Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Curr Addict Rep. Author manuscript; available in PMC 2017 June 01.

Published in final edited form as:

Curr Addict Rep. 2016 June ; 3(2): 145–156. doi:10.1007/s40429-016-0098-7.

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

Robert Miranda Jr. and **Hayley Treloar**

Center for Alcohol and Addiction Studies, Brown University.

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

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

Correspondence concerning this article should be addressed to Robert Miranda Jr., Center for Alcohol and Addiction Studies, Brown University, Box S121-5, Providence, RI 02912; Phone: (401) 863-6658, Fax: (401) 863-6647, Robert_Miranda_Jr@brown.edu.

Compliance with Ethics Guidelines

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.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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 U.S. 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 nonexistent. 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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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 demonstrate 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 substance use disorders 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.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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 naltrexone (25mg daily + 25mg 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 (NRT; i.e., nicotine gum, nicotine inhaler, nicotine lozenge, nicotine nasal spray, and nicotine patch) and two non-nicotinic pharmacotherapies (i.e., varenicline tartrate and buproprion 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, buproprion, and varenicline) for adolescent smoking, which included a laboratory study, three open-label trials, and 6 RCTs, Bailey and colleagues (40) concluded that the nicotine patch and buproprion 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 6 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 two 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 prodrug 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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

(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 two weeks. MET was delivered biweekly for a total of 3 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, ages 15 to 21 years (56). Participants were randomized to receive 2 weeks 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 nontobacco SUD (59).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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 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 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 7 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.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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 substance use disorders 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 Addictions 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, & topiramate) alter the reinforcing value of alcohol among nontreatment-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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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 under studied (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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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.

Acknowledgements

The National Institute on Alcohol Abuse and Alcoholism at the National Institutes of Health supported this work (AA07850). The funding source had no role in this research other than financial support. We thank Alexander Blanchard for his help with the literature review for this article.

References

Papers of particular interest, published recently, have been highlighted as:

* Of importance

1. Hingson R, White A. New research findings since the 2007 Surgeon General's Call to Action to Prevent and Reduce Underage Drinking: a review. Journal of studies on alcohol and drugs. 2014; 75(1):158–69. [PubMed: 24411808]
2. Swendsen J, Burstein M, Case B, Conway KP, Dierker L, He J, et al. Use and abuse of alcohol and illicit drugs in US adolescents: results of the National Comorbidity Survey- Adolescent Supplement. Archives of general psychiatry. 2012; 69(4):390–8. [PubMed: 22474107]
3. Services USDoHaH. The Surgeon General's Call to Action to Prevent and Reduce Underage Drinking. Jul.2007
4. Johnston LD, O'Malley PM, Miech RA, Bachman JG, Schulenberg J. Monitoring the Future Results on Drug Use: 1975-2014. Overview of Key Findings. 2015

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

5. Adolescent substance use: America's #1 Public Health Problem. Atlanta, GA: 2011. The National Center on Addiction and Substance Abuse (CASA) at Columbia University..
6. Center for Behavioral Health Statistics and Quality. Substance Abuse and Mental Health Services Administration. Rockville, MD: 2014. 2015. National Survey on Drug Use and Health: Detailed Tables..
7. Lubman DI, Yucel M, Hall WD. Substance use and the adolescent brain: a toxic combination? Journal of psychopharmacology. 2007; 21(8):792–4. [PubMed: 17984159]
8. Volkow N, Li TK. The neuroscience of addiction. Nat Neurosci. 2005; 8(11):1429–30. [PubMed: 16251981]
9. Schneider M. Puberty as a highly vulnerable developmental period for the consequences of cannabis exposure. Addiction biology. 2008; 13(2):253–63. [PubMed: 18482434]
10. Behrendt S, Wittchen HU, Hofler M, Lieb R, Beesdo K. Transitions from first substance use to substance use disorders in adolescence: is early onset associated with a rapid escalation? Drug and alcohol dependence. 2009; 99(1-3):68–78. [PubMed: 18768267]
11. Chen CY, Storr CL, Anthony JC. Early-onset drug use and risk for drug dependence problems. Addictive behaviors. 2009; 34(3):319–22. [PubMed: 19022584]
12. Dawson DA, Goldstein RB, Chou SP, Ruan WJ, Grant BF. Age at first drink and the first incidence of adult-onset DSM-IV alcohol use disorders. Alcoholism, clinical and experimental research. 2008; 32(12):2149–60.
13. Hingson RW, Zha W. Age of drinking onset, alcohol use disorders, frequent heavy drinking, and unintentionally injuring oneself and others after drinking. Pediatrics. 2009; 123(6):1477–84. [PubMed: 19482757]
14. Hingson RW, Heeren T, Winter MR. Age at drinking onset and alcohol dependence: age at onset, duration, and severity. Arch Pediatr Adolesc Med. 2006; 160(7):739–46. [PubMed: 16818840]
15. Wagner FA, Anthony JC. From first drug use to drug dependence; developmental periods of risk for dependence upon marijuana, cocaine, and alcohol. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2002; 26(4):479–88. [PubMed: 11927172]
16. Lopez-Quintero C, Perez de los Cobos J, Hasin DS, Okuda M, Wang S, Grant BF, et al. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Drug and alcohol dependence. 2011; 115(1-2):120–30. [PubMed: 21145178]
17. Winters KC, Tanner-Smith EE, Bresani E, Meyers K. Current advances in the treatment of adolescent drug use. Adolescent health, medicine and therapeutics. 2014; 5:199–210.
18. Lord S, Marsch L. Emerging trends and innovations in the identification and management of drug use among adolescents and young adults. Adolesc Med State Art Rev. 2011; 22(3):649–69, xiv. [PubMed: 22423469]
19. Tanner-Smith EE, Lipsey MW. Brief alcohol interventions for adolescents and young adults: a systematic review and meta-analysis. Journal of substance abuse treatment. 2015; 51:1–18. [PubMed: 25300577]
20. Carney T, Myers B. Effectiveness of early interventions for substance-using adolescents: findings from a systematic review and meta-analysis. Subst Abuse Treat Prev Policy. 2012; 7:25. [PubMed: 22697269]
21. Jensen CD, Cushing CC, Aylward BS, Craig JT, Sorell DM, Steele RG. Effectiveness of motivational interviewing interventions for adolescent substance use behavior change: a meta-analytic review. Journal of consulting and clinical psychology. 2011; 79(4):433–40. [PubMed: 21728400]
22. Belendiuk KA, Riggs P. Treatment of Adolescent Substance Use Disorders. Curr Treat Options Psychiatry. 2014; 1(2):175–88. [PubMed: 24855595]
23. Black JJ, Chung T. Mechanisms of change in adolescent substance use treatment: how does treatment work? Substance abuse : official publication of the Association for Medical Education and Research in Substance Abuse. 2014; 35(4):344–51.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

24. Mitchell SG, Gryczynski J, O'Grady KE, Schwartz RP. SBIRT for adolescent drug and alcohol use: current status and future directions. Journal of substance abuse treatment. 2013; 44(5):463–72. [PubMed: 23352110]
25. Clark DB. Pharmacotherapy for adolescent alcohol use disorder. CNS drugs. 2012; 26(7):559–69. [PubMed: 22676261]
26. Courtney DB, Milin R. Pharmacotherapy for adolescents with substance use disorders. Current Treatment Options in Psychiatry. 2015; 2(3):312–25.
27. Waxmonsky JG, Wilens TE. Pharmacotherapy of adolescent substance use disorders: a review of the literature. Journal of child and adolescent psychopharmacology. 2005; 15(5):810–25. [PubMed: 16262597]
28. Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. Jama. 2007; 297(15):1683–96. [PubMed: 17440145]
29. Mayes TL, Tao R, Rintelmann JW, Carmody T, Hughes CW, Kennard BD, et al. Do children and adolescents have differential response rates in placebo-controlled trials of fluoxetine? CNS spectrums. 2007; 12(2):147–54. [PubMed: 17277715]
30. Safer DJ. A comparison of risperidone-induced weight gain across the age span. Journal of clinical psychopharmacology. 2004; 24(4):429–36. [PubMed: 15232335]
31. Simkin DR, Grenoble S. Pharmacotherapies for adolescent substance use disorders. Child Adolesc Psychiatr Clin N Am. 2010; 19(3):591–608. [PubMed: 20682223]
32. Brown SA, McGue M, Maggs J, Schulenberg J, Hingson R, Swartzwelder S, et al. A developmental perspective on alcohol and youths 16 to 20 years of age. Pediatrics. 2008; 121(Suppl 4):S290–310. [PubMed: 18381495]
33. Spear LP. Adolescents and alcohol: acute sensitivities, enhanced intake, and later consequences. Neurotoxicology and teratology. 2014; 41:51–9. [PubMed: 24291291]
34. Upadhyaya, H.; Deas, D. Pharmacological interventions for adolescent substance use disorders.. In: Kaminer, Y.; Bukstein, OG., editors. Adolescent Substance Abuse: Psychiatric Comorbidity and High-Risk Behaviors. Routledge; New York, NY: 2008. p. 145-61.
35. Bailey JA, Samek DR, Keyes MA, Hill KG, Hicks BM, McGue M, et al. General and substance-specific predictors of young adult nicotine dependence, alcohol use disorder, and problem behavior: replication in two samples. Drug and alcohol dependence. 2014; 138:161–8. [PubMed: 24631001]
36. Kim Y, Myung SK, Jeon YJ, Lee EH, Park CH, Seo HG, et al. Effectiveness of pharmacologic therapy for smoking cessation in adolescent smokers: Meta-analysis of randomized controlled trials. Am J Health Syst Pharm. 2011; 68(3):219–26. [PubMed: 21258027]
37. Giedd JN. Structural magnetic resonance imaging of the adolescent brain. Annals of the New York Academy of Sciences. 2004; 1021:77–85. [PubMed: 15251877]
38. O'Malley SS, Corbin WR, Leeman RF, DeMartini KS, Fucito LM, Ikomi J, et al. Reduction of alcohol drinking in young adults by naltrexone: a double-blind, placebo-controlled, randomized clinical trial of efficacy and safety. J Clin Psychiatry. 2015; 76(2):e207–13. [PubMed: 25742208]
39*. DeMartini KS, Gueorguiva R, Leeman RF, Corbin WR, Fucito LM, Kranzler HR, O'Malley SS. Naltrexone for non-treatment seekiing young adult drinkers: One-year outcomes. Alcohlism: Clinical and Experimental Research. 2014; 38(Supplement 1):212A. [This article describes the follow up to a recent double-blind, placebo-controlled, randomized trial of naltrexone for treating alcohol misuse among young adults. This study reflects one of the few adequately power RCTs of a medication for treating alcohol misuse in young adulthood.]
40. Bailey SR, Crew EE, Riske EC, Ammerman S, Robinson TN, Killen JD. Efficacy and tolerability of pharmacotherapies to aid smoking cessation in adolescents. Paediatr Drugs. 2012; 14(2):91–108. [PubMed: 22248234]
41. Gray KM, Carpenter MJ, Baker NL, Hartwell KJ, Lewis AL, Hiott DW, et al. Bupropion SR and contingency management for adolescent smoking cessation. Journal of substance abuse treatment. 2011; 40(1):77–86. [PubMed: 20934835]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

42. Gray KM, Carpenter MJ, Lewis AL, Klintworth EM, Upadhyaya HP. Varenicline versus bupropion XL for smoking cessation in older adolescents: a randomized, double-blind pilot trial. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2012; 14(2):234–9. [PubMed: 21778151]

43*. Scherphof CS, van den Eijnden RJ, Engels RC, Vollebergh WA. Short-term efficacy of nicotine replacement therapy for smoking cessation in adolescents: a randomized controlled trial. Journal of substance abuse treatment. 2014; 46(2):120–7. [PubMed: 24029624] [This article describes a recent randomized, double-blind, placebo-controlled trial of the efficacy and safety of nicotine replacement therapy for adolescent smokers. Findings from this study suggest that nicotine replacement therapy, namely nicotine patches, may prove beneficial for helping adolescents-particularly those who are highly compliant with the treatment regimen - achieve smoking cessation.]

44. Mason BJ, Crean R, Goodell V, Light JM, Quello S, Shadan F, et al. A proof-of-concept randomized controlled study of gabapentin: effects on cannabis use, withdrawal and executive function deficits in cannabis-dependent adults. Neuropsychopharmacology:official publication of the American College of Neuropsychopharmacology. 2012; 37(7):1689–98. [PubMed: 22373942]

45. Gray KM, Carpenter MJ, Baker NL, DeSantis SM, Kryway E, Hartwell KJ, et al. A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents. The American journal of psychiatry. 2012; 169(8):805–12. [PubMed: 22706327]

46*. Miranda R Jr. Treloar H, Blanchard A, Justus A, Monti PM, Chun T, et al. Topiramate and Motivational Enhancement Therapy for Cannabis Use among Youth: A Randomized Placebo-Controlled Pilot Study. Addicton Biology. In press. [This article describes a recent double-blind, placebo-controlled, randomized trial of topiramate for treating cannabis misuse among adolescents and young adults. This is the first and only study of topiramate's effects of cannabis among adolescents or adults.]

47. Johnson BA, Ait-Daoud N, Bowden CL, DiClemente CC, Roache JD, Lawson K, et al. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. Lancet. 2003; 361(9370):1677–85. [PubMed: 12767733]

48. Johnson BA, Ait-Daoud N, Wang XQ, Penberthy JK, Javors MA, Seneviratne C, et al. Topiramate for the treatment of cocaine addiction: a randomized clinical trial. JAMA psychiatry. 2013; 70(12): 1338–46. [PubMed: 24132249]

49. Kranzler HR, Covault J, Feinn R, Armeli S, Tennen H, Arias AJ, et al. Topiramate treatment for heavy drinkers: moderation by a GRIK1 polymorphism. The American journal of psychiatry. 2014; 171(4):445–52. [PubMed: 24525690]

50. Miranda R Jr. MacKillop J, Monti PM, Rohsenow DJ, Tidey J, Gwaltney C, et al. Effects of topiramate on urge to drink and the subjective effects of alcohol: a preliminary laboratory study. Alcoholism, clinical and experimental research. 2008; 32(3):489–97.

51. Miranda R Jr. MacKillop J, Treloar H, Blanchard A, Tidey JW, Swift RM, et al. Biobehavioral mechanisms of topiramate's effects on alcohol use: an investigation pairing laboratory and ecological momentary assessments. Addiction biology. 2014

52. Oncken C, Arias AJ, Feinn R, Litt M, Covault J, Sofuoglu M, et al. Topiramate for smoking cessation: a randomized, placebo-controlled pilot study. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2014; 16(3):288–96. [PubMed: 24057996]

53. Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. Epilepsia. 2000; 41(Suppl 1):S3–9. [PubMed: 10768292]

54. Simeone TA, Wilcox KS, White HS. Subunit selectivity of topiramate modulation of heteromeric GABA(A) receptors. Neuropharmacology. 2006; 50(7):845–57. [PubMed: 16490221]

55. Marsch LA, Bickel WK, Badger GJ, Stothart ME, Quesnel KJ, Stanger C, et al. Comparison of pharmacological treatments for opioid-dependent adolescents: a randomized controlled trial. Archives of general psychiatry. 2005; 62(10):1157–64. [PubMed: 16203961]

56. Woody GE, Poole SA, Subramaniam G, Dugosh K, Bogenschutz M, Abbott P, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. Jama. 2008; 300(17):2003–11. [PubMed: 18984887]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

57. Heinzerling KG, Gadzhyan J, van Oudheusden H, Rodriguez F, McCracken J, Shoptaw S. Pilot randomized trial of bupropion for adolescent methamphetamine abuse/dependence. The Journal of adolescent health : official publication of the Society for Adolescent Medicine. 2013; 52(4):502–5. [PubMed: 23333007]

58*. Zhou X, Qin B, Del Giovane C, Pan J, Gentile S, Liu Y, et al. Efficacy and tolerability of antidepressants in the treatment of adolescents and young adults with depression and substance use disorders: a systematic review and meta-analysis. Addiction. 2015; 110(1):38–48. [PubMed: 25098732] [This systematic review article provides a meta-analysis of the efficacy and tolerability of anti- depressants for treating co-morbid substance use disorders and depression among youth. Given the high levels of comorbidity between depression and substance use disorders among adolescents, this article provides an important overview and discussion regarding the importance of integrated treatments for these co-occurring conditions.]

59. Riggs PD, Mikulich-Gilbertson SK, Davies RD, Lohman M, Klein C, Stover SK. A randomized controlled trial of fluoxetine and cognitive behavioral therapy in adolescents with major depression, behavior problems, and substance use disorders. Arch Pediatr Adolesc Med. 2007; 161(11):1026–34. [PubMed: 17984403]

60. Cornelius JR, Bukstein OG, Douaihy AB, Clark DB, Chung TA, Daley DC, et al. Double-blind fluoxetine trial in comorbid MDD-CUD youth and young adults. Drug and alcohol dependence. 2010; 112(1-2):39–45. [PubMed: 20576364]

61. Cornelius JR, Bukstein OG, Wood DS, Kirisci L, Douaihy A, Clark DB. Double-blind placebo-controlled trial of fluoxetine in adolescents with comorbid major depression and an alcohol use disorder. Addictive behaviors. 2009; 34(10):905–9. [PubMed: 19321268]

62. Riggs PD, Hall SK, Mikulich-Gilbertson SK, Lohman M, Kayser A. A randomized controlled trial of pemoline for attention-deficit/hyperactivity disorder in substance-abusing adolescents. Journal of the American Academy of Child and Adolescent Psychiatry. 2004; 43(4):420–9. [PubMed: 15187802]

63. Thurstone C, Riggs PD, Salomonsen-Sautel S, Mikulich-Gilbertson SK. Randomized, controlled trial of atomoxetine for attention-deficit/hyperactivity disorder in adolescents with substance use disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2010; 49(6):573–82. [PubMed: 20494267]

64. Wilens TE, Adler LA, Weiss MD, Michelson D, Ramsey JL, Moore RJ, et al. Atomoxetine treatment of adults with ADHD and comorbid alcohol use disorders. Drug and alcohol dependence. 2008; 96(1-2):145–54. [PubMed: 18403134]

65. Riggs PD, Winhusen T, Davies RD, Leimberger JD, Mikulich-Gilbertson S, Klein C, et al. Randomized controlled trial of osmotic-release methylphenidate with cognitive-behavioral therapy in adolescents with attention-deficit/hyperactivity disorder and substance use disorders. Journal of the American Academy of Child and Adolescent Psychiatry. 2011; 50(9):903–14. [PubMed: 21871372]

66. McKee SA, Weinberger AH, Shi J, Tetrault J, Coppola S. Developing and validating a human laboratory model to screen medications for smoking cessation. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2012; 14(11):1362–71. [PubMed: 22492085]

67. Litten RZ, Ryan ML, Falk DE, Reilly M, Fertig JB, Koob GF. Heterogeneity of alcohol use disorder: understanding mechanisms to advance personalized treatment. Alcoholism, clinical and experimental research. 2015; 39(4):579–84.

68. Cuthbert BN. The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. World Psychiatry. 2014; 13(1):28–35. [PubMed: 24497240]

69. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med. 2013; 11:126. [PubMed: 23672542]

70. Leggio L, Zywiak WH, Edwards SM, Tidey JW, Swift RM, Kenna GA. A preliminary double-blind, placebo-controlled randomized study of baclofen effects in alcoholic smokers. Psychopharmacology. 2015; 232(1):233–43. [PubMed: 24973894]

71. Davidson D, Palfai T, Bird C, Swift R. Effects of naltrexone on alcohol self- administration in heavy drinkers. Alcoholism, clinical and experimental research. 1999; 23(2):195–203.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

72. Davidson D, Swift R, Fitz E. Naltrexone increases the latency to drink alcohol in social drinkers. Alcoholism, clinical and experimental research. 1996; 20(4):732–9.
73. Drummond DC. Theories of drug craving, ancient and modern. Addiction. 2001; 96(1):33–46. [PubMed: 11177518]
74. Tiffany ST, Wray JM. The clinical significance of drug craving. Annals of the New York Academy of Sciences. 2012; 1248:1–17. [PubMed: 22172057]
75. O'Brien CP. Anticraving medications for relapse prevention: a possible new class of psychoactive medications. The American journal of psychiatry. 2005; 162(8):1423–31. [PubMed: 16055763]
76. American Psychiatric Association., American Psychiatric Association. DSM-5 Task Force. Diagnostic and statistical manual of mental disorders : DSM-5. 5th ed.. Vol. xliv. American Psychiatric Association; Washington, D.C.: 2013. p. 947
77. Ramirez J, Miranda R Jr. Alcohol craving in adolescents: bridging the laboratory and natural environment. Psychopharmacology. 2014; 231(8):1841–51. [PubMed: 24363093]
78. Spear LP. Adolescent neurobehavioral characteristics, alcohol sensitivities, and intake: Setting the stage for alcohol use disorders? Child Dev Perspect. 2011; 5(4):231–8. [PubMed: 22328900]
79. Spear LP, Varlinskaya EI. Sensitivity to ethanol and other hedonic stimuli in an animal model of adolescence: implications for prevention science? Dev Psychobiol. 2010; 52(3):236–43. [PubMed: 20222058]
80. Behar D, Berg CJ, Rapoport JL, Nelson W, Linnoila M, Cohen M, et al. Behavioral and physiological effects of ethanol in high-risk and control children: a pilot study. Alcoholism, clinical and experimental research. 1983; 7(4):404–10.
81. Collins RL, Morsheimer ET, Shiffman S, Paty JA, Gnys M, Papandonatos GD. Ecological momentary assessment in a behavioral drinking moderation training program. Experimental and clinical psychopharmacology. 1998; 6(3):306–15. [PubMed: 9725114]
82. Gwaltney CJ, Shiffman S, Paty JA, Liu KS, Kassel JD, Gnys M, et al. Using self-efficacy judgments to predict characteristics of lapses to smoking. Journal of consulting and clinical psychology. 2002; 70(5):1140–9. [PubMed: 12362964]
83. Muraven M, Collins RL, Morsheimer ET, Shiffman S, Paty JA. One too many: predicting future alcohol consumption following heavy drinking. Experimental and clinical psychopharmacology. 2005; 13(2):127–36. [PubMed: 15943545]
84. Muraven M, Collins RL, Morsheimer ET, Shiffman S, Paty JA. The morning after: limit violations and the self-regulation of alcohol consumption. Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors. 2005; 19(3):253–62. [PubMed: 16187803]
85. Muraven M, Collins RL, Shiffman S, Paty JA. Daily fluctuations in self-control demands and alcohol intake. Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors. 2005; 19(2):140–7. [PubMed: 16011384]
86. Shiffman S, Patten C, Gwaltney C, Paty J, Gnys M, Kassel J, et al. Natural history of nicotine withdrawal. Addiction. 2006; 101(12):1822–32. [PubMed: 17156182]
87. Miranda R Jr. Monti PM, Ray L, Treloar HR, Reynolds EK, Ramirez J, et al. Characterizing subjective responses to alcohol among adolescent problem drinkers. Journal of abnormal psychology. 2014; 123(1):117–29. [PubMed: 24661164]
88. Piasecki TM, Jahng S, Wood PK, Robertson BM, Epler AJ, Cronk NJ, et al. The subjective effects of alcohol-tobacco co-use: an ecological momentary assessment investigation. Journal of abnormal psychology. 2011; 120(3):557–71. [PubMed: 21443289]
89. Piasecki TM, Trela CJ, Hedeker D, Mermelstein RJ. Smoking antecedents: separating between- and within-person effects of tobacco dependence in a multiwave ecological momentary assessment investigation of adolescent smoking. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2014; 16(Suppl 2):S119–26. [PubMed: 23990475]
90. Treloar HR, Piasecki TM, McCarthy DE, Baker TB. Relations Among Caffeine Consumption, Smoking, Smoking Urge, and Subjective Smoking Reinforcement in Daily Life. J Caffeine Res. 2014; 4(3):93–9. [PubMed: 25229011]
91. Treloar H, Piasecki TM, McCarthy DM, Sher KJ, Heath AC. Ecological evidence that affect and perceptions of drink effects depend on alcohol expectancies. Addiction. 2015; 110(9):1432–42. [PubMed: 25959045]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

92. Hufford MR, Shields AL, Shiffman S, Paty J, Balabanis M. Reactivity to ecological momentary assessment: an example using undergraduate problem drinkers. Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors. 2002; 16(3):205–11. [PubMed: 12236455]

93. Litt MD, Cooney NL, Morse P. Ecological momentary assessment (EMA) with treated alcoholics: methodological problems and potential solutions. Health psychology : official journal of the Division of Health Psychology, American Psychological Association. 1998; 17(1):48–52.

94. Miranda R, Ray L, Blanchard A, Reynolds EK, Monti PM, Chun T, et al. Effects of naltrexone on adolescent alcohol cue reactivity and sensitivity: An initial randomized trial. Addiction biology. 2014; 19(5):941–54. [PubMed: 23489253]

95. Maisel NC, Blodgett JC, Wilbourne PL, Humphreys K, Finney JW. Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? Addiction. 2013; 108(2):275–93. [PubMed: 23075288]

96. Worley MJ, Witkiewitz K, Brown SA, Kivlahan DR, Longabaugh R. Social Network Moderators of Naltrexone and Behavioral Treatment Effects on Heavy Drinking in the COMBINE Study. Alcoholism, clinical and experimental research. 2015; 39(1):93–100.

97. Hanson K, Allen S, Jensen S, Hatsukami D. Treatment of adolescent smokers with the nicotine patch. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2003; 5(4):515–26. [PubMed: 12959789]

98. Killen JD, Robinson TN, Ammerman S, Hayward C, Rogers J, Stone C, et al. Randomized clinical trial of the efficacy of bupropion combined with nicotine patch in the treatment of adolescent smokers. Journal of consulting and clinical psychology. 2004; 72(4):729–35. [PubMed: 15301658]

99. Moolchan ET, Robinson ML, Ernst M, Cadet JL, Pickworth WB, Heishman SJ, et al. Safety and efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. Pediatrics. 2005; 115(4):e407–14. [PubMed: 15805342]

100. Roddy E, Romilly N, Challenger A, Lewis S, Britton J. Use of nicotine replacement therapy in socioeconomically deprived young smokers: a community-based pilot randomised controlled trial. Tob Control. 2006; 15(5):373–6. [PubMed: 16998171]

101. Muramoto ML, Leischow SJ, Sherrill D, Matthews E, Strayer LJ. Randomized, double- blind, placebo-controlled trial of 2 dosages of sustained-release bupropion for adolescent smoking cessation. Arch Pediatr Adolesc Med. 2007; 161(11):1068–74. [PubMed: 17984409]

102. Rubinstein ML, Benowitz NL, Auerback GM, Moscicki AB. A randomized trial of nicotine nasal spray in adolescent smokers. Pediatrics. 2008; 122(3):e595–600. [PubMed: 18762494]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Curr Addict Rep. Author manuscript; available in PMC 2017 June 01.

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) DeMartini et al. (39)	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; 25mg daily + 25mg 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 ≥ 0.08g% *Decreases in drinking across both conditions were maintained at the 1-year follow-up
Cannabis					
Gray et al. (45)	Double-blind, placebo-controlled, 8-week trial	*N*=116 Ages 15-21 73% Male Cannabis dependent	N-acetylcysteine (NAC; 1200mg) vs. placebo; all received contingency management (CM) + weekly cessation counseling	During tx, 4 wks 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 (200mg) 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 (≤ 21mg 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 wks 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 & motivated to quit	Nicotine patch (21mg) vs. nicotine gum (2mg & 4mg), 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 nonsignificant 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 & withdrawal with CO >5ppm	Nicotine patch (15mg/10mg/5mg) vs. placebo; all received 10-15 minute counseling session per visit	During tx, 13 wks 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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Reference	Study Design	Sample	Treatment	Follow-up	Outcome
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 (150mg or 300mg) vs. placebo; all participants received brief individual counseling	During tx, 12 & 26 wks post tx	*300mg increased abstinence during tx, but effects were not sustained post tx * No effect of 150mg
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 (≤ 300mg) with or without CM or placebo with or without CM (4 conditions)	During tx, 12 wks 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, 8-week trial	*N*=29 Ages 15-20 48%Male ≥ 5 cigarettes per day	Varenicline (≤ 2mg) vs. bupropion sustained release (≤ 300mg)	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 (≤ 21mg) vs. placebo	After 2 wks 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					
Marsch et al. (55)	Double-blind, double-dummy, 28-day trial	*N*=36 Ages 13-18 39% Male Opioid dependence	Outpatient detox with buprenorphine (≤ 8mg) + placebo patch vs. clonidine (≤ .3mg) patch + placebo tablets; thrice weekly individual behavioral therapy	During tx	*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).
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	Weeks 4, 8 and 12	*Week 4: positive urine tox for 61% of 14-day detox group & 26% of 12-week tx group *Week 8: positive urine tox for 54% of 14-day detox group & 23% of 12-week tx group *Week 12: positive urine tox for 51% of 14-day detox group & 43% of 12-week tx group
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	Fluoxetine (20 mg target) vs. placebo; all received 9 sessions of MET + CBT	End of tx	*No significant differences between groups

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Reference	Study Design	Sample	Treatment	Follow-up	Outcome
		Major depression + cannabis use disorder			*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

Note. RCT=Randomized Controlled Trial, tx=treatment, wk=week, MET=Motivational Enhancement Therapy, SUD=Substance Use Disorder, CUD=Cannabis Use Disorder, AUD= Alcohol Use Disorder, CBT= Cognitive Behavioral Therapy, ADHD = Attention Deficit Hyperactivity Disorder