that psychosocial interventions among adolescents produce small to moderate reductions in substance use that are most robust at treatment completion [19–21]. For a listing of evidence-based psychosocial interventions, please see the Substance Abuse and Mental Health Services Administration website (<http://www.nrepp.samhsa.gov/AdvancedSearch.aspx>).

On the whole, research shows psychosocial techniques to be modestly effective first-line treatments for adolescent substance misuse, but effects are often small and diminish over time [22–24]. Thus, despite clinical demands, substance abuse treatment initiatives for youth remain inadequate. It is clear that more effective treatments are essential for mitigating the adverse consequences of alcohol and other drug use during adolescence and for averting substance-related problems during later development.

Pharmacological Intervention Research

One potential way to improve treatment effects is to augment the best available psychosocial interventions with pharmacotherapy. For more than two decades, the National Institutes of Health (NIH) has mounted a concerted effort to identify medications that reduce alcohol and other drug use. Myriad pharmacotherapy trials with adults were funded, and the US Food and Drug Administration (FDA) approved medications for treating adults with alcohol, opioid, and nicotine dependence. While these efforts improved the quality of care for adults, no medication is indicated for adolescent substance use, and adequately powered controlled clinical trials with teenagers are almost non-existent. This gap raises key questions about if and how medications could benefit youth. Optimizing treatment options for youth will require closing this important gap in medication development research.

Medications are commonly successful for treating a broad array of psychiatric diagnoses in adolescents, yet they are infrequently used for treating adolescent SUDs [18, 22, 25–27]. The relevance of pharmacotherapies to the development of more effective, comprehensive care for adolescents is unclear, in part, because the quality of evidence on which to make recommendations is limited. Moreover, clinical trials with adults, typically defined as 18 years or older, are not designed to inform whether medications are safe and appropriate for pediatric use. Consequently, recent legislative changes require that medications indicated for adults also be tested with children. Indeed, compelling evidence from several branches of medicine demonstrates that the safety and efficacy of medication use with adolescents cannot be inferred from adult data [28–30], and this concern may be especially important in the substance abuse field [31]. There is

strong evidence that teenagers differ considerably from adults in terms of their symptom presentation, course, and associated features of SUDs, and these differences appear to be driven in part by substantial neuronal remodeling that occurs during adolescence [17, 32, 33]. These changes impact adolescents' sensitivity to alcohol and possibly other drugs; heighten their vulnerability to heavy drinking, other drug use, and the development of substance use problems; and possibly impact how they respond to medications [33].

Prior reviews of the literature on pharmacotherapy for adolescents with SUDs illustrate the scant nature of research in this area [22, 26, 31, 34–36]. Our primary objective for this review is not to duplicate recent surveys of the literature, but rather to review some of the limitations of existing medication development research with adolescents and outline novel methods to address these limitations. We first consider randomized controlled trials with suitable sample sizes that focused on substance use as the primary treatment target, reviewing findings for alcohol, nicotine, cannabis, opiates, and methamphetamines. We next consider medication trials that examined substance use as secondary targets in samples with a co-occurring psychiatric condition such as depression, conduct problems, or attention-deficit/hyperactivity disorder (ADHD). We then review an innovative paradigm for advancing pharmacotherapy for SUDs among adolescents, which builds on the models used to advance medication development in adults and provides a much needed mechanism for translating animal research on developmental aspects of addiction to human adolescents.

Current Status of the Field

The randomized controlled trial (RCT) is the gold standard for evaluating the efficacy of novel interventions, including pharmacotherapies. The vast majority of published reports on medications for treating SUDs among adolescents, however, are case reports and open-label studies. According to the FDA (21 CFR 814.3; 79 FR 1740, January 10, 2014), pediatric patients include individuals younger than age 22 years, with adolescents defined as youth ages 12 through 21 years. This window is generally consistent with neurodevelopmental evidence that adolescence extends to the early- to mid-twenties [37]. In this review, we focus on clinical trials that targeted youths 25 years of age or younger. Adult trials that employed a minimum age requirement of 18 years but did not specifically evaluate the efficacy of the study medication on the subset of patients younger than 25 years are not discussed. This review of the published RCTs for SUDs, which is organized by substance type, illustrates the limited scientific work in this area. Table 1 summarizes RCTs of the efficacy of pharmacotherapies for treating adolescent substance misuse.

Table 1 Summary of randomized controlled trials of the efficacy of pharmacotherapy for treating adolescent substance misuse

Reference	Study design	Sample	Treatment	Follow-up	Outcome
Alcohol O'Malley et al. [38]	Double-blind, placebo-controlled, 8-week trial	N = 128 Ages 18–25 69 % male ≥4 heavy drinking days in the month before tx	Naltrexone (NTX; 25 mg daily + 25 mg targeted daily) vs. placebo; all received motivational intervention	End of tx, 1 year post-tx	*NTX decreased number of drinks per drinking day at the end of the 8-week trial *NTX decreased the percentage of drinking days participants' estimated blood alcohol level ≥0.08 g% *Decreases in drinking across both conditions were maintained at the 1-year follow-up
DeMartini et al. [39•]	Double-blind, placebo-controlled, 8-week trial	N = 116 Ages 15–21 73 % male Cannabis dependent	N-acetylcysteine (NAC; 1200 mg) vs. placebo; all received contingency management (CM) + weekly cessation counseling	During tx, 4 weeks post-tx	*NAC increased odds of negative urine drug screen during treatment *NAC effect not maintained at 4-week follow-up
Miranda et al. [46•]	Double-blind, placebo-controlled, 6-week trial	N = 66 Ages 15–24 48 % male Heavy cannabis users	Topiramate (200 mg) vs. placebo; all received motivational intervention (MET)	During tx	*Topiramate + MET reduced the quantity use per use occasion, but had no effect on abstinence; both conditions showed significant reductions in the frequency of use
Nicotine Hanson et al. [97]	Double-blind, placebo-controlled, 13-week trial	N = 100 Ages 13–19 53 % male ≥10 cigarettes per day	Nicotine patch (≤21 mg tailored to baseline smoking levels) vs. placebo; all received 10 weeks of cognitive behavioral therapy (CBT) and CM	During tx	*Nicotine patch group experienced significantly lower craving score and overall withdrawal score *No treatment condition differences observed in abstinence rates
Killen et al. [98]	Double-blind, placebo-controlled, 10-week trial	N = 211 Ages 15–18 69 % male ≥10 cigarettes per day	Nicotine patch + bupropion sustained release (150 mg) vs. nicotine patch + placebo; all received group skills training	End of tx, 26 weeks post-tx	*Adding bupropion to the nicotine patch did not improve abstinence rates at either time point
Moolchan et al. [99]	Double-blind, placebo-controlled, 12-week trial	N = 120 Ages 13–17 30 % male ≥10 cigarettes per day and motivated to quit	Nicotine patch (21 mg) vs. nicotine gum (2 and 4 mg), vs. placebo patch/gum; all received weekly group CBT	During tx, 3 months post-tx	*Nicotine patch had greater abstinence rates than the placebo but not gum during tx and similar non-significant trends emerged at study completion and 3 months post-tx *No significant effects for the nicotine patch vs. gum or gum vs. placebo
Roddy et al. [100]	Placebo-controlled, 6-week trial	N = 98 Ages 11–21 40 % male >1 cigarette per day or <1 cigarette per day and withdrawal with CO >5 ppm	Nicotine patch (15/10/5 mg) vs. placebo; all received 10–15-minute counseling session per visit	During tx, 13 weeks post-tx	*Low adherence to tx *Abstinence at 4 weeks with nicotine patch = 5 participants; placebo = 2 *Abstinence at 13 weeks with nicotine patch = 0; placebo = 0
Muramoto et al. [101]	Double-blind, placebo-controlled, 6-week trial	N = 312 Ages 14–17 46 % male ≥6 cigarettes per day	Bupropion sustained release (150 or 300 mg) vs. placebo; all participants received brief individual counseling	During tx, 12 and 26 weeks post-tx	*300 mg increased abstinence during tx, but effects were not sustained post tx. *No effect of 150 mg
Gray et al. [41]	Double-blind, placebo-controlled, 6-week trial	N = 134 Ages 12–21 58 % male ≥5 cigarettes per day	Bupropion sustained release (≤300 mg) with or without CM or placebo with or without CM (4 conditions)	During tx, 12 weeks post-tx	*Bupropion + CM increased abstinence rates during tx *Combined tx may be superior to either bupropion or CM alone
Gray et al. [42]	Double-blind, placebo-controlled, 8-week trial	N = 29 Ages 15–20 48 % male ≥5 cigarettes per day	Varenicline (≤2 mg) vs. bupropion sustained release (≤300 mg)	During tx, 12 weeks post-tx	*Significant time effects on cigarettes per day and abstinence rates for both conditions *No condition or interaction effects
Scherphof et al. [43•]	Double-blind, placebo-controlled, 6- to 9-week trial	N = 257 Ages 12–18 47 % male ≥7 cigarettes per day	Nicotine patch (≤21 mg) vs. placebo	After 2 weeks of tx, end of tx	*Nicotine patch increased odds of abstinence at 2 weeks post-tx onset compared to placebo *After adjusting for covariates of smoking cessation, nicotine patch only predicted end of tx abstinence among adolescents with higher compliance rates
Opiates		N = 36		During tx	

Table 1 (continued)

Reference	Study design	Sample	Treatment	Follow-up	Outcome
Marsch et al. [55]	Double-blind, double-dummy, 28-day trial	Ages 13–18 39 % male Opioid dependence	Outpatient detox with buprenorphine (≤ 8 mg) + placebo patch vs. clonidine (≤ 3 mg) patch + placebo tablets; thrice weekly individual behavioral therapy	Weeks 4, 8, and 12	*72 % randomized to buprenorphine completed detox.; 39 % randomized to clonidine completed detox. *Buprenorphine provided mean of 64 % negative urine tox screens vs. 32 % for clonidine (ITT analysis). *Week 4: positive urine tox for 61 % of 14-day detox group and 26 % of 12-week tx group *Week 8: positive urine tox for 54 % of 14-day detox group and 23 % of 12-week tx group *Week 12: positive urine tox for 51 % of 14-day detox group and 43 % of 12-week tx group
Woody et al. [56]	Double-blind, 12-week trial	$N = 152$ Ages 15–21 59 % male Opioid dependence with physiological features who sought outpatient tx	14-day outpatient detoxification (≤ 14 mg of buprenorphine) vs. 12 weeks buprenorphine-naloxone (≤ 24 mg); both groups received weekly individual and group counseling		
Methamphetamines Heinzerling et al. [57]	Placebo-controlled, 8-week trial	$N = 19$ Ages 14–21 47 % male Meth abuse or dependence	Bupropion SR 150 mg twice daily or matching placebo; both groups received twice weekly outpatient group counseling	During tx	*Placebo group had significantly fewer negative urine toxicology screens
Comorbid psychiatric conditions Riggs et al. [59]	Double-blind, placebo-controlled, 16-week trial	$N = 126$ Ages 13–19 67 % male Concurrent depression, conduct disorder, and SUD	Fluoxetine (20 mg) vs. placebo; all received weekly individual CBT	During tx	*Overall decrease in self-reported substance use but no significant difference between groups *Proportion of negative tox screens higher in placebo versus fluoxetine group
Cornelius et al. [60]	Double-blind, placebo-controlled, 12-week trial	$N = 70$ Ages 14–25 61 % male Major depression + cannabis use disorder	Fluoxetine (20 mg target) vs. placebo; all received 9 sessions of MET + CBT	End of tx	*No significant differences between groups *Both groups experienced a significant reduction in the number of clinically significant cannabis dependence symptoms
Cornelius et al. [61]	Double-blind, placebo-controlled, 12-week trial	$N = 50$ Ages 15–20 44 % male Major depression + AUD	Fluoxetine (20 mg target) vs. placebo; all received 9 sessions of MET + CBT	End of tx	*No significant differences between groups *Both groups experienced a significant reduction in the number of clinically significant alcohol use disorder symptoms
Riggs et al. [62]	Double-blind, placebo-controlled, 12-week trial	$N = 69$ Ages 13–19 84 % male ADHD, conduct disorder + SUD	Pemoline (≤ 112.5 mg) vs. placebo	End of tx	*Neither group reduced substance use
Thurstone et al. [63]	Double-blind, placebo-controlled, 12-week trial	$N = 70$ Ages 13–19 79 % male ADHD + SUD	Atomoxetine hydrochloride (≤ 100 mg) vs. placebo; all received psychosocial intervention for substance use	End of tx	*No effect of atomoxetine on ADHD or substance use
Riggs et al. [65]	Double-blind, placebo-controlled 16-week trial	$N = 303$ Ages 13–18 79 % male ADHD + SUD	Osmotic release methylphenidate (≤ 72 mg) vs. placebo; all received individual CBT for substance use	End of tx	*Both groups experienced a significant reduction in the number of substance using days during the study, but no between-group differences *The medication group had significantly more negative tox screens.
Rubinstein et al. [102]	Randomized, open-label 12-week trial	$N = 40$ Ages 15–18 46 % male	Nasal nicotine spray (≤ 40 mg) for 6 weeks plus 8 weeks of group counseling vs. 8 weeks of group counseling	End of tx	*No difference in cessation rates, numbers of cigarettes smoked per day or cotinine levels between groups

RCT randomized controlled trial, tx treatment, MET motivational enhancement therapy, SUD substance use disorder, AUD alcohol use disorder, CBT cognitive behavioral therapy, ADHD attention deficit hyperactivity disorder

Alcohol There are only a handful of published reports on pharmacotherapy for adolescent drinking. Most are case studies or open label trials, and all reports bear substantial limitations that preclude inferences about the efficacy of the medication studies. In terms of RCTs, there are no adequately powered trials with adolescents younger than 18 years. One recent well-designed RCT of naltrexone with young adult drinkers, ages 18 to 25 years, showed that naltrexone (25 mg daily + 25 mg targeted) plus a brief motivational intervention reduced the number of drinks per drinking day by the end of the 8-week treatment period [38]. At the 12-month follow-up assessment, there were no differences between conditions but drinking reductions observed during the active treatment phase were maintained [39•].

Nicotine The FDA has approved nicotine replacement therapies (NRTs; i.e., nicotine gum, nicotine inhaler, nicotine lozenge, nicotine nasal spray, and nicotine patch) and two non-nicotinic pharmacotherapies (i.e., varenicline tartrate and bupropion hydrochloride) for treating nicotine dependence among adults. At present, however, none of these treatment options are indicated for pediatric use. In a review of the literature on pharmacotherapies (i.e., NRT, bupropion, and varenicline) for adolescent smoking, which included a laboratory study, three open-label trials, and six RCTs, Bailey and colleagues [40] concluded that the nicotine patch and bupropion produced beneficial effects immediately post-treatment. But these effects were transient and no medication showed long-term effects on smoking cessation. In a second review, which involved a meta-analysis of the six RCTs described by Bailey and colleagues [40], Kim and colleagues [36] found no short- or mid-term benefit of pharmacological treatment for adolescent smoking. Since these reviews, three additional RCTs were published. Gray and colleagues tested the efficacy of bupropion, with and without contingency management, and found that the combination of bupropion and contingency management was superior to placebo plus contingency management in terms of abstinence rates [41]. In a second study, Gray and colleagues compared varenicline and bupropion among adolescent smokers and found a main effect of time on smoking outcomes but no differences were observed between the conditions [42]. Most recently, Scherphof and colleagues examined the efficacy of the nicotine patch on smoking outcomes among 12- to 18-year-old youths [43•]. The nicotine patch, as compared to placebo, increased the odds of quitting smoking after 2 weeks of treatment.

Cannabis RCTs of medications for treating cannabis dependence are few, and most, but not all [44], have produced null findings. Two controlled pharmacotherapy trials have studied adolescents to date. The first trial examined the effects of *N*-acetylcysteine, combined with contingency management and

weekly cessation counseling, among adolescents with cannabis dependence. *N*-acetylcysteine is a pro-drug of the amino acid cysteine thought to affect glutamate regulation. *N*-acetylcysteine increased the odds of abstinence during the 8-week trial, but this effect was not sustained at the 4-week follow-up [45].

We recently conducted a double-blind, placebo-controlled, pilot study of topiramate plus motivational enhancement therapy (MET) for treating cannabis use among adolescents and young adults, ages 15 to 24 years [46•]. Topiramate is a sulfamate-substituted fructopyranose derivative that reduced alcohol, cocaine, and nicotine use in clinical trials with adults [47–52]. It has multiple mechanisms of action, including blockade of voltage-sensitive sodium and calcium channels, potentiation of γ -aminobutyric acid (GABA), enhancement of GABA_A receptor function, antagonism of AMPA/kainate glutamate receptors, and inhibition of carbonic anhydrase [53, 54]. Sixty-six heavy cannabis users were randomized to one of two 6-week treatment conditions: topiramate plus MET or placebo plus MET. Topiramate was titrated over 4 weeks then stabilized at 200 mg/day for 2 weeks. MET was delivered biweekly for a total of three sessions. Only 48 % of youths randomized to topiramate completed the 6-week trial ($n=19$), compared to 77 % of youths in the placebo condition ($n=20$). Adverse medication side effects were the most frequent reason for withdrawal among participants in the topiramate group. The most common side effects included neurocognitive effects, decreased appetite and weight loss, and paresthesias. Topiramate, combined with MET, demonstrated efficacy for reducing how much cannabis adolescents smoked when they used but did not affect abstinence rates. The magnitude of this effect was modest, however, and topiramate was poorly tolerated by youths, which calls into question the clinical importance of these findings.

Opiates There are two published RCTs of a pharmacotherapy, to our knowledge, for treating opiate dependence. The first trial examined the use of buprenorphine, as compared to clonidine, as a medication-assisted withdrawal treatment for 28 days in 36 adolescent outpatients with opiate dependence [55]. Results showed that buprenorphine was associated with a significantly higher percentage of urine toxicology screens that were negative for opiates. The second RCT tested the efficacy of extended use of buprenorphine-naloxone in 152 adolescents and young adults, aged 15 to 21 years [56]. Participants were randomized to receive 2 or 12 weeks of the study medication and provided with a weekly psychosocial intervention. Findings indicated that continued treatment beyond the first 14-day period was associated with improved outcomes in terms of urine toxicology results.

Methamphetamines In one pilot RCT, researchers randomized 19 adolescents and young adults with methamphetamine

abuse or dependence, ages 14 to 21 years, to bupropion or placebo for 8 weeks [57]. Bupropion treatment, as compared to placebo, was associated with a greater number of positive urine toxicology screens for methamphetamine, suggesting this treatment may yield iatrogenic effects in youths.

Psychiatric comorbidity In addition to examining the effects of medications among adolescents with SUDs, researchers have also evaluated the effects of pharmacotherapy for co-occurring psychiatric conditions, such as depression and ADHD, among adolescents with an SUD and examined its effects on substance use outcomes. In terms of depression, Zhou and colleagues [58•] included five RCTs in a meta-analysis comparing antidepressants, namely, selective serotonin reuptake inhibitors, to placebo for treatment of co-occurring unipolar depression and SUD (e.g., alcohol, cannabis, and other substances) in youth aged ≤ 25 years. Overall, antidepressant medication produced modest reductions in depressive symptoms, but improvement in substance use outcomes did not surpass the effect of placebo. In one of the reviewed studies, Riggs and colleagues tested the effects of fluoxetine, as compared to placebo, on substance use outcomes in a sample of adolescents, ages 13 to 19 years, with concurrent depression, conduct disorder, and at least one non-tobacco SUD [59]. All participants received a weekly psychosocial intervention that specifically targeted substance use. Across groups, adolescents reduced their substance use. There was no significant difference between conditions in terms of self-reported substance use, however, and results of urine toxicology tests indicated the placebo group had more negative screens than did the fluoxetine group. Another trial examined the efficacy of fluoxetine in youths with comorbid depression and cannabis use disorder and found no effect [60].

In another RCT, Cornelius and colleagues tested the effects of fluoxetine among 50 adolescents, ages 15 to 20 years, with comorbid major depressive disorder and alcohol use disorder [61]. Youths were randomized fluoxetine or placebo for 12 weeks; all participants received a psychosocial intervention. Results showed no differences between treatment conditions in terms of alcohol use outcomes; both groups showed significant reductions in drinking.

Three RCTs examined the effects of pharmacotherapy for ADHD on substance use outcomes among adolescents. In the first trial, 69 adolescents, ages 13 to 19 years, with comorbid conduct disorder, ADHD, and SUD, were randomized to 12 weeks of treatment with pemoline, a stimulant drug withdrawn from the market in 2005 due to side effects, or placebo [62]. Results showed no differences between conditions in terms of substance use outcomes. In the second trial, 70 adolescents, ages 13 to 19 years, with comorbid ADHD and an SUD, were randomized to atomoxetine hydrochloride, a selective norepinephrine reuptake inhibitor, or placebo for 12 weeks [63]. Participants in both conditions received a

psychosocial intervention that targeted substance use. This study found no effect of atomoxetine on either ADHD symptoms or substance use. Interestingly, these findings contrast with an RCT of atomoxetine among adults with ADHD and an alcohol use disorder, which found that atomoxetine was associated with reduced ADHD symptoms and alcohol use [64]. There were several notable differences between these studies, however, that may account for these discrepant findings. The adult trial enrolled recently abstinent individuals with an alcohol use disorder and examined the effects of atomoxetine on drinking outcomes [64]. By contrast, the adolescent trial enrolled youths with a variety of SUDs, including cannabis, nicotine, and alcohol use disorders, and examined the effects of atomoxetine on any substance use as a single aggregate outcome [63]. Only seven participants randomized to atomoxetine in the adolescent trial met criteria for an alcohol use disorder. In addition, participants in the adult trial were not permitted to receive any psychosocial intervention for substance use, aside from 12-step participation, while enrolled in trial [64]. In the adolescent trial, however, all youths received a robust multifaceted psychosocial intervention (e.g., anger management, communication skills, mood management, drug refusal skills, problem solving skills, etc.) that targeted substance misuse [63].

In the third trial, 303 adolescents, ages 13 to 18 years, were randomized to osmotic-release methylphenidate, a psychostimulant medication, or placebo for 16 weeks; all participants received a psychosocial intervention designed to target substance use [65]. No differences between conditions were observed in terms of self-reported substance use, but the methylphenidate group had more negative urine toxicology screens.

Summary of reviewed studies On the whole, medication development research for adolescent substance misuse has yielded limited effects of pharmacotherapies on substance use outcomes in youth. Research in this area is scarce, however, and null findings may be attributed to inadequate sample sizes that might have rendered most studies underpowered for detecting treatment effects. Moreover, the safety and tolerability pharmacotherapy for adolescent SUDs remains largely unstudied and information regarding the most efficacious medication dose, duration of treatment to maximize maintenance of beneficial effects, and strategies for integrating medications with psychosocial interventions is unknown. Similarly, our knowledge about how medications may help reduce substance use among youth (i.e., putative mechanisms of action) is limited and, thus, at present, pharmacologic intervention approaches with adolescents are based almost entirely on treatment targets identified in adult studies, such as attenuating craving. Additional information is needed regarding the most salient treatment targets during adolescence in order to tailor interventions and maximize treatment effects.

Challenges in Pharmacological Research with Adolescents

Along with the many advantages of the RCT approach, including a robust test of the efficacy or effectiveness of the experimental treatment, it has drawbacks. Randomized clinical trials require large sample sizes to be adequately powered and lengthy intervention and follow-up periods, and, consequently, they often take many years to yield information about the potential utility of the intervention studied. Moreover, adequately powered clinical trials are costly. In light of these limitations, for nearly three decades, clinical scientists have developed human laboratory paradigms to identify promising medications for treating adults with SUDs and to help elucidate how efficacious medications exert their beneficial effects. These experimentally controlled human laboratory analogues provide efficient and cost-effective assays of key characteristics of addiction, such as subjective responses to alcohol and other drugs, craving, and substance use itself [66].

An Emerging Conceptual Framework for Precision Medicine in Addiction Treatment

Litten and colleagues [67] recently provided a conceptual framework that associates human laboratory paradigms with corresponding animal models and sorts these paradigms according to a three-stage addiction cycle. This classification system, which concentrates on the core mechanisms that underlie pathological substance use, is modeled after the Research Domain Criteria developed by the National Institute of Mental Health [68, 69]. We believe this three-stage framework can be employed across addictive substances. The first stage, which involves incentive salience and habit engagement and may be especially relevant to adolescents, is the *binge-intoxication stage*. Laboratory models that target this stage include alcohol administration and self-administration, which is based on the presumed association between drinking behavior in experimentally controlled conditions and drinking in the natural environment. Using these paradigms, researchers have examined how a host of medications (i.e., baclofen, naltrexone, ondansetron, sertraline, and topiramate) alter the reinforcing value of alcohol among non-treatment-seeking adults with alcohol dependence [70], heavy drinkers [71], and social drinkers [72]. Other human laboratory paradigms that target this stage of the addiction process involve inhibitory control (e.g., delay discounting, stop task). There is considerable evidence, both from animal and human research, that certain medications (e.g., naltrexone and other opioid antagonists) may facilitate inhibitory control and reduce impulsive behavior, presumably by altering dopaminergic signaling in the prefrontal cortex.

The second stage of the addiction process within this conceptual framework is the *withdrawal-negative affect stage*,

which involves reward deficits and stress sensitization. Laboratory models designed to test medication effects during this stage include response bias to negative cues and tension reduction paradigms. Lastly, the third stage is the *preoccupation-anticipation stage*, which involves dysregulation of executive function, reward craving, and relief craving. The paradigms used to test this stage include alcohol-induced craving, cue-induced craving, and stress-induced craving. Indeed, craving is a chief motivational determinant of drug use in most contemporary theoretical models of addiction [73]. Reviews of the empirical literature consistently conclude that craving holds clinical importance for understanding and treating addiction in adulthood [74, 75], and the most recent revision of the Diagnostic and Statistical Manual of Mental Disorders [76] introduced craving as a new criterion to advance clinical detection of pathological substance use along an addiction continuum.

Although human laboratory studies have advanced pharmacotherapy research with adults, this methodology is rarely used with adolescents. Randomized pharmacotherapy trials for adolescent substance use have almost exclusively relied on traditional RCT methods, and most, but not all, produced null findings—possibly due to inadequate sample sizes. This reliance on traditional clinical trial methods stemmed in part from uncertainty about how human laboratory models used with adults translate to adolescent substance use. An important consideration for human laboratory studies is their reliance on paradigms that capture phenotypes that predict clinical outcomes. For example, medications are presumed to reduce substance use via several mechanisms, such as altering subjective effects of alcohol and other drugs and blunting craving. The relevance of these mechanisms to adolescent substance misuse, however, is largely speculative. For example, the relevance of craving, a major focus of adult research, to adolescent substance misuse was, until recently, largely understudied [77]. Moreover, even with evidence that adolescents experience craving, questions remain about its relevance to addiction in this age group [77].

Another important basis for the almost exclusive reliance on traditional clinical trial methods with adolescents is that human laboratory methods that rely on alcohol or other drug administration cannot be used with adolescents due to legal and ethical restrictions. This limitation is especially relevant to medication development research for adolescents given compelling evidence from animal research that suggests youth respond differently to some substances, namely, alcohol, than adults in ways that may explain why youth are especially susceptible to substance misuse and possibly affect how they respond to medications. For example, research shows that adolescent animals, as compared to adults, are hypersensitive to alcohol's stimulant effects and less sensitive to its sedative effects [78]. Neither differences in blood alcohol levels nor rates of alcohol metabolism explained these effects, which

appear to be more pronounced after chronic alcohol exposure [79]. Only one human laboratory study published in 1983 [80] examined alcohol's effects (mean peak BAC of 0.04 mg/mL) on boys, ages 8 to 15 years ($N=22$). The lab study found that alcohol increased sedation and decreased stimulation as blood alcohol levels rose [80]. In addition, behavioral monitoring data indicated that the participants showed no outward signs of intoxication [80]. The clinical significance of these human laboratory findings is uncertain inasmuch as youths' alcohol response profile may differ in the natural environment or vary depending on their drinking histories, and it is unknown if and how these effects prospectively predict real-world drinking behavior.

Leveraging Technology to Advance the Field

Over the past decade, we developed a research program that pairs human laboratory paradigms with ecological momentary assessment (EMA) methods to provide an efficient test of the effects of novel medications on substance-related behaviors among adults and, more recently, adolescents. This work embodies our philosophy of conducting interdisciplinary, translational work that is specifically focused on laboratory paradigms with direct clinical relevance. The innovative methods we use test key cognitive, affective, and behavioral mechanisms by which medications are presumed to reduce substance use. These proposed mechanisms include, for example, altering the subjective effects of substance use and blunting craving, measured in the lab, and in real time, in the natural environment. Rapid advances in knowledge about promising medications require not only data from experimentally controlled laboratory settings but also essential information about how laboratory findings generalize to behavior in the natural environment. Consequently, we have demonstrated that human laboratory medication development research is most comprehensively studied using multiple paradigms that target an array of behavioral, physiological, and neurocognitive phenotypes.

Using EMA methods (also referred to as experience sampling), data on momentary events are collected in real time in participants' natural environments, affording a truly prospective analysis of the relationship between specific events and substance use. Momentary assessments are particularly important when the phenomena of interest are subject to rapid change, as are substance use, craving, and the acute subjective effects of alcohol and other drugs. We (and many others) have used this approach to study precursors and consequences of drinking alcohol (i.e., mood, cognitions) with adult and adolescent social and heavy drinkers, as well as patterns and effects of nicotine use with heavy smokers [77, 81–91]. Notably, studies show that self-monitoring using EMA has little or no

effect on drug use [92, 93]. Thus, the field would be remiss to overlook EMA when designing medication trials.

Although the identification of pharmacotherapeutics for adults is greatly advanced by human laboratory studies, EMA studies in daily life can provide important information not readily available in most laboratory paradigms, for adults and adolescents alike. For example, a medication may be shown to effect a putative mechanism of action (e.g., blunting craving) in the laboratory, but this is only the first step of the proposed causal chain from medication to the target mechanism, leaving the second step from the mechanism to the substance use outcome to be implied from other research. Therefore, even when laboratory administration is permitted for adolescents, these paradigms often fall short of identifying the temporal sequence of putative mechanisms on substance use. In contrast, EMA has the potential to yield a deeper understanding of not only whether medications work but also how they work to reduce substance use. Indeed, our research shows that this pairing of human laboratory paradigms with EMA is a viable strategy for disentangling mechanisms of change for alcohol and other substance use in adolescents and adults. Moreover, by pairing human laboratory paradigms with EMA, we are able to identify SUD-related phenotypes (e.g., subjective responses to substance use, cue-elicited craving) and thus the human laboratory paradigms that are best suited for identifying the most promising candidate drug compounds.

In recent years, we extended our adult EMA methods to study adolescents. By pairing controlled laboratory-based cue reactivity assessments with EMA data collected in the natural environment, we were able to show that alcohol cues will elicit craving in the laboratory and in the natural environment, especially among youth with more alcohol problems. And, perhaps most importantly, we found that higher levels of craving (outside of drinking episodes) prospectively predict greater subsequent drinking levels in the natural environment [77]. These findings implicate craving as an important treatment target for pharmacotherapy. We also recently applied these methods to characterize adolescents' subjective responses to alcohol use [87]. Prior to this advance, because of legal and ethical restrictions on administering alcohol to underage youths in the laboratory, our understanding of how alcohol affects teenagers relied entirely on retrospective reports, animal models, and one small alcohol administration study with boys, ages 8 to 15, nearly 35 years ago [80]. By developing methods that capture, in real time and in the natural environment, alcohol's effects in adolescents, we are now able to better test hypotheses about mechanisms of medication effects in youth that involve subjective response to effects of substance use and real-time experience of craving.

In our first application of this methodology to study pharmacotherapy for adolescent substance use, we randomized 22 adolescent drinkers, ages 15 to 19 years, in a double-blinded,

placebo-controlled, crossover study of naltrexone's effects on alcohol use and related behaviors [94]. In most clinical trials with adult samples, naltrexone lowered the risk of relapse and reduced the frequency of drinking and heavy drinking days, with a modest effect size ($g=0.20$; [95]). Secondary analyses of the adult clinical trials indicate that naltrexone, when combined with behavioral therapies, is especially effective for individuals who drink less frequently at baseline but who continue to drink while taking the medication. In addition, other secondary analyses show that naltrexone plus behavioral therapy is more potent for patients with greater numbers of and contact with frequent drinkers in their social network [96]. These findings suggest that naltrexone might be particularly well suited for adolescents because their drinking patterns are characterized by episodic heavy drinking rather than more frequent drinking and because youth may be less likely to embrace abstinence as a treatment goal [17].

In our study, participants completed an alcohol cue reactivity assessment under experimentally controlled conditions in the human laboratory while in both arms (i.e., naltrexone and placebo) of the crossover trial. In addition, alcohol use, subjective responses to alcohol consumption, and alcohol-cue-elicited craving were assessed in the natural environment using EMA methods. Results showed that naltrexone reduced the likelihood of drinking and heavy drinking during the 10-day treatment period, blunted craving in the human laboratory during a cue exposure paradigm and in the natural environment when youths were in the presence of alcohol cues, and altered subjective responses to alcohol consumption during the 10-day treatment period in the natural environment. These findings are similar to those reported by O'Malley and colleagues [38] in a trial with young adults in terms of the effects of naltrexone on the quantity of alcohol use on drinking days and support the utility of pairing human laboratory and EMA methods to conduct proof-of-concept trials in adolescents to examine effects of medication on proposed mechanisms of action, such as blunting of craving and alteration of subjective response to the effects of alcohol use.

Conclusions

Behavioral, physiological, and neurocognitive assays measured in controlled laboratory settings have been leveraged to advance knowledge of how medications impact alcohol and other substance use among adults. These efforts have advanced medication development research and consequently the available treatment options for adults with SUDs. Yet, despite considerable clinical demand, treatment initiatives for youth depend primarily on psychosocial interventions that yield modest effects. By contrast with adults, pharmacotherapy research with adolescents has been hampered by overreliance on case reports, open-label trials, and underpowered

RCTs. We recently developed an innovative strategy for testing the efficacy of medications in youths, which builds on medication development with adults and pairs human laboratory paradigms with EMA methods. The laboratory paradigms test medication effects in experimentally controlled settings, while EMA allows us to examine medication effects on hypothesized mechanisms of action, such as altered subjective responses to substance use and blunting of craving in real time in the natural environment. With this novel combination of methods, we can evaluate the efficacy of promising medications for adolescent substance misuse in a timely and cost-efficient manner within a precision medicine framework for the treatment of addictions.

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Compliance with Ethical Standards

Conflict of Interest Robert Miranda Jr. and Hayley Treloar declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

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