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Pharmacotherapy for Substance Use Disorders in Youths

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Abstract

Despite recent advances in psychosocial treatments targeting adolescent substance use disorders (SUD), effect sizes generally remain small to modest, and few treatment-enrolled youth achieve sustained abstinence. Among adults, SUD-targeted pharmacotherapies have emerged as viable options to complement psychosocial treatments and enhance outcomes. Developmental differences exist in pharmacodynamics and treatment-response, and comparatively little research has focused on SUD-targeted pharmacotherapies for youth. This article provides a review and synthesis of relevant published clinical trials focusing on youth SUDs and co-occurring/comorbid psychiatric and substance use disorders. It offers recommendations for clinical practice and further research based on the limited findings to date.

Keywords

pharmacotherapy; substance use disorders; youth; adolescence

Introduction

Most adults with substance use disorders (SUD) began using during adolescence, a developmental stage characterized by heightened risk for substance initiation and adverse consequences of use (Casey & Jones, 2010). Despite this, the large majority of research and clinical efforts to address SUD have focused on adults, potentially compromising the potential to deliver efficacious care at a critical developmental window.

To address this issue, recent advances have been made with clinical trials of psychosocial treatments for SUD in youth, demonstrating that a number of motivational, cognitive-behavioral, and family-oriented therapies are efficacious, while contingency management (CM) may enhance outcomes when combined with other modalities (Hogue et al., 2014). However, in most cases, effect sizes are small to modest, and treatments are rarely associated with significant improvements in sustained substance abstinence.

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A significant advance in the adult SUD treatment literature is the identification of pharmacotherapies to complement psychosocial treatments. To date, the United States Food and Drug Administration (FDA) has approved nicotine replacement therapy, sustained-release bupropion, and varenicline for tobacco use disorder (TUD); benzodiazepines (acute detoxification only), disulfiram, naltrexone, and acamprosate for alcohol use disorder (AUD); and methadone, naltrexone, and buprenorphine/naloxone for opioid use disorder (OUD). These advances, alongside advances in the understanding of the neurobiology of SUD in youth and adults, provide a template for the investigation of pharmacotherapies to enhance treatment outcomes for youth with SUD.

To date, a small number of clinical trials have evaluated pharmacotherapies for TUD, cannabis use disorder (CUD), AUD, and OUD in youth. Additionally, important trials have been undertaken to examine the potential role of pharmacotherapy in youth with co-occurring substance use and psychiatric disorders. The goal of this review article is to provide a synthesis of findings from these trials, along with recommendations for clinical practice and further directions for research.

Methods

We conducted a series of English-language medical literature searches using PubMed, the Cochrane Library, PsycINFO, EMBASE, and CINAHL databases (from January 1, 1970 to August 1, 2014) using the search terms “adolescent”, “youth”, “medication”, “pharmacotherapy”, “psychopharmacology”, “substance abuse”, “substance dependence”, “substance use disorder”, “addiction”, and the specific substances: “tobacco”, “nicotine”, “alcohol”, “marijuana”, “cannabis”, “stimulants”, “cocaine”, “opiates”, “opioids”, and “heroin”. We used search terms for substance-related disorders using diagnostic categories from DSM-III, DSM-IV (both using substance abuse and dependence diagnoses), and DSM-5 (substance use disorders) as many of the studies reviewed predated the release of DSM-5 in 2013. Studies included in the review were cited with reference to the inclusionary criteria and edition of the DSM manual used. We manually searched reference lists of pertinent original research articles, review articles, and textbooks for relevant citations that our searches missed. Articles were selected if they involved human subjects (12-25 years of age) and included original clinical data on pharmacotherapies targeting any SUD in adolescent samples. We also included pharmacotherapy trials targeting comorbid/co-occurring psychiatric and substance use disorders in youth if they reported on substance-related health outcomes. These trials included double-blind randomized clinical trials (RCTs) comparing one medication with placebo or another medication, nonrandomized open-label trials, and prospective cohort studies if they reported on substance-related health outcomes. Two investigators independently reviewed each title and abstract for studies marked for possible inclusion. If reviewers disagreed, each reviewer independently examined the full original research manuscript and related information pertaining to the trial. Conflicts were resolved by consensus.

Results and Discussion

Tobacco Use Disorder

Despite substantial prevention efforts, tobacco use remains the leading cause of preventable death in the United States and worldwide, and the large majority of adult smokers began smoking before age 18 (Backinger et al., 2003). Adolescents are particularly prone to progress from smoking initiation to tobacco use disorder (TUD) (Doubeni & DiFranza, 2010). While many adolescent smokers are interested in quitting, most do not seek help, and those that make “self-quit” attempts are very rarely successful (Chassin et al., 2000; Stanton et al., 1996; Zhu et al., 1999). Psychosocial interventions have been shown to improve quit success, but only modestly so (Sussman et al., 2006). Pharmacotherapy has now become a well-established component of treatment for smoking cessation in adults, reflected in FDA approval of nicotine replacement therapy (patch, gum, lozenge, inhaler, nasal spray), bupropion SR, and varenicline. However, very little work has focused on evaluating these pharmacotherapies for adolescent smoking cessation. Results to date are mixed but in some cases encouraging.

To our knowledge, only eight controlled trials of pharmacotherapy for adolescent smoking cessation have been published (see Table 1). While a number of open-label, non-controlled studies have been conducted, we judged the controlled trials to be more informative for the purpose of the review.

Nicotine replacement therapy (NRT), an agonist-based harm reduction approach, has been evaluated in a number of adolescent studies, most of which have focused on nicotine patch. In the first, 100 adolescent smokers were randomized to receive a 10-week course of nicotine patch or placebo, each added to cognitive-behavioral therapy (CBT) and contingency management (CM) (Hanson et al., 2003). End-of-treatment abstinence, confirmed by carbon monoxide breathalyzer, was achieved by 28% of those in the nicotine patch group and 24% of those in the placebo group, a difference that was not statistically significant. A subsequent study evaluated a 12-week course of nicotine patch, nicotine gum, or placebo treatment, added to group-based CBT, in 120 adolescent smokers (Moolchan et al., 2005). Carbon monoxide breathalyzer confirmed abstinence, both at end of treatment and at post-treatment follow-up, was achieved by 21% of those in the nicotine patch group, compared to 9% of nicotine gum participants and 5% of placebo participants. Compliance with nicotine gum was noted to be poor in this study. The end of treatment abstinence difference between the nicotine patch and placebo groups was statistically significant. A small (N=40) 10-week study evaluated the effects of nicotine nasal spray, added to weekly counseling, compared to a counseling-only group (no spray) on smoking cessation in adolescents, yielding discouraging results (Rubinstein et al., 2008). Compliance with the nicotine nasal spray was poor in the active treatment group, and no participants in that group, compared with 12% of those in the counseling-only group, achieved end of treatment abstinence. A recently published 6- to 9-week adolescent trial (longer course for participants smoking more than 20 cigarettes per day) of nicotine patch versus placebo patch, without psychosocial intervention aside from an initial informational meeting, yielded mixed results (Scherphof et al., 2014a, 2014b). At end of treatment 14.8% of active and 13.1% of placebo

patch participants achieved self-reported abstinence, though rates in the subset of highly patch-compliant participants were 22.4% and 14.5%, respectively, a statistically significant difference. Post-treatment follow-up at weeks 26 and 52 revealed abstinence rates of 8.1% versus 5.7% and 4.4% versus 6.6%, respectively. These differences were not statistically significant. In sum, trials of NRT in adolescent smokers suggest that nicotine patch may be efficacious in the short-term, but relapse after treatment remains a significant concern.

Sustained-release bupropion (bupropion SR) is FDA approved in adults for smoking cessation. The first controlled trial of this medication in adolescents (*N*=211) evaluated bupropion SR 150 mg versus placebo daily, added to nicotine patch and group skills training, for an 8-week course of treatment (Killen et al., 2004). Carbon monoxide breathalyzer confirmed abstinence at end of treatment was achieved by 23% of bupropion SR participants and 28% of placebo participants. At post-treatment follow-up, 8% versus 7% were abstinent. These rates were not statistically significantly different, suggesting that either (a) the embedded nicotine patch treatment may have obscured the ability to evaluate the efficacy of bupropion SR, or (b) the bupropion SR dose was not sufficient for efficacy. A large (n=312) 6-week trial compared the efficacy of bupropion SR 300 mg, bupropion SR 150 mg, versus placebo, each added to brief weekly individual counseling (Muramoto et al., 2007). Urine cotinine confirmed end of treatment abstinence was achieved by 14% of 300 mg participants, compared to 11% of 150 mg participants and 6% of placebo participants. Carbon monoxide breathalyzer confirmed post-treatment follow-up abstinence rates were 14%, 3%, and 10%, respectively. The 300 mg group's abstinence rates were statistically superior to those of the placebo group at the end of treatment and superior to those of the 150 mg group at post-treatment follow-up. A more recent trial evaluated the potential synergy of bupropion SR and contingency management (CM) for adolescent smoking cessation, randomizing 136 adolescent smokers to receive a 6-week course of bupropion SR 300 mg + CM, bupropion SR 300 mg + no CM, placebo + CM, or placebo + no CM, each added to weekly individual counseling and medication management (Gray et al., 2011). Urine cotinine confirmed end of treatment abstinence was superior in the combined treatment group, with abstinence rates by group of 27%, 8.3%, 10.3%, and 9.4%, respectively. Post-treatment follow-up revealed no statistically significant between-group differences in abstinence, with rates of 10.8%, 5.6%, 0%, and 6.3%. Taken together, the trials of bupropion SR demonstrate that the 300 mg per day (150 mg in the morning and 150 mg in the afternoon) dose may be necessary for efficacy. Additionally, combining bupropion SR with behavioral interventions, such as CM, may yield improved abstinence rates. However, like with NRT trials, it may be challenging to translate within-treatment efficacy to long-term post-treatment abstinence.

Varenicline, an α4β2 nicotinic receptor partial agonist, has been FDA approved for smoking cessation in adults since 2006. A pharmacokinetic trial of varenicline provided guidance for dosing and evidence of tolerability in adolescent smokers (Faessel et al., 2009). To date, only one trial of varenicline for adolescent smoking cessation has been published (Gray et al., 2012). In this study, 29 adolescents were randomized to receive an 8-week course of varenicline (goal dose 1 mg twice daily) or extended-release bupropion (bupropion XL, goal dose 300 mg), each added to brief weekly individual counseling and medication management. Both groups demonstrated reductions in cigarettes per day, and carbon

monoxide confirmed end of treatment abstinence was achieved by 26.7% of varenicline participants and 14.3% of bupropion XL participants. This difference was not statistically significant, given the small sample size. At present, two large-scale placebo-controlled trials of varenicline for adolescent smoking cessation are ongoing.

Providers should be aware of United States FDA label warnings for both bupropion SR and varenicline, which emerged based on post-marketing spontaneous reports of psychiatric adverse events, such as suicidality. Analyses of controlled trials and large-scale observational studies in adults do not confirm causal associations between these medications and serious psychiatric adverse events, but caution and careful monitoring are warranted, especially when prescribing for adolescents (Hughes, 2015; Thomas et al., 2013).

Results of the few controlled trials of smoking cessation pharmacotherapies in adolescents suggest at least short-term benefits from nicotine patch and from bupropion SR (at the 300 mg dose), particularly when combined with psychosocial/behavioral treatment. However, long-term abstinence remains a significant challenge. Practitioners treating adolescents who do not respond adequately to psychosocial smoking cessation treatments may consider either nicotine patch or bupropion SR to enhance cessation outcomes. More work is needed to evaluate varenicline's potential role in adolescent smoking cessation. In sum, pharmacotherapy may play a complementary or even synergistic role with smoking cessation psychosocial interventions, but more research is needed on treatments that may yield improved long-term abstinence rates.

Cannabis Use Disorder

Cannabis is the most commonly used illicit substance among adolescents in the United States and the world. Onset of use typically occurs in adolescence, and the peak prevalence of use is among young adults. Amid recent state-level policy changes regarding cannabis for medicinal and recreational use, adolescent perceptions of marijuana-associated risks have fallen and rates of use, including daily use, have increased (Johnston et al., 2014). A confluence of findings demonstrates that cannabis use is associated with many adverse health outcomes, particularly among adolescents (Volkow et al., 2014). Among those is the development of cannabis use disorder (CUD) (Chen & Anthony, 2003). While cannabis is the most common substance prompting adolescent admission to SUD treatment (SAMHSA, 2013), existing psychosocial treatment strategies are only modestly efficacious, and few treatment-involved adolescents with CUD achieve long-term abstinence.

No medications are FDA indicated for CUD treatment in any age group, and investigation of potential pharmacotherapies even in adults is a relatively new pursuit. Amid preliminary trials of a variety of candidate pharmacotherapies in adults, a recent randomized placebo-controlled trial of the glutamate modulating agent *N*-acetylcysteine (NAC) evaluated its efficacy in adolescents with a DSM-IV-TR diagnosis of cannabis dependence (N=116) (Gray et al., 2012) (see Table 1). Participants were randomized to receive an 8-week course NAC 1200 mg or placebo twice daily (total daily NAC dose 2400 mg), each added to brief weekly cessation counseling and a contingency management (CM) intervention. Those in the NAC group achieved superior abstinence outcomes, compared with those in the placebo group. Negative urine cannabinoid tests were achieved at 41% of visits in the NAC group,

compared to 27% of visits in the placebo group. Overall, participants in the NAC group had 2.4 times the odds of submitting a negative urine cannabinoid test during treatment compared to those in the placebo group. End of treatment abstinence was achieved by 36% of NAC participants and 21% of placebo participants. Post-treatment follow-up abstinence rates were not statistically significantly different, but the trial was not adequately powered to evaluate this outcome.

A 12-week placebo-controlled trial of NAC for CUD in adults is currently underway in the NIDA Clinical Trials Network (CTN). If findings from the adolescent trial are replicated in this population, they will provide further support for NAC as an efficacious agent to augment psychosocial/behavioral treatment of CUD. At present, the adolescent findings suggest that NAC may be safely and effectively used to enhance cannabis cessation outcomes in adolescents enrolled in a CM and brief counseling intervention.

Alcohol Use Disorder

Alcohol is the main psychoactive substance used by adolescents in the United States and internationally, and remains a significant public health concern today. Binge drinking (defined as the consumption of five or more drinks in a single episode) is common among youth and associated with multiple negative health consequences including high-risk sexual behaviors, sexually transmitted diseases, teen pregnancy, fatal automobile accidents, and alcohol related injuries, as well as increased rates of psychiatric and addictive disorders later in life (Deas & Clarke, 2009). In 2002, 1.4 million adolescents met DSM-IV criteria for an alcohol use disorder (AUD) and only 227,000 received treatment. The proximal and distal consequences of hazardous drinking among adolescents underscores the importance of alcohol treatment for this age group.

Over the past twenty years, much progress has been made in the development and implementation of prevention and intervention treatment approaches for adolescent AUDs. Behavioral and psychosocial interventions represent the mainstay of treatment for adolescent AUDs at this time, with well-controlled studies demonstrating efficacy across multiple behavioral interventions including cognitive-behavioral, family-based, multisystemic, and motivational therapies (Deas & Clarke, 2009). Additional information on behavioral and psychosocial approaches can be found in other comprehensive reviews (Hogue et al., 2014). While pharmacotherapy has expanded the treatment options for adults with alcohol use problems, pharmacologic approaches to treating adolescent AUDs has lagged behind.

Pharmacotherapy for the treatment of AUD in adults has been used to target acute withdrawal syndromes, subjective and physiological responses to alcohol (i.e. alcohol cue response and craving states), and to improve abstinence rates and lower risk of relapse (Jonas et al., 2014; Achunine & Taylor, 2012). The FDA has approved several medications for the treatment of adults with AUD. In the acute setting, benzodiazepines are used to treat alcohol withdrawal syndrome (Mayo-Smith et al., 1997). Shortly following medication-assisted withdrawal/detoxification, naltrexone, disulfiram, and acamprosate can be used for the treatment of AUD and maintenance of abstinence, especially in combination with psychosocial interventions. Limited data is available on the safety and efficacy of these

medications in adolescent populations. Of the few studies that have been performed, most are pilot studies not powered to detect significant between-group differences (see Table 1).

No systemic studies on pharmacological interventions for alcohol withdrawal syndrome in adolescent samples are available. Treatment approaches for adolescents experiencing alcohol withdrawal syndrome are extrapolated from the adult literature and anecdotal evidence (Clark, 2012). While alcohol withdrawal syndrome is uncommon among adolescents with AUD (with 5-10% experiencing withdrawal symptoms), severe alcohol withdrawal remains a life-threatening emergency due to the risk for withdrawal-related seizures and delirium (Martin et al., 1995; Chung et al., 2002). An adolescent meeting criteria for AUD should be evaluated for symptoms of alcohol withdrawal and be risk-stratified according to the same principles as adults (Hall and Zador, 1997). Benzodiazepines are the first line pharmacotherapy for treatment of AWS in adults and may be used in adolescents with severe AUD who experience severe alcohol withdrawal symptoms in supervised inpatient settings (Mayo-Smith et al., 1997; Clark, 2012).

Naltrexone is an opiate receptor agonist that has demonstrated efficacy in adults with AUD. Across several clinical trials, naltrexone has been found to decrease the quantity and frequency of drinking, the number of heavy drinking days, and lower the risk for relapse (Maisel et al., 2013). In adolescent populations, two pilot studies have examined the safety, tolerability, and efficacy of naltrexone in AUD. Deas and colleagues (2005) completed a six-week open label clinical trial of naltrexone in five treatment-seeking adolescents meeting DSM-IV criteria for Alcohol Dependence (Deas et al., 2005). They found a significant reduction in number of drinks per day (reduction of 7.5 drinks per day) and a reduction in alcohol-related thoughts/obsessions. Naltrexone was well tolerated with few side effects reported and no adverse events. As follow-up, Deas and colleagues are currently completing a 12-week randomized placebo-controlled trial of naltrexone the results of which have not been released. Another study using ecological momentary assessments and laboratory-based alcohol cue assessments has also provided preliminary support for the use of naltrexone in adolescent heavy drinkers(Miranda et al., 2013). Researchers examined 28 adolescent non-treatment seeking heavy drinkers with no prior treatment for AUDs using a double-blind, placebo-controlled crossover design with randomization into a naltrexone condition and a placebo condition for 8-10 days with washout period in between conditions. Naltrexone blunted alcohol cravings in both natural and laboratory settings and was associated with decreased likelihood of drinking on a study day and drinking heavily.

Ondansetron, a selective 5-HT_3 (serotonin) receptor antagonist, has demonstrated promise for treating early-onset adult AUD and a series of small studies have shown positive results in young adults with AUDs starting before the age of 25 (Johnson et al., 2000; Kranzler et al., 2003; Sellers et al. 1994). A prospective open-label trial of ondansetron for the outpatient treatment of adolescent AUDs was recently completed (Dawes et al., 2005). Researchers recruited 12 adolescents meeting DSM-IV diagnostic criteria for alcohol dependence from the community and conducted an 8-week prospective study using ondansetron dosed at 4μg/kg twice daily. Outcome measures included incidence and perseverance of adverse events as well as self-reported alcohol consumption using time-line follow back methods. Results of the study are difficult to interpret as only 6 of the 12

participants completed the 8-week study. None of the dropouts were related to medication associated adverse events. Ondansetron was well tolerated with mild transient side effects including changes in appetite, nausea, fatigue, and gastrointestinal symptoms. Intention-to-treat analyses showed significant decrease in drinks per drinking day and trends for improvement in drinks per day and percentage of days abstinent.

The safety, tolerability, and efficacy of disulfiram have also been studied in adolescents with AUD in a 90-day double-blind placebo-controlled trial (Niederhofer & Staffen 2003). Researchers admitted a group of 26 adolescents meeting DSM-IV criteria for alcohol dependence and no psychiatric comorbidities to an inpatient hospital for alcohol detoxification. Study participants were randomized to receive disulfiram (200 mg/day) versus placebo, and alcohol use outcomes were assessed by self-report and psychiatric interview. Disulfiram was well tolerated with no adverse events reported and no significant differences reported between active medication and placebo groups on frequency and severity of side effects. With regard to efficacy, the proportion of patients who remained abstinent through 90 days was higher and the mean cumulative abstinence duration was significantly greater in the disulfiram group compared to the placebo group.

In summary, adolescents with AUDs differ in important ways from adults and developmental differences may impact expectancies, response to interventions, adherence, and treatment outcomes (Deas et al., 2000a). Preliminary pharmacotherapy trials are encouraging. Initial pilot studies of naltrexone, ondansetron, and disulfiram suggest that these medications are safe and tolerable in adolescents with problematic alcohol use and that they may reduce subjective response to alcohol. Fully powered placebo controlled trials are needed to determine efficacy of these medications in reducing alcohol use, and their role in clinical treatment of AUD in youth. Behavioral and psychosocial interventions remain the first-line treatment for adolescents with AUDs. Targeted pharmacotherapy may complement but not replace these psychosocial interventions, potentially enhancing abstinence and reducing relapse.

Opioid Use Disorder

Opioid use among adolescents has increased dramatically over the past decade, driven primarily by prescription opioid misuse. Non-medical use of prescription opioids has doubled during this period (4.7% to 9.0%) and is now second only to cannabis as the most frequently used illicit drug among 12 to 17 year olds (Johnston et al., 2010). Comparatively, annual use of heroin has remained stable at 1%. Adolescent opioid use disorder (OUD) and problematic opioid use, compared to cannabis and alcohol use disorders, in youth are associated with elevated psychiatric comorbidity, increased risk for relapse, poorer treatment outcomes, increased risk for human immunodeficiency virus (HIV) and hepatitis C infections, and increased risk for polysubstance and opioid-related overdose and death (Subramaniam et al., 2009). In context of increasing prevalence and poor functional outcomes among adolescents with OUD, effective evidence-based interventions in adolescent populations are sorely needed.

Among adults with OUD, detoxification followed by maintenance pharmacotherapy administered in conjunction with behavioral counseling is the treatment standard of care

(Mattick et al., 2008; Mattick et al., 2009). Four medications, all targeting the opioid receptor system, have been approved by the FDA for the treatment of OUD in adults: methadone (full agonist), buprenorphine and buprenorphine/naloxone combination (partial agonist with and without a non-orally available antagonist to reduce intravenous abuse potential), and naltrexone (antagonist). Options for adolescents with OUD remain limited and few controlled studies have been performed in this population. Despite efficacy in adults with OUD, agonist-based harm reduction approaches are controversial in adolescents and young adults. Maintenance therapy with agonists (methadone and buprenorphine) is associated with reductions in opioid use, intravenous drug use (IVDU), and associated criminal behaviors in adults, but agonists are not considered the primary intervention in youths due to the stigma associated with medications that promote a prolonged state of physical dependence and concerns about the impact of long-term maintenance medication on neurodevelopment (Lowinson et al., 1992). A few small studies completed in the 1970s examined methadone and 1-alpha-acetyl-methadol (LAAM) maintenance in youth meeting DSM-III diagnostic criteria for heroin dependence, suggesting clinical benefit (Hopfer et al., 2003; Rosenberg & Patch, 1972; Lehmann, 1976). Today, methadone is not available for youth under the age of 18 and is not a feasible treatment option for adolescents due to its restricted use in highly specialized opioid treatment programs. LAAM is no longer available in the United States for treatment of OUD due to concerns over cardiac toxicity. Buprenorphine, a schedule III, mu-opioid partial agonist, which is FDA-approved for treatment of individuals aged 16 years and older, may present a better detoxification and maintenance medication option in adolescents, especially as it can be prescribed by trained licensed physicians in outpatient clinic settings.

In youth with OUD only two clinical trials have been completed to date (See Table 1). Marsch and colleagues (2005) completed a double-blind, randomized controlled trial comparing the efficacy of two pharmacotherapies, buprenorphine and clonidine, for opioid detoxification in 36 adolescents meeting DSM-IV diagnostic criteria for opioid dependence in an outpatient clinic setting (Marsch et al., 2005). Treatment groups were randomized and run in parallel in a 28-day detoxification program. Both groups received behavioral counseling three times weekly and contingency incentives for opioid negative urines. At the end of the 28-day detoxification, 72% of participants randomized to receive buprenorphine remained in treatment compared to 39% of those randomized to receive clonidine. The buprenorphine and behavioral intervention group had a significantly higher percentage of opioid negative urine tests, were significantly more likely to transition to extended medication assisted therapy with naltrexone, and had less opioid-related HIV risk behaviors during the study period compared to the clonidine and behavioral intervention group. These results, though preliminary, suggest that buprenorphine in combination with behavioral interventions may be the opioid detoxification treatment of choice for adolescents with OUDs.

A recent NIDA CTN multisite randomized clinical study examined short-term buprenorphine-naloxone detoxification for two weeks versus twelve weeks of buprenorphine-naloxone extended medication assisted therapy for the treatment of OUD in adolescents (Woody et al., 2008). One hundred and fifty two adolescents aged 15-21 who met DSM-IV criteria for opioid dependence were recruited across six sites and randomized

to buprenorphine-naloxone 2-week outpatient detoxification or buprenorphine-naloxone 12-week maintenance/extended medication assisted treatment. Both groups received behavioral counseling. Primary outcome measures included opioid urine tests at weeks 4, 8, and 12. Adolescents randomized to receive buprenorphine-naloxone extended treatment were less likely to provide opioid positive urine tests at weeks 4 and 8 but not week 12 compared to those randomized to receive buprenorphine-naloxone detoxification. In both treatment groups the rate of relapse was high. At 6-months and 12-months more than half of adolescents in both groups had relapsed (at 12 months72% and 53% in detoxification and 12-week extended treatment group respectively). Secondary analyses of predictors of treatment outcome found that adolescents with IVDU, more severe OUD, and comorbid psychiatric conditions receiving ancillary treatment were more likely to have lower opioid use at the study endpoint (Subramaniam et al., 2011). The results of this study do not suggest that short-term opiate agonist treatment is effective for adolescents with OUD. Maintenance therapy with agonists may have a role in youths with more advanced illness and/or comorbidity. Additional trials will need to be performed to clarify the efficacy and safety of long-term agonist treatment in this population.

Treatment with the opioid receptor antagonist naltrexone may represent another treatment approach for adolescents with OUD. Naltrexone is available in daily oral (oral naltrexone) and monthly injectable (extended-release naltrexone [XR-naltrexone]) formulations. Fishman and colleagues (2010) retrospectively examined a series of sixteen adolescents and young adults with OUD treated with XR-naltrexone in an outpatient setting and found that XR-naltrexone was a well-tolerated and feasible intervention in this population (Fishman et al., 2010). A randomized controlled trial comparing buprenorphine-naloxone with oral naltrexone for the treatment of OUD in adolescents and young adults is currently underway.

To date, the primary intervention for OUD among youth remains medically-assisted detoxification followed by counseling and behavioral interventions. There may be a role for maintenance pharmacotherapy, especially in youth with advanced disease (i.e. severe OUD, IVDU, psychiatric comorbidities). Preliminary studies have demonstrated that buprenorphine is safe and well tolerated, and may be the pharmacotherapy of choice for detoxification in this population. Evidence supporting the use of maintenance pharmacotherapy is sparse at this time as the NIDA CTN trial demonstrated that short-term buprenorphine-naloxone treatment in conjunction with counseling, while beneficial in the short term, did not reduce long-term risk of relapse. Secondary analyses suggest that buprenorphine-naloxone may be more effective in adolescents with more advanced addiction and comorbidities, but additional studies are needed. Naltrexone (oral or XR) may also represent a promising maintenance pharmacotherapy in the future.

Comorbid Psychiatric and Substance Use Disorders

Comorbidity is defined as the coexistence of two or more diagnosable mental health disorders. For the purposes of this article, comorbidity will refer to the co-occurrence of at least one psychiatric and at least one substance use disorder (also termed dual diagnosis although in many cases more than two diagnosable disorders are present). Comorbid or co-occurring psychiatric and substance use disorders are common among adolescents with over

70% of adolescents with a substance use disorder also having one or more psychiatric disorder (Kaminer & Bukstein, 2008). Comorbid/co-occurring psychiatric disorders may temporally precede, follow, or be concurrent with chronic substance use and comorbidity is associated with increased addiction severity, increased risk for relapse, and poorer treatment outcomes, especially among adolescents (Bukstein & Horner, 2010). The psychiatric disorders which most commonly co-occur with SUD during adolescence include conduct disorder, attention deficit/hyperactivity disorder (ADHD), mood disorders (including depression and bipolar), anxiety disorders, and trauma and stress-related disorders (including post-traumatic stress disorder [PTSD], acute stress disorder, and disorders of extreme stress not otherwise specified) (Grella et al., 2001; Chan et al., 2008; Clark et al., 1997).

In parallel to clinical psychopharmacology trials targeting SUD among adolescents, there is a paucity of data on pharmacotherapies for combined psychiatric and substance use disorders. No controlled studies to date have examined co-occurring anxiety disorders or trauma and stress-related disorders with SUD in adolescents, despite these being among the most common co-occurring disorders. The most well studied comorbid psychiatric disorders with substance use disorders include mood disorders and ADHD, and recent clinical trials have focused on the comorbidity of psychiatric and substance use disorders as overlapping drug treatment targets, examining the psychopharmacologic impact on psychiatric symptoms as well as substance use outcomes (see Table 2).

Six randomized pharmacotherapy clinical trials to date have examined comorbid mood disorders and SUD, five focusing on comorbid Major Depressive Disorder (MDD) and one focusing on comorbid Bipolar Disorder (see Table 2). For specific SUDs, controlled pharmacotherapy studies have examined cannabis use disorders (CUD) and alcohol use disorders (AUD) in relation to mood disorders. Cornelius and colleagues (2010) completed a 12-week, double-blind randomized placebo-controlled trial of fluoxetine for treatment of depressive symptoms and cannabis use among seventy youths (ages 14-25) with comorbid DSM-IV diagnoses of current major depressive disorder (MDD) and CUD, with all participants receiving manualized individual cognitive behavioral therapy/motivational enhancement therapy (CBT/MET) (Cornelius et al., 2010). No fluoxetine versus placebo treatment group differences were noted for depression or cannabis use but both groups demonstrated significant improvement in their depressive symptoms and cannabis use severity from baseline to week 12. Two double-blind placebo-controlled 12-week trials of antidepressants have assessed the treatment of depressive symptoms and alcohol use in adolescents with comorbid AUD and MDD (Cornelius et al. 2009; Deas et al. 2000b). Cornelius and colleagues (2009) recently completed a clinical trial examining the effect of fluoxetine in combination with individual manualized CBT versus placebo with CBT over 12 weeks on depression and alcohol use in fifty adolescents meeting DSM-IV criteria for current MDD and AUD. They found significant improvements in depressive symptoms and level of drinking in both groups (fluoxetine + CBT and placebo + CBT) and no significant group-by-time interactions. Deas et al. (2000b) completed a similar 12-week study examining sertraline and group-format CBT versus placebo and group-format CBT in a sample of 10 adolescents with comorbid DSM-IV diagnoses of MDD and AUD also finding no group-by-time effects (i.e. no difference between sertraline + group-CBT and placebo +

group-CBT) and clinical improvement in both groups from baseline to study-endpoint on depressive symptoms and level of alcohol use. Both Cornelius et al. (2009) and Deas et al. (2000b) found that depression treatment response was associated with alcohol use—that is, adolescents whose depression remitted demonstrated reductions in their alcohol use and adolescents whose depressive symptoms remained elevated were more likely to maintain problematic drinking behaviors. Riggs and colleagues (2007) examined the safety and efficacy of fluoxetine on mood and non-tobacco substance use in a group of 126 adolescents (aged 13-19) meeting DSM-IV criteria for current MDD, lifetime CD, and at least one non-tobacco SUD using a 16-week, double-blind, placebo-controlled, randomized study design with a manualized CBT behavioral treatment platform (Riggs et al., 2007). They found that fluoxetine + CBT compared to placebo was associated with significantly greater reduction in depression symptoms as measured by the children's depression rating scale-revised score (CDRS-R; effect size = 0.78) but not for clinical improvement (as measured by a CGI score of 1 or 2). No differences were observed between treatment groups for days of non-tobacco substance use or CD symptom counts. Another study also examining fluoxetine for treatment of adolescent comorbid depressive disorder and SUD found no significant treatment group effects for depressive symptoms or negative urine drug screens and was stopped after an interim futility analysis (Findling et al., 2009). Lastly, one 6-week double-blind placebo-controlled study examined the safety, efficacy and tolerability of pharmacokinetically-dosed lithium for the treatment of 25 adolescents meeting DSM-III diagnostic criteria forcomorbid Bipolar Disorder and Substance Dependence Disorders (88 % of which were AUD) (Geller et al. 1998). Lithium was well tolerated, though significant between group differences were noted in side effects for thirst, polyuria, nausea, vomiting, and dizziness. Researchers found that adolescents randomized to lithium, compared to those in the placebo group, had significantly fewer positive urine drug tests and had greater clinical improvement.

A recent review has suggested that ADHD and SUD are "inextricably intertwined" in adolescents and that pharmacological treatment of ADHD during pre-adolescence may reduce the risk for adolescent-onset SUD (Harstad et al., 2014; Wilens et al., 2003). Questions remain regarding pharmacotherapy of comorbid ADHD and SUD during adolescence and five psychopharmacological studies have been completed to date (see Table 2). Two studies have examined long-acting formulations of methylphenidate for the treatment of co-occurring ADHD and SUDs in adolescents, both studies using DSM-IV criteria (Riggs et al, 2011; Szobot et al., 2008). The largest study to date, by Riggs and colleagues, a 16-week, double-blind, placebo-controlled multi-site clinical trial through the NIDA CTN examined the safety and efficacy of osmotically-controlled release oral delivery system methylphenidate (OROS-MPH) with a CBT behavioral platform for symptoms of ADHD and non-tobacco substance use. They found no significant OROS-MPH + CBT versus placebo + CBT treatment effects for primary ADHD and substance use outcome measures, but did observe that treatment with OROS-MPH as compared with placebo was associated with significant reductions in secondary outcome measures for both ADHD (ADHD Rating Scale-Parent form) and substance use (number of negative urine drug toxicology screens). Both treatment groups demonstrated significant improvements over time, evidenced by reductions in ADHD symptoms and days of non-tobacco substance use,

suggesting that the manualized CBT for SUD may have efficacy for both substance use and ADHD. While there were more side effects reported among the adolescents randomized to receive active study medication, OROS-MPH was generally well tolerated. Importantly, no differences were noted in misuse or diversion of study medication. Another study examined spheroidal oral drug absorption system methylphenidate (MPH-SODAS) for treatment of adolescents with DSM-IV diagnoses of ADHD and either a cannabis or cocaine use disorder in a 6-week, single blind, placebo-controlled, cross-over study (Szobot et al., 2008). Significant MPH-SODAS medication effects compared to placebo were found for ADHD symptomatology and for clinical improvement of attentional deficits, but not for self-reported cannabis or cocaine use or number of positive urine drug toxicology tests. Riggs and colleagues have also studied the safety and efficacy of pemoline in a controlled trial of adolescents with comorbid DSM-IV diagnoses of ADHD, CD, and a non-tobacco SUD (Riggs et al., 2004). Pemoline treatment, compared to placebo, was associated with significant clinical improvement in attentional deficits (in both intention to treat and completer analyses) and significant reductions in ADHD symptoms (in completer analysis), but did not affect substance use or CD symptoms. While pemoline was found to be safe and well tolerated in this study, FDA post-market surveillance studies found increased risk for liver toxicity, and pemoline was removed from the market in 2005. Non-stimulant medications such as atomoxetine, a selective norepinephrine reuptake inhibitor, and buproprion, a norepinephrine and dopamine reuptake inhibitor, have also been examined in adolescents with ADHD and SUD (Thurstone et al., 2010; Riggs et al., 1998; Sohlkhan et al., 2005). Thurstone and colleagues examined the safety and efficacy of atomoxetine (100mg/day) in seventy adolescents with ADHD and at least one non-tobacco SUD using a 12-week, double-blind, placebo-controlled study design with manualized CBT behavioral intervention platform (Thurstone et al., 2010). Parallel to previous studies, both treatment groups (atomoxetine + CBT and placebo + CBT) experienced significant reductions in ADHD symptomatology and substance use from baseline to week 12, but no significant between-group differences were noted for any ADHD or substance use outcomes. Lastly, two open-label pilot studies have shown positive preliminary results for the efficacy of buproprion for treatment of ADHD and SUD in youth, and a randomized controlled trial is currently underway (Riggs et al., 1998; Sohlkhah et al., 2005).

In summary, the literature on pharmacotherapy for treatment of co-occurring psychiatric symptoms and substance use in dually diagnosed adolescents remains unclear. For co-occurring mood disorders and SUD, most studies did not support the efficacy of antidepressants over placebo for treatment of depressive symptoms or substance use in comorbid adolescents. Mood and substance use symptoms improved over time regardless of treatment group, suggesting a possible role of CBT-based interventions (for studies with a behavioral intervention platform), placebo or engagement-in-treatment effect, or waxing and waning symptoms as part of the natural course of the illnesses. Among adolescents with comorbid SUDs and mood disorders, remission of mood symptoms was associated with reduction in drug and alcohol use. Thus, aggressive treatment of the mood disorder may improve outcomes in both mood and substance use domains. If the depressive symptoms do not improving within the early course of a behavioral intervention, it would be reasonable to consider antidepressant medications (e.g., fluoxetine or sertraline) with careful monitoring in

adolescents with co-occurring mood and substance use disorders, especially given that these agents appear well tolerated in dually diagnosed youth. For co-occurring adolescent ADHD and SUD, there may be a role for long-acting methylphenidate or non-stimulant medications (e.g., atomoxetine or buproprion) but additional studies are needed. These medications appear to be well tolerated, and may have lower abuse or diversion potential than short-acting stimulants, but do not appear to have an impact of level of substance use involvement among dually diagnosed youth (Waxmonsky & Wilens, 2005; Bukstein, 2008). As with the studies of co-occurring mood disorders, studies of co-occurring ADHD and SUD showed improvements in ADHD and substance use outcomes regardless of treatment group, suggesting that treatment engagement strategies and behavioral interventions (e.g., CBT) should be a part of the treatment plan for adolescents with co-occurring ADHD and SUD.

Overall, the results from these clinical studies suggest that an integrative and aggressive management approach should be used to treat co-occurring psychiatric and substance use symptoms which should include behavioral and possibly pharmacologic interventions. Behavioral interventions remain the first-line treatments for adolescent SUD, regardless of whether co-occurring psychiatric disorders are or are not present. Psychotropic medications with a broad range of classes, mechanisms of action, pharmacokinetics/pharmacodynamics, and side-effect profiles appear to be well tolerated and safe among adolescents with co-occurring psychiatric disorders and substance use disorders, even during active drug use. While additional research is needed, combining these approaches may improve outcomes for both psychiatric and substance use disorders, especially in those patients with co-occurring mood or attentional disorders.

Limitations

There are a number of limitations of this review. Few high-quality controlled studies have examined pharmacotherapies for adolescent SUD to date, and many of the studies are underpowered and unable to control for the effects comorbidities and other confounding variables. Most studies were of short-duration and few followed patients after the active medication period, limiting our knowledge of long-term effectiveness of these interventions. Bioethical issues related to informed consent from parents/guardians and assent of adolescent participants, and methodological issues related to recruitment in the context of reporting an illegal behavior (drug use), stigma associated with SUD and treatment, and medication compliance complicate the study of adolescent SUD (Brody and Waldron, 2000). This literature review was subject to publication bias as positive studies are more likely to be published than negative studies. The authors attempted to control for publication bias by also examining and reporting on current studies in clinicaltrials.gov. Future randomized controlled studies are needed to better understand the real-world efficacy, medication compliance, abuse liability, and drug-to-drug interactions of these SUD pharmacotherapies.

Conclusions

Adolescent SUD and co-occurring psychiatric disorders are important public health problems, and advances in treatment outcomes targeting these issues are needed. Amid significant progress in psychosocial treatment development, a small but increasing literature

describes studies evaluating pharmacotherapies to augment psychosocial treatments. Findings to date are mixed. This may in part be explained by the dearth of adequately powered trials to formally evaluate efficacy. It is also clear that the modality and intensity of "embedded" psychosocial treatment in pharmacotherapy trials may have notable implications for overall findings. On one hand, some research suggests that pharmacotherapy and behavioral treatment (CM) may be synergistic for adolescent smoking cessation (Gray et al., 2011). On the other hand, inclusion of intensive psychosocial treatments may compromise the potential to evaluate medication versus placebo effects on outcomes, with both groups benefiting significantly from psychosocial interventions (leading to an "elevated floor" effect) (Riggs et al., 2011). We believe it is important to evaluate potential pharmacotherapies within the framework of efficacious psychosocial treatments, both for ethical purposes (avoiding placebo-only treatment for adolescents seeking treatment) and to optimally inform practice. Ideally, trials will be designed and structured similarly, regardless of the specific pharmacotherapy or the specific target SUD, to allow for improved across-study comparison of outcomes. It is unlikely that pharmacotherapy will ever emerge as a standalone treatment for adolescent SUD, so careful consideration must be made to include "embedded" psychosocial treatment in future trials that (a) reflect the current evidence base, and (b) may be feasibly carried out in real-world practice.

While the current literature suggests potentially promising pharmacotherapies, including nicotine patch and bupropion SR for TUD, *N*-acetylcysteine for CUD, and buprenorphine/naloxone for OUD, additional work is needed to more firmly establish the appropriate role for pharmacotherapy in the context of treatment for SUD in adolescents. It is also critical to more systematically and routinely evaluate the safety and efficacy of medications for adolescent psychiatric disorders among adolescents with co-occurring SUD, as this group is all too common in "real world" practice. The existing literature provides a strong initial framework to inform future clinical trials and real-world clinical practice.

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Table 1

Clinical Trials for Adolescent Substance Use Disorders

Clinical Trial	Aims	Sample	N	Design	Intervention and Comparator dosing (mg/day)	Behavioral Intervention	Outcome measures	Results
Tobacco Use Disorder (TUD)								
Hanson et al., 2003	To determine the safety, tolerability, and efficacy of nicotine patch for adolescent TUD	Treatment-seeking adolescents (ages 13-19) smoking ≥10 CPD for ≥6 months	100	10-week, double-blind, placebo-controlled, randomized clinical trial	Nicotine patch (21 mg for 6 weeks, 14 mg for 2 weeks, and 7 mg for 2 weeks for those smoking ≥15 CPD; 14 mg for 6 weeks, 7 mg for 4 weeks for those smoking 10-14 CPD) versus placebo patch	Weekly CBT + CM	Nicotine craving and withdrawal (Nicotine Withdrawal Symptom Checklist) 2 weeks post-quit date; CO-confirmed 7-day PPA at EOT	Nicotine patch group had lower withdrawal (p=0.025) and craving (p=0.011) scores than the placebo patch group two weeks post-quit date 7-day EOT PPA 28% in nicotine patch group vs. 24 % in placebo patch group, OR = 1.2 (p=*ns*) Nicotine patch was well-tolerated
Moolchan et al., 2005	To determine the safety, tolerability, and efficacy of nicotine replacement therapy approaches (nicotine patch and nicotine gum) for treatment of adolescent TUD	Treatment-seeking adolescents (ages 13-17) smoking ≥10 CPD with Fagerström Test for Nicotine Dependence score ≥5	120	12-week, double-blind, double-dummy, placebo-controlled, randomized clinical trial	Nicotine patch (21 mg for those smoking ≥20 CPD, 14 mg for those smoking <20 CPD), Nicotine gum (4 mg for those smoking ≥24 CPD, 2 mg for those smoking <24 CPD) versus placebo patch and placebo gum	Weekly group-based CBT	CO-confirmed prolonged abstinence from quit date to end-of-treatment	Nicotine patch, but not nicotine gum, was associated with significantly improved prolonged abstinence at end of treatment (18% in nicotine patch group vs. 6.5% in nicotine gum group vs. 2.5% in placebo group; nicotine patch vs. placebo p=0.043; nicotine patch vs. nicotine gum p=*ns*; nicotine gum vs. placebo p=*ns*); effects were not significant at post-treatment follow-up Compliance was poor with nicotine gum Nicotine patch and nicotine gum were both well tolerated
Rubinstein et al., 2008	To determine the tolerability, safety, and efficacy of nicotine nasal spray for treatment of adolescent TUD	Treatment-seeking adolescents (ages 15-18) smoking ≥5 CPD	40	8-week, open-label, clinical trial	Nicotine nasal spray (1 mg dosing as needed) versus no nasal spray	Weekly brief individual counseling	CO-confirmed 7-day PPA at EOT	0% in nicotine nasal spray group vs. 12% in no spray group EOT PPA (p=*ns*) Compliance was poor with nicotine nasal spray

Clinical Trial	Aims	Sample	N	Design	Intervention and Comparator dosing (mg/day)	Behavioral Intervention	Outcome measures	Results
Scherphof et al., 2014a,b	To determine efficacy and safety of nicotine patch for treatment of adolescent TUD	Treatment-seeking adolescents (ages 12-18) smoking ≥7 CPD	257	6-to-9-week, double-blind, placebo-controlled, randomized, clinical trial	Nicotine patch (21 mg for 3 weeks, 14 mg for 3 weeks, 7 mg for 3 weeks for those smoking ≥20 CPD; 14 mg for 3 weeks, 7 mg for 3 weeks for those smoking <20 CPD) versus placebo patch	Brief smoking cessation training session at intake meeting	Self-reported 7-day PPA at Week 2; self-reported continuous abstinence from Week 2 to EOT; self-reported 30-day PPA at Week 26 post-treatment follow-up; cotinine-confirmed 30-day PPA at Week 52 post-treatment follow-up	Week 2: 31.9% in nicotine patch group vs. 21.3%, in placebo patch group (OR 2.02, $p<0.05$); EOT: 14.8% vs. 13.1% (OR 1.21, *p=ns*), Week 26: 8.1% vs 5.7% (OR 1.54, *p=ns*); Week 52: 4.4% vs 6.6% (OR 0.64, *p=ns*) Nicotine patch was well tolerated
Killen et al., 2004	To determine the efficacy of bupropion SR, combined with nicotine patch, for treatment of adolescent TUD	Treatment-seeking adolescents (ages 15-18) smoking ≥10 CPD	211	8-week, double-blind, placebo-controlled, randomized clinical trial	Bupropion SR, oral, 150 mg daily versus placebo, added to nicotine patch (21 mg for 4 weeks, 14 mg for 2 weeks, 7 mg for 2 weeks for those smoking >15 CPD; 14 mg for 6 weeks, 7 mg for 2 weeks for those smoking ≤15 CPD	Weekly group skills training	CO-confirmed 7-day PPA at EOT and at Week 26 post-treatment follow-up	EOT: 23% in bupropion SR group vs. 28% in placebo group (OR 0.8, *p=ns*), Week 26: 8% vs 7% (OR 1.2, *p=ns*)
Muramaoto et al., 2007	To examine efficacy of burpropion SR for treatment of adolescent TUD	Treatment-seeking adolescents (ages 14-17) smoking ≥6 CPD	312	6-week, double-blind, placebo-controlled, randomized clinical trial	Bupropion SR, oral, 150 mg daily versus Bupropion SR, oral, 300 mg daily versus placebo	Weekly brief individual counseling sessions	Cotinine-confirmed 7-day PPA at EOT; CO-confirmed 7-day PPA at Week 26 post-treatment follow-up	EOT: 14% in 300 mg group vs. 11% in 150 mg group vs. 6% in placebo group (300 mg vs. placebo OR 2.6, p=0.02), Week 26: 14% vs. 3% vs. 10% (300 mg vs. placebo OR 1.5, p=0.049)
Gray et al., 2011	To determine efficacy of bupropion SR and CM for treatment of adolescent TUD	Treatment-seeking adolescents (ages 12-21) smoking ≥5 CPD	136	6-week, double-blind, placebo-controlled, randomized clinical trial	Bupropion SR, oral, 300 mg daily versus placebo; CM versus no CM (2×2 four-group design)	Weekly brief individual counseling sessions	Cotinine-confirmed 7-day PPA at EOT and at Week 12 post-treatment follow-up	Week 6: 27% in bupropion+CM group vs. 8.3% in bupropion+no CM group vs. 10.3% in placebo+CM group vs. 9.4% in placebo+no CM group (bupropion+CM vs. placebo+no CM OR 3.6,

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Clinical Trial	Aims	Sample	N	Design	Intervention and Comparator dosing (mg/day)	Behavioral Intervention	Outcome measures	Results
								p<0.10) Week 12: 10.8% vs. 5.6% vs. 0% vs. 6.3% (all p=*ns*)
Gray et al., 2012a	To examine the feasibility a trial of varenicline versus bupropion XL for treatment of adolescent TUD, preliminarily exploring safety and efficacy	Treatment-seeking adolescents (ages 14-20) smoking ≥5 CPD	29	8-week, double-blind, randomized clinical trial	Varenicline, oral, 1 mg twice daily versus Buproprion XL, oral, 300 mg daily	Weekly brief individual counseling sessions	Self-report smoking reduction from baseline; cotinine confirmed 7-day PPA at EOT	Varenicline participants reduced from 14.1±SD 6.3 to 0.9±2.1 CPD and bupropion XL participants reduced from 15.8±4.4 to 3.1±4.0 CPD; 4/15 (26.7%) of varenicline participants and 2/14 (14.3%) of bupropion XL participants achieved EOT abstinence
Cannabis Use Disorder (CUD)								
Gray et al., 2012b	To determine the efficacy of *N*-acetylcysteine (NAC) for treatment of adolescent CUD	Treatment-seeking adolescents (ages 15-21) meeting DSM-IV criteria for Cannabis Dependence	116	8-week, double-blind, placebo-controlled, randomized clinical trial	NAC, oral, 1200 mg twice daily versus placebo	Weekly brief individual counseling sessions and twice-weekly CM	Odds of negative urine cannabinoid tests during active treatment	NAC vs. placebo group OR of negative urine cannabinoid tests during treatment OR 2.4, p=0.029; 2-week self-reported EOT abstinence, confirmed by negative urine cannabinoid tests OR 2.3, p=0.054)
Alcohol Use Disorder (AUD)								
Deas et al., 2005	To determine the safety and tolerability of outpatient treatment with naltrexone in adolescents with AUD	Treatment-seeking adolescents meeting DSM-IV criteria for Alcohol Dependence	5	6-week, open-label clinical trial	Naltrexone, oral, flexible dosing 25 or 50 mg/day, no comparator	None	Alcohol use (TLFB), A-OCDS at week 3	Average number of drinks per day showed significant reduction of 7.61 standard drinks (p< 0.001) Significant reduction in A-OCDS total score (−11.5 points, p=0.001) Naltrexone was safe and well tolerated
Miranda et al., 2013	To determine the effects of naltrexone on adolescent problem drinker's drinking, reactivity to alcohol cues (in laboratory and natural settings), and subjective	Adolescent non-treatment seeking drinkers (ages 15-19) who report drinking ≥ 2 times per week in the past 30 days and who have not	28	Double-blind, placebo-controlled, cross-over study with randomization into each	Naltrexone, oral, 50 mg/day versus placebo	None	Alcohol use (EMA and TLFB), craving analogue scale, subjective	Naltrexone compared to placebo decreased the likelihood of drinking on a study day (OR 0.7, p=0.03) and of drinking heavily (OR 0.5, p=0.003)

Clinical Trial	Aims	Sample	N	Design	Intervention and Comparator dosing (mg/day)	Behavioral Intervention	Outcome measures	Results
	response to alcohol utilizing an EMA measure and laboratory cue assessment	received treatment for AUD or OUD		condition for 8-10 days with 4-11 day washout period between conditions			response to alcohol (2-item BAES)	Naltrexone blunted cravings in laboratory and natural settings (p<0.04) and altered subjective response to alcohol (p<0.01) Naltrexone was safe and well tolerated
Niederhofer & Staffen, 2003	To determine safety, tolerability, and efficacy of disulfiram in treating adolescents with AUD	Treatment-seeking adolescents (ages 16-19) meeting DSM-IV criteria for Alcohol Dependence with no psychiatric comorbidities admitted to inpatient unit for detoxification and after completion of detox were abstinent for 5 days	26	90-day, double-blind, placebo-controlled, randomized, clinical trial	Disulfiram, oral, 200 mg/day versus placebo	None	Interviewer assessed and self-reported alcohol use at day 0, 30, 90	Higher proportion of patients remained abstinent through 90 days in the disulfiram group compared to the placebo group (7 vs. 2 subjects, p=0.0063) Mean cumulative abstinence duration was significantly greater in the disulfiram compared to the placebo group (68.5 vs. 29.7 days, p =0.01) Disulfiram was safe and well tolerated.
Dawes et al., 2005	To determine the safety, tolerability, and efficacy of ondansetron for outpatient treatment of drinking in adolescents with AUD	Treatment-seeking adolescents (aged 14-20) meeting DSM-IV criteria for Alcohol Dependence referred from the community	12	8-week, open-label, prospective clinical trial	Ondansetron, oral, 4 μg/kg b.i.d., no comparator	Individual CBT/MET sessions weekly	Alcohol use (TLFB), safety and tolerability (adverse events)	Only 6 of 12 subjects completed the 8-week pilot study ITT analyses showed significant within-group decreases in drinks/drinking day(−1.7 drinks, t=−3.1, p=0.01) and trends for improvement in drinks/day (t=−2.0, p=0.06) and percentage of days abstinent (t=1.5 p=0.18) Ondansetron was safe and well tolerated
Opioid Use Disorder (OUD)								

Clinical Trial	Aims	Sample	N	Design	Intervention and Comparator dosing (mg/day)	Behavioral Intervention	Outcome measures	Results
Marsch et al., 2005	To evaluate relative efficacy of 2 pharmacotherapies (buprenorphine and clonidine) in the detoxification of adolescents with opioid use disorder in an outpatient setting	Adolescents (aged 13-18 years of age) who met DSM-IV Criteria for Opioid Dependence	36	Double-blind, double-dummy, parallel-group, randomized controlled trial of 28-day detoxification regimen	Buprenorphine-HCL, sublingual, initial dose estimated by age and use (8 or 6 mg) versus Clonidine-HCL, transdermal patch, initially dosed at 0.1-0.3 mg per day depending upon withdrawal symptoms, medications tapered over 28 days	Both groups received behavioral counseling (3x weekly) and incentives contingent on opiate abstinence	Treatment retention, opiate abstinence (opiate negative urine tests), HIV risk behavior scale	Buprenorphine detoxification group had greater percentage retained in treatment (72% vs. 39%, $p<0.05$), higher percentage of opiate negative urine tests (64% vs. 32%, $p=0.01$), and were more likely to transition to extended medication assisted therapy with naltrexone (61% vs. 5%) compared to clonidine group Both buprenorphine and clonidine were effective at relieving withdrawal symptoms (F=15.8, $p<0.001$) Drug related HIV risk behaviors decreased from baseline reaching significant at week1 in both treatment groups (F=9.5, $p=0.005$)
Woody et al., 2008	To evaluate the efficacy of continuing buprenorphine-naloxone for 12-weeks vs. 2-week detoxification in adolescents with OUD in an outpatient setting	Adolescents (aged 15-21) who met DSM-IV criteria for Opioid Dependence	152	NIDA Clinical Trials Network, multisite clinical trial, randomized	Buprenorphine-naloxone (2 mg/0.5 mg ratio) 12 week maintenance/extended medication assisted treatment with dosing up to 24 mg/day versus Buprenorphine-naloxone 2 week outpatient detoxification	Both groups received behavioral counseling	Opiate use (opiate positive urine tests) at 4, 8, and 12 weeks	Buprenorphine 2 week detoxification patients were more likely to provide opiate positive urine tests when compared to 12-week buprenorphine maintenance at week 4 (61% vs. 26%, OR 7.1, $p<0.001$) and week 8 (54% vs. 23%, OR 5.1, $p<0.001$) but not week 12 (51% vs. 43%, OR 1.8, *p=ns*) Patients in the buprenorphine 2 week detoxification group were less likely to remain in the assigned treatment (20% vs. 70%, $p<0.001$)

Abbreviations: A-OCDS= adolescent obsessive compulsive drinking scale (Deas et al., 2001), AUD= alcohol use disorder, BAES= biphasic alcohol effects scale (Martin et al., 1993), CBT= cognitive behavioral therapy, CBT/MET= cognitive behavioral therapy/motivational enhancement therapy, CM= contingency management, CO= carbon monoxide, CPD= cigarettes per day, CUD= cannabis use disorder, EMA= ecological momentary assessment, EOT= end of treatment, ITT= intention to treat, OR= odds ratio, OUD= opioid use disorder, PPA= point prevalence abstinence, SR= sustained release, TLFB= time line follow-back (Sobell et al., 1988), TUD= tobacco use disorder , XL= extended release.

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Table 2

Clinical Trials in Adolescents with Comorbid Psychiatric and Substance Use Disorders

Clinical Trial	Aims	Sample	N	Design	Intervention and Comparator dosing (mg/day)	Behavioral Intervention	Outcome measures	Results
Comorbid MDD and SUDs								
Cornelius et al., 2010	To evaluate the efficacy of fluoxetine for the treatment of depressive symptoms and cannabis use in youths with comorbid MDD and CUD	Treatment-seeking adolescents and young adults (ages 14-25) who meet DSM-IV criteria for current MDD and an CUD	70	12-week, double-blind, placebo-controlled, randomized, clinical trial	Fluoxetine, oral, 20 mg/day versus placebo	9 session manualized CBT/MET	Cannabis use (TLFB), Depression (BDI, HAM-D-27)	No significant group-by-time interactions were noted for any depression-related (BDI: F=0.4, *p*= ns; HAM-D-27: F=0.4, *p*=ns) or cannabis-related (days of cannabis use, F=1.3, *p*=ns; DSM-IV CUD symptom count, F=0.5, *p*= ns) outcome variables Both treatment groups demonstrated significant within-group improvement in depressive symptoms greater than 50% reduction in BDI (F=40.0, *p*<0.001) and HAM-D-27(F=30.7, *p*<0.001)] and in DSM-IV CUD diagnostic criteria(39% reduction, F=4.7, *p*=0.035) Fluoxetine was well tolerated No significant reduction in cannabis use days in either treatment group (F=1.4, *p*=ns)
Cornelius et al., 2009	To evaluate the efficacy of fluoxetine for the treatment of depressive symptoms and drinking in adolescents with comorbid MDD and AUD	Treatment-seeking adolescents (ages 15-20) who meet DSM-IV criteria for current MDD and an AUD	50	12-week, double-blind, placebo-controlled, randomized, clinical trial	Fluoxetine, oral, 20 mg/day versus placebo	9 session CBT/MET	Alcohol use (TLFB), Depression (BDI, HAM-D-27)	No significant group-by-time interactions were noted for any depression-related (BDI: F=0.7,p=ns; HAM-D-27: F=0.4,p=ns) or drinking-related (TLFB, DSM-IV AUD Sx Ct, *p's*=ns) outcome variables Both treatment groups demonstrated significant within-group reductions in depressive symptoms

Clinical Trial	Aims	Sample	N	Design	Intervention and Comparator dosing (mg/day)	Behavioral Intervention	Outcome measures	Results
								(BDI: F=4.3, *p*=0.019; HAM-D-27: F=6.4, *p*=0.003) and level of drinking (DSM-IV AUD Sx Ct (F=8.0, *p*=0.007) Fluoxetine was well tolerated Number of heavy drinking days was significantly associated with lack of remission of depressive symptoms (BDI score< 8) at both the midpoint (F=6.8, *p*=0.013) and end of the study (F=9.1, *p*=0.009)
Findling et al., 2009	To evaluate the efficacy of fluoxetine for the treatment of depressive symptoms in adolescents with comorbid depressive disorder and SUD	Treatment-seeking adolescents (ages 12-17) with DSM-IV diagnosis of current MDD or other depressive disorder and a comorbid SUD	34	8-week, double-blind, placebo-controlled, randomized clinical trial	Fluoxetine, oral, 20 mg/day versus placebo	Continuation of their pre-randomization psychotherapy or if with no current psychotherapy offered a referral to community-based resources (e.g. Alcoholics Anonymous)	Depression (CDRS-R, BDI), positive UDS at weeks 2,4,8, and 12, clinical improvement (CGI, CGAS)	No significant fluoxetine versus placebo group × time interactions were noted for depressive symptoms (CDRS-R)(mean diff= 0.2, F=0.1, *p*=ns) or number of positive UDS (F=0.2, *p*=ns) at interim futility analysis after 50% of subjects had completed study
Riggs et al., 2007	To evaluate the efficacy of fluoxetine versus placebo for the treatment of MDD, SUD, and CD in adolescents	Treatment-seeking adolescents (ages 13-19) meeting DSM-IV criteria for current MDD, lifetime CD, and at least one non-tobacco SUD	126	16-week, double-blind, placebo-controlled, randomized clinical trial	Fluoxetine, oral, 20 mg/day versus placebo	Individual manualized CBT sessions weekly	Depression (CDRS-R), clinical improvement (CGI), substance use (TLFB), UDS(weekly), CD (DSM-IV symptom count)	Fluoxetine + CBT compared to placebo + CBT was associated with a significantly greater reduction in depression rating (CDRS-R score) by week 12 and continuing through week 16 (mean diff=5.7, F=2.8, *p*=0.04, effect size = 0.78) but not for clinical improvement (CDI score 1 or 2)(76% vs. 67% of subjects, RR 1.1, *p*=ns) No significant between group differences were noted for days of non-tobacco substance use (F=1.9, *p*=ns, effect size= 0.07) or CD

Clinical Trial	Aims	Sample	N	Design	Intervention and Comparator dosing (mg/day)	Behavioral Intervention	Outcome measures	Results
								symptoms (F=1.9, *p*=ns, effect size=0.22)
Deas et al., 2000	To evaluate the safety, tolerability, and efficacy of sertraline in the treatment of adolescents with comorbid MDD and AUDs	Treatment-seeking adolescents (mean age 16.6 years), meeting DSM-IV criteria for current MDD and AUD, presenting to an outpatient substance abuse treatment center	10	12-week, double-blind, placebo-controlled, randomized, clinical trial	Sertraline, oral, flexible dosing, 25 to 100 mg/day versus placebo	Non-manualized, cognitive-behavioral group therapy	Alcohol use (TLFB), Depression (HAM-D)	No significant group-by-time interactions were noted for any depression-related or drinking-related outcome variables (*p's* for all analyses=ns) Both treatment groups demonstrated significant within-group reduction in depressive symptoms (HAM-D: 9.8 point reduction, F=26.1, p<0.001) and level of drinking (21% reduction in drinking days, F=8.9, *p*=0.02; −4.7 drinks per day, F=20.8, *p*=0.002) Sertraline was safe and well tolerated Depression responders tended to have higher alcohol use at baseline and reduction in depressive symptoms was associated with reduction in alcohol use (r=0.57, *p*=0.09)
Comorbid Bipolar Disorder and SUDs								
Geller et al., 1998	To evaluate the safety, tolerability, and efficacy of pharmacokinetically-dosed Lithium for treatment of adolescents with Bipolar Disorder and Substance Dependence Disorders	Treatment-seeking adolescents (ages 12-18) with DSM-III diagnosis of Bipolar Disorder and Substance Dependency Disorder (88% AUDs)	25	6-week, double-blind, placebo-controlled, randomized, clinical trial	Lithium pharmacokinetically-dosed to allow for 4-weeks at maintenace lithium levels of 0.9-1.3 mEq/L versus placebo (dosed in parallel to Lithium)	Interpersonal therapy weekly	Alcohol and other drug use outcomes measured by urine drug screens, clinical improvement (CGAS)	On both ITT and completer analyses, Lithium group had significantly fewer positive UDS ($\chi 2$=4.8, *p*=0.03) and exhibited greater global clinical improvement (F=5.3, *p*=0.034) while outcomes related to mood did not differ between the groups Active responders mean serum lithium level was

Clinical Trial	Aims	Sample	N	Design	Intervention and Comparator dosing (mg/day)	Behavioral Intervention	Outcome measures	Results
								0.9 mEq/L Significant differences were noted in side effects between the lithium and placebo group for thirst, polyuria, nausea, vomiting, and dizziness
Comorbid ADHD and SUDs								
Riggs et al., 2011	To evaluate the safety and efficacy of OROS-MPH for treatment of ADHD symptoms and substance use in adolescent ADHD and SUD	Treatment-seeking adolescents (ages 13-19) who meet DSM-IV criteria for ADHD (current) and at least one non-tobacco SUD	303	16-week, double-blind, placebo-controlled, randomized, multi-site, clinical trial	OROS-MPH, oral, 72 mg/day (or highest dose tolerated) titrated to dose over 2 weeks versus placebo	Individual manualized CBT weekly	ADHD-RS (primary), days of non-tobacco substance use in past 28 days (TLFB) (primary), ADHD-RS Parent form (secondary), negative UDS (secondary), CGI (secondary)	On ITT analyses, no significant group-by-time interactions were noted for primary outcome measures for ADHD (p=ns) or substance use ($\chi 2$=3.5, p=ns). Both OROS-MPH/CBT and placebo/CBT groups demonstrated significant within-group improvements in ADHD symptoms (ADHD-RS Score: −19.2 vs. −21.2, both p<0.001) and level of substance use (number of nontobacco substance use days: −5.7 vs. −5.2, both p<0.001) OROS-MPH + CBT as compared to placebo + CBT was associated with significant reductions in secondary outcome measures for ADHD (ADHD-RS Parent Score: mean diff 6.7 p<0.001) and substance use (negative UDS: 3.8 vs. 2.8 p=0.05, effect size=0.22) OROS-MPH was well tolerated but was associated with more adverse events (2.4 vs. 1.6 events, p=0.02)

Clinical Trial	Aims	Sample	N	Design	Intervention and Comparator dosing (mg/day)	Behavioral Intervention	Outcome measures	Results
								No differences were noted in abuse/misuse or diversion of study medication
Thurstone et al., 2010	To evaluate the safety efficacy of atomoxetine for the treatment of ADHD symptoms and substance use in adolescent ADHD and SUD	Treatment-seeking Adolescents (ages 13-19) who meet DSM-IV criteria for ADHD (current) and at least one non-tobacco SUD	70	12-week, double-blind, placebo-controlled, randomized, clinical trial	Atomoxetine, oral, 100 mg/day (or 1.1-1.5mg/kg if the participant weighed less than 70kg), titrated to dose over three weeks versus placebo	Individual manualized MI/CBT weekly	ADHD-CL-Clinician (primary), days of non-tobacco substance use in past 28 days (TLFB) (primary), ADHD-CL Parent form (secondary, negative UDS (secondary)	No significant group-by-time interactions were noted for any ADHD or substance use primary or secondary outcome variables (all analyses *p's*=ns) Both Atomoxetine/MI-CBT and placebo/MI-CBT groups demonstrated significant within-group reductions in ADHD-CL-Clinician (overall reduction of 18.6 points, t=−10.6, $p<0.001$) and days of non-tobacco substance use between baseline and week 12 (−4.0 days, t=−3.3, $p=0.0015$) Atomoxetine was well tolerated
Szobot et al., 2008	To evaluate the safety and efficacy of escalated doses of MPH-SODAS for treatment of ADHD symptoms in an outpatient sample of adolescents with ADHD and SUD	Treatment-seeking adolescent males (ages 15-21) with DSM-IV diagnosis of ADHD (current) and SUD (cannabis or cocaine)	16	6-week, single-blind, placebo-controlled, randomized cross-over study (weeks 1-3 on MPH-SODAS or placebo and then cross-over for weeks 4-6 to opposite study medication)	MPH-SODAS, oral, in escalating doses of 0.3, 0.7, and 1.2 mg/kg/day for weeks 1, 2, and 3 of active study medication versus placebo	None	SNAP-IV (primary), CGI (primary), number of days of drug use per week (secondary), number of smoked cannabis cigarettes (weekly) (secondary), and UDS (weeks 3,6) (secondary)	Significant MPH-SODAS compared to placebo treatment effect were noted on ADHD symptoms (SNAP-IV: $F=42.9$, $p<0.001$) and clinical improvement (CGI: $F=25.3$, $p<0.001$) with no significant sequence or period effects No significant MPH-SODAS versus placebo treatment, sequence, or period effects were observed for any drug use outcome variables (days of drug use per week, cannabis cigarettes smoked per week, and positive UDS, *p's*=ns) MPH-SODAS was well tolerated

Clinical Trial	Aims	Sample	N	Design	Intervention and Comparator dosing (mg/day)	Behavioral Intervention	Outcome measures	Results
Riggs et al., 2004	To evaluate the safety and efficacy of pemoline for treatment of ADHD and CD symptoms and substance use in adolescents with comorbid ADHD, CD, and SUDs	Treatment-seeking adolescents (ages 13-19) meeting DSM-IV criteria for ADHD (current), CD (lifetime), and one non-tobacco SUD referred from outpatient settings and the community	69	12-week, double-blind, placebo-controlled, randomized clinical trial	Pemoline, oral, 75 to 112.5 mg/day dose (highest dose tolerated), titrated to dose over four weeks versus placebo	None	CGI-I (primary), CHI-Parent (primary), DSM-IV CD symptom count (primary), days of non-tobacco substance use in past 28 days (TLFB) (primary), negative UDS (primary)	Pemoline treatment compared to placebo was associated with a significant clinical improvement (CGI-I 1 or 2) in ADHD symptoms on ITT analysis (32 vs. 12 subjects, p=0.05, effect size 0.5) and on parent-rated ADHD symptoms (change in CHI-P: −22.5 vs. −10.8, p=0.01) on completers but not ITT analysis No significant between group differences were noted for days of non-tobacco substance use (−1.3 vs. −0.7 days, p=ns), negative UDS (2.4 vs. 3.1, p=ns), or CD symptoms (−0.8 vs. −0.5, p=ns) Pemoline was well tolerated and no elevation in liver enzymes or serious adverse events were observed
Riggs et al., 1998	To evaluate the safety, tolerability, and efficacy of buproprion for treatment of ADHD symptoms in adolescents with ADHD, CD, and SUD	Treatment-seeking adolescents males (ages 14-17) meeting DSM-IV criteria for ADHD (current), CD (lifetime), and one non-tobacco SUD residing in a long-term unlocked residential treatment program	13	5-week, open-label, prospective, pilot study	Buproprion , oral, 300 mg/day, titrated to dose over two weeks, no comparator	None	CGI-S, CHI-Teacher	Buproprion treatment was associated with improvements in teacher-rated ADHD symptoms (CHI-T: 13% reduction, p<0.01) and clinician-rated improvement (CGI: 39% improvement, p<0.002) from baseline to week 5 Buproprion was safe and well tolerated
Solhkhah et al., 2005	To evaluate the safety, tolerability, and efficacy of buproprion for outpatient treatment of attentional deficits and mood symptoms in adolescents with ADHD, a mood disorder, and SUD	Treatment-seeking outpatient adolescents (ages 12-19) meeting DSM-IV criteria for ADHD, a mood disorder, and a non-tobacco SUD referred for outpatient	14	6-month, open-label, naturalistic study with retrospective analysis	Buproprion SR, oral, started at 100mg once-daily and titrated up to a maximum dose of 400mg once-daily over 6 months (average dose	Monthly outpatient appointments over the six months but no formal psychotherapy	ADHD-CL, HAM-D, DUSI-R, CGI scores for Substance abuse, ADHD, Anxiety,	Buproprion SR treatment was associated with significant within-group reductions in substance use (DUSI-R: 39% reduction, p<0.05), ADHD (ADHD-CL: 43% reduction,

Clinical Trial	Aims	Sample	N	Design	Intervention and Comparator dosing (mg/day)	Behavioral Intervention	Outcome measures	Results
		treatment			307mg/day at six months), no comparator		Depression at baseline, 3-months, and 6-months	$p<0.001$), and depression (HAM-D: Buproprion SR was well tolerated with no significant adverse events

Abbreviations: ADHD= attention deficit/hyperactivity disorder, ADHD-CL-C= ADHD checklist-clinician administered (American Psychiatric Association, DSM 4th Edition, 1994), ADHD-CL-P= ADHD checklist-parent form (American Psychiatric Association, DSM 4th Edition, 1994), ADHD-RS-C= ADHD rating scale-clinician administered (DuPaul et al., 1998), ADHD-RS-P= ADHD rating scale-parent form (DuPaul et al., 1998), AUD= alcohol use disorder, BDI= Beck depression inventory (Beck, 1972), CD= conduct disorder, CDRS-R = children's depression rating scale-revised (Poznanski et al., 1985), CGAS = children's global assessment scale (Shaffer et al., 1983), CGI = clinical global impression scale with subscales for severity (CGI-S) and improvement (CGI-I) (NIMH, 1985), CHI-P= Connor's hyperactivity impulsivity scale-parent form, a subscale of the Connor's ADHD rating scale (Connors et al., 1998), CHI-T= Connor's hyperactivity impulsivity scale-teacher form, a subscale of the Connor's ADHD rating scale (Connors et al., 1998), CUD=cannabis use disorder, DUSI-R= drug use screening inventory-revised (Tartar et al., 1992), HAM-D = Hamilton depression scale (Hamilton, 1960), HAM-D-27= Hamilton depression scale-27 item version, ITT= intention to treat, MDD=major depressive disorder, MI/CBT= motivational interviewing/cognitive behavioral therapy, MPH-SODAS= spheroidal oral drug absorption system methylphenidate, OR=odds ratio, OROS-MPH= osmotically-controlled release oral delivery system methylphenidate, RR= relative risk, SNAP-IV= Swanson, Nolan, Pelham scale (Swanson, 1992), SR= sustained release, SUD= substance use disorder, Sx Ct= symptom count, TLFB= time line follow-back (Sobell et al., 1988), UDS= urine drug screen