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The role of pharmacotherapy in the treatment of adolescent substance use disorders

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Summary

Adolescent substance use disorders (SUDs) are associated with elevated morbidity and mortality, and represent a significant public health cost. While psychosocial interventions for adolescent SUDs have demonstrated short-term efficacy, many youth relapse after treatment. A potential approach to improve treatment response is to use adjunctive pharmacotherapy. An increasing number of medications have been shown to improve SUD treatment outcomes for alcohol, tobacco, and opioid use disorders in adults. Although relatively few randomized controlled medication trials have been conducted in adolescents, results suggest that pharmacotherapies when added to psychosocial interventions may hold similar promise for improving outcomes for adolescents with SUDs. This article provides a review of current research on the safety and efficacy of pharmacotherapies used in the treatment of adolescent SUDs.

Keywords

adolescence; development; substance use disorder; addiction; pharmacotherapy; medication

1. Introduction

Despite national efforts, substance use disorders (SUDs) and the excessive use of alcohol and other drugs remains a significant public health issue that has been estimated to cost the United States over $400 billion annually.[1] More than 90% of U.S. adults who develop SUDs started using alcohol and other drugs during adolescence.[2, 3] Growing evidence suggests that SUDs can be viewed as developmental disorders with genetic, temperamental, and environmental antecedents that emerge during early childhood.[4] Substance use initiation, progression to regular use, and the development of SUDs peaks during adolescence and

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young adulthood, and declines throughout the rest of the lifespan.[5, 6] SUDs represent a major source of morbidity and mortality in the teenage years.[7–11]

Many youth meet criteria for SUDs and a major treatment gap exists, with fewer than one in ten adolescents who are in need of treatment receiving it.[12] Data on national admissions to substance use treatment between 2002 and 2012 found that 75% of all adolescent SUD treatment admissions were related to cannabis, 13% to alcohol, 3% to opioids, 3% to methamphetamines or amphetamines, and 1% to cocaine.[13]

A number of psychosocial interventions have demonstrated short-term efficacy in clinical trials, but effect sizes for these interventions remain small to moderate, and few youth achieve sustained abstinence.[14–20] In light of the limited treatment response and elevated morbidity and mortality associated with adolescent SUDs, the field of addiction science is focused on expanding treatment approaches that may enhance treatment response and improve outcomes.[15] A potential approach to improve treatment response is to use adjunctive pharmacotherapy.

Growing evidence indicates that pharmacotherapy when added to psychosocial interventions improves treatment outcomes in adult SUDs.[21, 22] As such, a primary question for the field is can pharmacotherapies, when added to psychosocial interventions, improve outcomes for adolescent SUDs. To address this question, this article presents a comprehensive clinical review of the state of the evidence of pharmacotherapy for adolescent SUDs. It focuses on recent randomized controlled trials (RCTs) using medications in combination with psychosocial interventions to treat SUDs in individuals aged 13–25 years (see Table 1).

1.1 The Role of Pharmacotherapy in the Treatment of Substance Use Disorders

Medication assisted treatments are defined as the use of a U.S. Food and Drug Administration (FDA)-approved medication in combination with evidence-based psychosocial intervention to provide a ‘whole-patient’ approach to treatment of SUDs.[21] Numerous controlled trials in adults have shown that medications targeting alcohol[23], tobacco[24], and opioid use disorders[25, 26] have been associated with improved treatment outcomes[23–25], reductions in total treatment costs[27–29], and reduction in SUD-related morbidity and mortality.[23–26] As such, treatments that combine pharmacotherapies with psychosocial interventions (i.e., medication assisted treatments) are now thought of as a central component of SUD management for adults with those disorders. As the term ‘medication assisted therapy’ has been used primarily in relation to the treatment of opioid use disorders with medications and psychosocial treatments, in this chapter we will use the term ‘pharmacotherapy’.

Pharmacotherapy research has focused on developing medications to (1) reduce craving and the urge to drink or use drugs, (2) decrease acute and post-acute/protracted withdrawal symptoms, and (3) decrease impulsive or situational alcohol or drug use.[23, 24] Studies in adults suggest that integrating FDA-approved SUD pharmacotherapy with psychosocial treatments can have a synergistic effect on improving treatment outcomes.[23–26] Despite positive findings in the adult SUD pharmacotherapy literature, it is unclear if adjunctive pharmacotherapy improves outcomes in a similar way in adolescents with SUDs.

1.2 Treatment of Adolescents versus Adults: Developing Brains and Different Pharmacokinetics and Pharmacodynamics

A major problem with extrapolating adolescent treatment guidelines from adult SUD pharmacotherapy trials is that adolescents are not just 'little adults'. Adolescents with SUDs differ from their adult counterparts in important ways. Developmental differences may impact the biological or physiological effects of the substance of abuse and the psychotropic medication. Developmental differences may also influence psychological aspects of drug and medication taking and subjective drug and medication experience, such as expectancies and medication adherence.[30] These differences likely impact adolescent response to both the substances of abuse as well as the psychotropic medication prescribed to treat the SUD.

Adolescence is a period of marked changes in bodily systems.[31] Developmental differences exist in neurobiology, pharmacodynamics, and pharmacokinetics, when comparing children and adolescents to adults.[31, 32] Age-related changes in the body fat, extracellular water, and hepatic and renal function alter the bioavailability, metabolism, and clearance of drugs, leading to different pharmacokinetic profiles by age.[33, 34] Neurotransmitter systems, including dopaminergic, serotonergic, noradrenergic, GABAergic, and glutamatergic systems, mature across adolescence.[35, 36] These developmental changes affect biochemical and physiological effects of medications, which may explain age-related differences in therapeutic response and medication side effect profiles.[33, 37]

2. Pharmacotherapy for Alcohol Use Disorders (AUDs)

Alcohol is the most common drug of abuse used by adolescents[3], and the second most common drug for which adolescents present for SUD treatment.[13] The pathophysiology of AUDs involves allostatic brain changes in glutamatergic and GABAergic neurotransmission, altering excitatory-to-inhibitory balance with repeated heavy drinking episodes.[39] Pharmacotherapy for alcohol withdrawal syndrome (AWS) targets the neuronal-hyper excitability and GABA-glutamate imbalance that produce the core withdrawal symptoms. Maintenance pharmacotherapies for AUD act to decrease alcohol cravings, post-acute/protracted withdrawal symptoms, and the rewarding effects of alcohol, thereby decreasing alcohol use and reducing the likelihood of relapse. To date, FDA has approved four medications for the treatment of AUD in adults:

1. naltrexone (oral),
2. extended-release injectable naltrexone (XR-naltrexone) (intramuscular),
3. disulfiram, and
4. acamprosate.

Additionally, non-benzodiazepine anticonvulsants (NBACs), including gabapentin and topiramate, have emerged as potential pharmacotherapy options in adults.[40] There is limited safety and efficacy data available on these medications in adolescent samples.

2.1 Pharmacotherapy for Alcohol Withdrawal Syndrome

Alcohol withdrawal and AWS is rare in adolescents, and clinical guidelines and treatment principles are extrapolated from the adult literature.[41] To date, no controlled studies have examined pharmacotherapy interventions for AWS in adolescents. Five to 10% of adolescents with AUDs report experiencing withdrawal symptoms.[42] A minority of these cases will present with severe AWS which represents a life-threaten emergency due to risk for AWS-related seizures or delirium tremens. As such, all youth who present for AUD treatment should be evaluated for symptoms of alcohol withdrawal and risk-stratified. Treatment principles from adult AWS treatment should guide management.[43]

Benzodiazepines—While a number of NBACs are being studied for the treatment of AWS and AUD in adults[40], benzodiazepines currently remain the first line pharmacotherapy for treatment of AWS.[43] Consensus guidelines suggest that adolescents with severe AUD who present with moderate to severe AWS should be treated with benzodiazepines in inpatient treatment settings.[41, 44]

2.2 Pharmacotherapy for Maintenance Treatment of AUDs

To date, RCTs examining the short-term efficacy of maintenance pharmacotherapy for adolescent AUDs have been completed for naltrexone (oral) and disulfiram. Small open-label and randomized pilot studies exist for ondansetron and topiramate. Collectively, these studies include five small trials, and a total of 78 subjects.

Naltrexone—Naltrexone is a long-acting opiate receptor antagonist. When combined with psychosocial interventions, naltrexone has been shown to reduce relapse rates during active treatment and follow-up, and is associated with reductions in drinking days, drinks per drinking day, and alcohol consumption during treatment of adults with AUDs.[45, 46] Alcohol's reinforcing effects are, in part, mediated by endogenous opioid activity in the midbrain dopaminergic system.[23] Naltrexone acts by attenuating the rewarding effects of alcohol and reducing alcohol cravings in alcoholics, enhancing abstinence and reducing heavy drinking.[47]

Two small pilot studies provide preliminary evidence for naltrexone's tolerability, safety, and efficacy in adolescents AUDs. First, Deas et al (2005) completed an outpatient-based 6-week open-label pilot study of naltrexone (flexible dosing 25–50 mg/day) for treatment of adolescents meeting DSM-IV criteria for alcohol dependence.[48] Average drinks per day and alcohol-related obsessions and compulsions decreased significantly and naltrexone was well-tolerated in all subjects. Deas and colleagues have followed-up that open-label pilot study with a 12-week randomized double-blind placebo-controlled study of naltrexone for adolescent AUD, but the results are pending at this time. Second, Miranda and colleagues (2013) completed a small randomized double-blind, placebo-controlled cross-over study using self-reported alcohol use collected in real-time using ecological momentary assessment (EMA) approaches and laboratory-based subjective-response and cue-reactivity to alcohol as outcome measures.[49] Twenty eight non-treatment seeking heavy drinking youth (ages 15–19 years) were randomized to receive naltrexone (oral, 50 mg/day) or placebo for 8–10 days followed by a washout period and then switch to the opposite medication for 8–

10 days. Naltrexone as compared to placebo decreased the likelihood of heavy drinking (odds ratio [OR] = 0.5), drinking on a study day (OR = 0.7), and attenuated alcohol cravings and subjective response to alcohol in the laboratory protocol.

Disulfiram—Disulfiram is FDA-approved for the treatment of AUDs in adults, and known as an alcohol-sensitizing/aversive agent. It irreversibly binds to aldehyde dehydrogenase, leading to a rapid increase in acetaldehyde when alcohol is consumed, resulting in aversive symptoms.[23] Emerging data suggests that disulfiram also acts in the central nervous system (CNS) by altering dopaminergic function, via inhibition of dopamine beta-hydroxylase, which may contribute to its efficacy.[50]

Neiderhofer and Staffen (2003) completed a randomized double-blind placebo-controlled study in treatment-seeking adolescents (ages 16–19 years) with DSM-IV diagnosis of alcohol dependence who were admitted to inpatient detoxification.[51] Participants underwent detoxification for AWS and were randomized to either disulfiram (200 mg/day) or placebo after 5 days of alcohol abstinence and then followed weekly for 90 days. The disulfiram group compared to placebo had significant greater mean cumulative days of abstinence (69 vs. 30 days) and significantly more participants who remained abstinent at 90 days (7 vs. 2 participants). Participants tolerated disulfiram and reported few side effects.

Ondansetron—Ondansetron is a selective serotonin 5-HT^3 receptor antagonist that is FDA-approved for treatment of nausea and vomiting. An early RCT examining ondansetron for adults with AUDs discovered that individuals with early-onset adult AUD had a better treatment response, and subsequently a number of pharmacogenetics and translational studies have examined ondansetron in relation to serotonin gene function and age of AUD onset.[52–55]

No RCTs of ondansetron have been conducted in adolescents with AUD. However, a small (n=12) 8-week open-label pilot study of ondansetron in alcohol-dependent adolescents receiving weekly individual motivational interviewing with cognitive behavioural therapy (MI-CBT) reported that ondansetron to be relatively well-tolerated, with mild transient side effects of fatigue, nausea, and reduced appetite reported. Given the open-label design and lack of a comparison group, it is unclear to whether ondansetron contributed to the reported reduction in drinks per day (−1.7) beyond the effects MI-CBT/psychosocial treatment alone.

Topiramate—Topiramate is a NBAC that is FDA-approved for the treatment of seizure disorders and migraines in both children and adults. Its mechanisms of action includes blocking voltage-dependent sodium channels and L-type calcium channels, inhibiting carbonic anhydrase, and increasing GABAergic transmission via direct action on α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA)/kainite receptors and $GABA_A$ receptors.[56, 57] Topiramate has been shown to be efficacious for reducing heavy drinking and relapse to alcohol for AUD in adults in a number of RCTs and prospective longitudinal studies as described in a recent systematic review.[40]

Monti and colleagues (2010) recently presented preliminary findings from a small, 5-week, randomized double-blind placebo-controlled pilot study comparing topiramate (escalating

dose up to 200 mg/day) versus placebo for non-treatment seeking adolescent and young adult heavy drinkers (ages 14–24).[58] Topiramate was well-tolerated with no serious adverse events and few side effects. Over 5-weeks, the topiramate group reported an average reduction of – 1.8 drinks per week (3.8 to 2.0) compared to the placebo group, whose drinking did not decrease from baseline levels.

Summary of Evidence for AUDs—Taken together these preliminary studies suggest that naltrexone, disulfiram, ondansetron, and topiramate may be relatively safe and well-tolerated medications that show some promise as adjunctive treatment for adolescents with AUDs. Larger randomized controlled trials are warranted.

3. Pharmacotherapy for Tobacco Use Disorders (TUDs)

Tobacco use continues to be the number one preventable cause of death in the U.S. and internationally, and over 90% of adults with TUDs report first smoking before 18 years of age.[59] In adults with TUDs, meta-analyses show that the combination of psychopharmacology and evidence-based psychosocial interventions is more effective for smoking cessation than either medication or psychosocial intervention alone.[24] Consensus guidelines recommend that practitioners encourage all adult patients attempting to quit to use effective medications except when contraindicated.[24] Seven medications are FDA-approved for the treatment of TUDs in adults:

1. nicotine replacement therapy (NRT) in five different formulations
    a. nicotine patch,
    b. nicotine nasal spray,
    c. nicotine inhaler,
    d. nicotine lozenge, and
    e. nicotine gum;
2. bupropion sustained-release (SR); and
3. varenicline.

Compared to adult TUD pharmacotherapy trials, adolescent studies have reported more mixed findings to date.

Kim *et al.* (2011) published a meta-analysis examining the safety and efficacy of pharmacotherapies for adolescent smokers (ages 12–20).[60] Six RCTs conducted between 1991 and 2009, including 816 participants, were included in the review. Pharmacotherapies were not associated with lower rates of smoking cessation compared to controls (Relative Risk=1.38; 95% CI =0.92–2.07; 6 RCTs). The authors concluded that the quality of the evidence was low, due to the small sample size of most studies. A number of pharmacotherapy RCTs for adolescent smoking cessation have been published since 2009. To date, eight RCTs have examined pharmacotherapies for adolescent TUDs and smoking cessation.

Nicotine Replacement Therapy

NRT is an agonist-based pharmacotherapy approach that is available over the counter, and is FDA-approved for individuals ages 18 and older for smoking cessation. The use of NRT (monotherapy or combined) is associated with increased likelihood of successful tobacco cessation (OR's = 1.5–3.5) and abstinence rates (19–37%) compared to placebo in adult smokers.[24] To date, five studies including a total of 728 subjects, have examined NRT for the treatment of tobacco cessation in adolescents. Hanson and colleagues conducted the first study of NRT in adolescent smokers (ages 13–19 years), a 10-week, randomized double-blind placebo-controlled study comparing nicotine patch and placebo, with both treatment groups receiving weekly CBT and contingency management (CM).[61] They found no significant differences between the nicotine patch group and placebo group in end-of-treatment abstinence confirmed by carbon monoxide (CO) breathalyzer (28% vs. 24%). This was followed by a 12-week randomized double-blind, double-dummy placebo-controlled study comparing nicotine patch, nicotine gum, and placebo conditions (placebo patch and placebo gum), added to group CBT, in 120 adolescents with TUDs.[62] Both NRT formulations (patch and gum) were well tolerated, but nicotine gum compliance was poor. CO breathalyzer-confirmed abstinence for end of treatment and follow-up arms of the study were achieved by 21% of the nicotine patch group compared to 9% of the nicotine gum and 5% of placebo groups. The differences in abstinence observed between nicotine patch and placebo were statistically significant.

A recent study by Scherphof and colleagues (2014), used a randomized double-blind, placebo-controlled design and followed adolescents for 6-to-9 weeks, to examine the efficacy of nicotine patch versus placebo in adolescent smokers.[63, 64] While nicotine patch was associated with increased abstinence compared to placebo at week 2 (32% vs. 21%)[63], there were no differences in end of treatment abstinence (15% vs. 13%) or in abstinence at 6-month (8% vs. 6%) or 12-month (4% vs. 7%) post-treatment follow-up visits.[64] A secondary analysis examining a subgroup of highly compliant patch users showed increased end of treatment abstinence rates for nicotine patch versus placebo patch (22% vs. 15%).[65]

The efficacy of nicotine nasal spray for adolescent TUD was examined in a small, 10-week, open label pilot study, which included a nicotine nasal spray group (1 mg intranasal as needed) and a no nasal spray control group, with both groups receiving weekly counseling.[66] Nasal spray compliance was poor, and no significant group differences were observed between the nicotine nasal spray and no nasal spray groups in end of treatment CO breathalyzer-confirmed abstinence (0% vs. 12%).

These findings collectively suggest that nicotine patch, but not nicotine gum or nasal spray, has short-term efficacy for tobacco cessation in adolescents, but that relapse after discontinuation of NRT remains elevated.

Bupropion

Sustained-release bupropion (bupropion SR) is FDA-approved in adults for the treatment of TUDs. Preclinical studies suggest that bupropion acts as an inhibitor of dopamine and norepinephrine reuptake and as a nicotinic acetylcholinergic receptor antagonist.[67] These

mechanisms are thought to attenuate withdrawal symptoms (dopaminergic and noradrenergic neurotransmission) and the reinforcing effects of nicotine (nicotinic antagonism), thereby reducing the likelihood of relapse.

Four RCTs, including a total of 688 subjects, have examined bupropion for the treatment of adolescent smoking cessation published to date. Killen and colleagues completed the first study, an 8-week double-blind placebo-controlled RCT comparing bupropion SR and placebo, added on to nicotine patch treatment in 211 adolescent daily smokers (ages 15–18 years).[68] All youth also received weekly group skills training. No significant differences in abstinence were found between treatment groups at end of treatment or 6-month post-treatment follow-up visit. CO breathalyzer-confirmed end of treatment abstinence was 23% in the bupropion SR + nicotine patch group, and 28% in the placebo + nicotine patch group. At 6-month post-treatment follow-up, 8% versus 7% were abstinent. While bupropion did not improve abstinence rates, potential efficacy may have been masked by the NRT that both treatment groups received. A second randomized double-blind placebo-controlled study compared two doses of bupropion SR (300 mg and 150 mg) versus placebo, added to weekly individual counseling, for 312 adolescents with TUDs (ages 14–17 years), over a 6-week treatment interval.[69] They found urine cotinine-confirmed end of treatment abstinence was 14% for the bupropion 300 mg/day treatment group, 11% for the bupropion 150 mg/day treatment group, and 6% for the placebo group. At 6-month post-treatment follow-up, CO breathalyzer-confirmed abstinence rates were 14% versus 3% versus 10% respectively for the bupropion 300 mg/day, bupropion 150 mg/day, and placebo groups. Bupropion 300 mg/day was statistically superior to placebo at end of treatment (OR=2.6, p=0.02) and statistically superior to bupropion 150 mg/day at 6-month follow-up (OR=1.5, p=0.05). Secondary analyses of predictors of outcome demonstrated that medication compliance, noted to be highest in the bupropion 300 mg/day group, was associated with elevated CO breathalyzer-confirmed abstinence rates (21% vs. 0% abstinence in high vs. low compliance group).[70] Gray and colleagues (2011) recently completed a 6-week double-blind placebo-controlled RCT examining if abstinence-incentivized CM would increase the efficacy of bupropion SR 300 mg.[71] One hundred thirty six adolescents (ages 12–21 years) were randomized into four different treatment arms: bupropion 300 mg + CM, placebo + CM, bupropion 300 mg + no CM, and placebo + no CM for 6-weeks of treatment. All groups received weekly brief individual counseling and medication management. Urine cotinine-confirmed end of treatment abstinence was superior in combined bupropion + CM group (27%) compared to bupropion + no CM (8%), placebo + CM (10%), and placebo + no CM (9%) groups. Abstinence rates were 11%, 6%, 0%, and 6% respectively, at 6-weeks post-treatment follow-up, with no statistically significant between-group differences observed.

In sum, bupropion SR at the 300 mg/day dosing may improve tobacco abstinence in adolescents with TUDs, especially when combined with psychosocial interventions and CM.

Varenicline

Varenicline is an α4β2 nicotinic receptor partial agonist that is FDA-approved for tobacco cessation in adults. It is thought to aid in cessation by modulating dopaminergic

neurotransmission to counteract nicotine withdrawal symptoms (nicotinic agonism) while at the same time reducing smoking satisfaction (nicotinic antagonism).[72]

To date, two published studies have examined varenicline for the treatment of adolescent TUDs. An open-label pharmacokinetic dose-finding pilot study demonstrated tolerability and safety at standard adult dosing (2 mg/day).[73] This was followed by a recent 8-week RCT comparing varenicline to bupropion for adolescent smoking cessation.[74] Gray and colleagues randomized 29 adolescent smokers to receive varenicline (2 mg/day) or extended-release bupropion (bupropion XL, 300 mg daily), added to brief weekly individual counseling and medication management. CO breathalyzer-confirmed end of treatment abstinence was 27% for the varenicline group and 14% for the bupropion XL group, with reductions in cigarettes per day in both treatment groups. While there were no statistically significant between group differences on any of the outcome measures, given the sample size the study was underpowered. Currently, two large-scale randomized double-blinded placebo-controlled studies of varenicline for adolescent smoking cession are underway.

Post-marketing surveillance reports of suicidality and psychiatric adverse events led the FDA to add warning labels to both varenicline and bupropion SR. Large-scale controlled trials and naturalistic studies have not confirmed the association between varenicline and bupropion SR with serious psychiatric adverse events.[75] In light of the FDA warning labels, practitioners should be cautious, ask about co-occurring psychiatric disorders, and monitor for changes in psychiatric symptoms and suicidality, especially when prescribing for adolescents.

Summary of Evidence for TUDs

Growing evidence exists for improved adolescent tobacco cessation rates during active treatment when psychosocial interventions are combined with nicotine patch and bupropion SR. Still, the impact of these pharmacotherapy approaches on long-term abstinence remains unclear, and real-world effectiveness studies are needed. While initial data is promising for varenicline, results need to be replicated. Practitioners may consider trials of nicotine patch or bupropion SR in adolescent smokers who fail to response to psychosocial treatments.

4. Pharmacotherapy for Cannabis Use Disorders (CUDs)

Cannabis remains the most commonly used illicit drug in the U.S.[3], and is the most common drug for which adolescents present for SUD treatment.[13] No FDA-approved medications exist for CUDs. Cannabis use modulates glutamatergic[76] and GABAergic[77, 78] activity, and drugs that target these systems represent promising CUD pharmacotherapies. While a number of potential pharmacotherapies for CUDs have been examined, n-acetylcysteine (NAC) (glutamatergic modulator)[79, 80] and gabapentin (GABAergic modulator)[81] are the only medications with positive findings. Three studies examining adolescent CUD pharmacotherapies have been published to date, including one open-label pilot study and two controlled pharmacotherapy trials, which enrolled a combined total of 200 subjects.

N-acetylcysteine

NAC is a cysteine prodrug that modulates intra- and extra-cellular glutamate by way of the cystine-glutamate exchanger.[82] Preclinical studies suggest that it may normalized frontostriatal function and prevent relapse to chronic drug use.[83] It is safe and well-tolerated in humans, and has been studied in a number of neuropsychiatric disorders.[84]

Gray and colleagues initially completed a 4-week open-label pilot study of NAC (1200 mg twice daily) in 24 cannabis dependent young adults (ages 18–21 years) finding that it was safe and well-tolerated, and associated with a significant reduction in self-reported cannabis use and cannabis-related cravings.[79] This pilot study was then followed by a large (n=116) 8-week randomized double-blind placebo-controlled trial.[80] Adolescents (ages 15–21 years) meeting DSM-IV-TR criteria for cannabis dependence were randomized to receive NAC (1200 mg twice daily) or placebo, added to brief weekly counseling. All participants also received a CM intervention. NAC, compared to placebo, was associated with superior treatment outcomes and significant reductions in cannabis. Odds of a negative urine cannabinoid test during study visits was 41% for participants in the NAC + CM group and 27% for participants in the placebo + CM group (OR=2.4, p=0.03). Urine cannabinoid-confirmed end of treatment abstinence from cannabis was 36% in the NAC group and 21% in the placebo group (OR=2.3, p=0.05).

The NIDA Clinical Trials Network (CTN) is currently completing a 12-week, multisite, randomized double-blind placebo-controlled trial for CUD in adults.[85] If the findings for this adult CUD study are positive, this will provide further support for NAC pharmacotherapy for CUDs. The preliminary adolescent findings suggest that NAC may enhance cannabis cessation outcomes when combined with psychosocial interventions and CM.

Topiramate

A recent randomized double-blind placebo-controlled pilot study examined the potential efficacy of topiramate plus MI for treatment of adolescent heavy cannabis users (ages 15–24 years).[86] Sixty six participants were randomized to receive either topiramate (titrated over 4 weeks to 200 mg/day and stabilized at 200 mg/day for 2 weeks) or placebo, added to 3 MI sessions, over a 6-week treatment interval. Topiramate was poorly tolerated in the study. Only 48% (19 participants) randomized to topiramate completed the 6-week study, compared to 77% (20 participants) randomized to placebo. Adverse medication side effects were the most commonly reported reason for treatment dropout. The topiramate + MI group, compared to the placebo + MI group, was significantly more likely to report depression, anxiety, difficulty with coordination or balance, weight loss, and paresthesia. Latent growth models showed that topiramate + MI compared to placebo + MI, was associated with a reduction in the number of grams of cannabis smoked per day, but was not associated with abstinence, days of cannabis use, or urine cannabis testing. In light of the poor tolerability and inconsistent effect on cannabis use outcome measures, topiramate likely does not have a role in the treatment of adolescent CUDs.

Summary of Evidence for CUDs

Early stage evidence for CUD pharmacotherapy is promising. Preliminary data from an open-label pilot study and a large RCT suggest that NAC may reduce cannabis use in adolescents with CUDs. Results of the NIDA CTN study should guide future clinical practice guidelines for this medication.

5. Pharmacotherapy for Opioid Use Disorders (OUDs)

Over the past decade, opioid use has increased significantly among adolescents and young adults due to a large increase in prescription opioid misuse.[3, 87] As OUDs among adolescents are associate with increased morbidity and mortality in comparison to other adolescent SUDs[88], identifying and treating these youth is of vast importance.

Pharmacotherapy in OUDs is used for acute detoxification of the opioid withdrawal syndrome (OWS) and for maintenance OUD treatment. Consensus guidelines for treatment of adult OUDs recommend detoxification for OWS, followed by OUD maintenance pharmacotherapy plus psychosocial interventions.[89, 90] Buprenorphine, methadone, and alpha-2-agonists, such as clonidine, are commonly used to treat OWS in adults.[91] OUD maintenance pharmacotherapy can be categorized as agonist-based versus antagonist-based treatments. OUD maintenance therapy in adults is associated with reductions in opiate use, HIV risk behaviors, IVDU, opioid-overdoses, and associated morbidity and mortality.[25, 26, 89–91] The FDA has approved 5 medications for the maintenance treatment of OUDs in adults:

1. methadone,
2. buprenorphine,
3. buprenorphine-naloxone,
4. naltrexone (oral), and
5. XR- naltrexone.

While there have been a number of open-label and observational treatment studies in adolescents with OUDs, few controlled studies exist. Only two RCTs have been published to date.

5.1 Pharmacotherapy for Opioid Withdrawal Syndrome

Clonidine and Buprenorphine—A small (n=36) randomized double-blind double-dummy parallel-group study compared buprenorphine versus clonidine for treatment of OWS in adolescents with DSM-IV opioid dependence during a 28-day outpatient detoxification.[92] All participants received behavioral counseling three times weekly and opioid negative urine incentivized CM. Outcomes included treatment retention, opiate abstinence, HIV-risk behaviors, and opioid withdrawal. Buprenorphine was superior to clonidine across a number of treatment outcomes. Seventy two percentage of participants in the buprenorphine group were retained in treatment compared to 39% of participants in the clonidine group. The buprenorphine participants, compared to the clonidine participants, had a significantly higher percentage of opiate negative urine screens (64% vs. 32%) and

significant reductions in HIV-risk behaviors. There were no differences in opioid withdrawal between the groups. At the end of detoxification, 61% of the buprenorphine group compared to 5% of the clonidine group initiated naltrexone maintenance therapy. Buprenorphine's efficacy for treatment of OWS in adolescents with opiate dependence was confirmed as a secondary outcome by another RCT comparing extended- and short-term treatment.[93]

Minozzi et al. (2014) recently published a *Cochrane Systematic Review* of detoxification treatments for adolescent OUDs, but was unable to draw conclusions across studies, as only one controlled study for adolescent OWS has been published.[94] Current evidence suggests that buprenorphine, rather than clonidine, should be used for OWS treatment in adolescents with OUDs.

5.2 Pharmacotherapy for Maintenance Treatment of OUDs

A recent *Cochrane Systematic Review* of maintenance treatments for opiate-dependent adolescents was completed in 2014 analyzing data from 2 RCTs, including 189 participants.[95] Like the opioid detoxification review [94], the authors could not draw conclusions, as differences in study design and outcome precluded the ability to meta-analyze the data. Evidence from observational studies and a single RCT suggests that agonist therapies, including methadone and buprenorphine, may be effective during active treatment. Still, agonist-based therapy is controversial in adolescents due to concerns over the impact of chronic opioid agonism on brain and endocrine system development, and the effects of inducing a prolonged state of physical dependence in youth.[96]

Methadone—To date, no controlled studies have examined methadone maintenance therapy (MMT) for treatment of adolescent OUD. Hopfer and colleagues completed a systematic review of the treatment and descriptive literature for adolescent heroin use, and found 9 treatment studies including a total of 6,263 adolescents and young adults with heroin use.[97] Most of the studies were completed in the 1970s and used naturalistic or observational designs. Few compared across different treatments. A large observational study by Sells and Simpson (1979) compared MMT, detoxification, therapeutic community, and abstinence-based treatments for 5,407 adolescents (age ≤ 19) across multiple U.S. drug abuse treatment programs.[98] They found that daily opiate using adolescents were more likely to require MMT, and that MMT was associated with higher treatment retention rates.

Methadone for OUD maintenance therapy can only be prescribed in licensed and regulated specialty clinics. Adolescents, even those under the age of 16 years, can be treated with MMT, but the Department of Health and Human Services regulations require documentation of two treatment failures of drug free detoxification followed by psychosocial interventions before they may be referred.

Buprenorphine—Buprenorphine is a μ-opioid receptor partial agonist that is FDA-approved for the treatment of individuals, ages 16 years and older, with an OUD. As an FDA schedule III medication, it can be prescribed by trained licensed physicians in outpatient clinical settings.

The NIDA CTN recently completed a large (n=152) multisite RCT in adolescents meeting DSM-IV criteria for opioid dependence comparing 2-week short-term buprenorphine-naloxone detoxification versus 12-week extended pharmacotherapy with buprenorphine-naloxone.[93] All participants received behavioral counseling, and the outcome measures were percentage of opioid positive urine tests at weeks 4, 8, and 12. While adolescents randomized to extended-treatment buprenorphine-naloxone had significantly fewer opioid positive urine tests at weeks 4 (26% vs. 61%) and 8 (23% vs. 54%), by week 12, after the buprenorphine-naloxone had been tapered and discontinued, there were no between-group differences in opioid negative urine tests (43% vs. 51%). Rates of opioid relapse were high in both groups. By 12-months post-treatment, 53% of participants randomized to buprenorphine-naloxone extended-treatment and 72% participants randomized to detoxification had relapsed. An analysis of predictors of treatment response observed lower end of treatment opioid use for adolescents with higher opioid use severity, psychiatric comorbidity, and those with IVDU.[99] Results suggest that combined maintenance pharmacotherapy with buprenorphine-naloxone and counseling is more effective than detoxification followed by behavioral counseling, but that after the buprenorphine-naloxone is discontinued, opioid dependent youth quickly relapse and there are no differences in 12-month outcomes. Thus, maintenance or long-term treatment with buprenorphine-naloxone may be necessary to sustain treatment gains. This result would be consistent with findings from adult studies, where maintenance as compared to short-term treatment is associated with improved outcomes.[90, 91] As higher-risk youth had better treatment outcomes, pharmacotherapy with buprenorphine-naloxone may be appropriate for this subgroup of adolescents with OUDs. Future controlled studies should examine pharmacotherapy with buprenorphine-naloxone in this subgroup.

Naltrexone—Naltrexone is an effective FDA-approved OUD maintenance pharmacotherapy for adults. To date, a single open-label prospective case series has examined XR-naltrexone for the treatment of adolescent and young adult OUD.[100] Sixteen youth meeting DSM-IV criteria for OUD were admitted to inpatient detoxification at a community substance use treatment center and started on XR-naltrexone (380 mg intramuscular injection once per month). Clinical data from chart review on opioid use, side effects, tolerability were examined. XR-naltrexone was well tolerated and associated with clinical improvements. There are currently two controlled studies examining XR-naltrexone for the treatment of adolescents (ages 15–21 years) with OUDs that are underway.

5.2 Pharmacotherapy for Opiate Overdose

Rates of opioid overdose deaths have increased dramatically in the past decade.[101] While the majority of opioid overdose deaths occur in individuals aged 25–54, many opioid users started using prior to 18 years of age and adolescents with OUDs are at elevated risk for overdose-related deaths.[88]

Intranasal naloxone—Naloxone is an opioid antagonist rescue agent used to treat opioid overdose. The World Health Organization strongly recommends that people likely to witness an opioid overdose (i.e., family and friends) should have access to naloxone and be trained to administer it for emergency management of suspected opioid overdose, as manifested by

respiratory or CNS depression.[102] In November 2015, the FDA approved intranasal naloxone for opioid overdose.[103] Practitioners who treat adolescents with OUDs should strongly consider prescribing intranasal naloxone, and provide education and training about the signs/symptoms of opioid intoxication and what to do in the event of a suspected overdose.[104]

Summary of Evidence for OUDs—The current standard of treatment for adolescent OUD remains medically-assisted detoxification followed by behavioral counseling. Results from the current literature suggest that buprenorphine is more effective than clonidine for treatment of OWS and may be associated with improvements in treatment retention. With regard to OUD maintenance treatment, there may be a role for outpatient-based pharmacotherapy approaches including buprenorphine-naloxone combined with counseling for adolescents, ages 16 years and older, with more severe opioid addiction, IVDU, comorbid psychiatric disorders, and those who fail detoxification plus behavioral counseling. MMT is also an option for youth if they have > 2 documented treatment failures after detoxification and behavioral counseling. Additional studies are need to clarify the efficacy naltrexone in adolescent samples.

6. Conclusions

Adolescent SUDs remain a major public health burden, and clinical strategies that enhance treatment response are necessary to improve long-term outcomes. Combining pharmacotherapies with evidence-based psychosocial interventions may be an effective enhancement strategy. Over the past decade a growing number of studies have begun to examine pharmacotherapies for adolescent SUDs. To date, the results of these studies have been promising, but the quality of the evidence is poor. Most studies are not adequately powered, did not include post-treatment follow-up, and some lacked biochemically-verified outcomes. Medication compliance varied across studies but was, in general, associated with better outcomes.[65, 70] Use of adequately powered, controlled study designs with randomization, allocation concealment, proper blinding, ITT analyses, biochemically-verified endpoints, and adequate follow-up are necessary to improve the quality of the evidence base for adolescent SUD pharmacotherapy. Additional research is needed to clarify appropriate treatment settings, target symptoms, and patient-level predictors of outcomes for pharmacotherapies with preliminary positive findings.

Early evidence for short-term efficacy of adding pharmacotherapies to psychosocial interventions is encouraging. Psychotropic medications across a broad range of classes, mechanisms of action, and side-effect profiles appear to be safe and well tolerated among adolescents with SUDs. These studies indicate that, like in adults, combining pharmacotherapy and behavioral interventions may synergistically reduce substance use.[71] Consistent with adult SUD studies, preliminary evidence indicates that medications may improve substance-specific outcomes when used adjunctively with psychosocial interventions in adolescents with TUDs (nicotine patch; bupropion SR), OUDs (buprenorphine-naloxone), and to a lesser extent, CUDs (n-acetylcysteine).

Practitioners providing SUD treatment to adolescents who do not respond adequately to psychosocial interventions may consider a medication trial using the above described pharmacotherapies to enhance treatment response and reduce risk of relapse (Box 1). To date buprenorphine is the only pharmacotherapy to date with an FDA-approved indication for the treatment of adolescent SUDs. As such, the use of other medications described in this article, while evidence-based, would be considered 'off-label' use. Concerns about potential short- and long-term medication side effects should be weighed against the risk of continued drug use and related morbidity and mortality. Medications should only be prescribed in the context of appropriate psychosocial interventions and regularly monitored for safety and emergent adverse side effects. Developing a monitoring plan with families, and providing incentives for medication compliance (i.e., CM) is recommended, as compliance may improve outcomes.[71, 105]

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Box 1. Rationale for Adolescent SUD Pharmacotherapy and Clinical Considerations

When to consider pharmacotherapy for SUDs in adolescents

- Moderate to severe SUD
- Comorbid/Co-occurring psychiatric disorders±
- Youth has failed psychosocial interventions (e.g., ≥2 prior detoxification attempts for adolescent OUDs to consider methadone)
- Youth is engaged in psychosocial interventions but is not improving (no change in drug use, no functional improvement)
- High-risk for morbidity and mortality (intravenous drug use, drunk or drugged driving, unprotected sexual intercourse, accidents)
- Family or parents/guardians are engaged in treatment planning and willing to monitor medication

What factors should be considered in choosing a medication

- Patient's past experience with SUD maintenance medications
- Patient and family's opinions and beliefs
- Family and parent/guardian involvement in treatment plan (for monitoring)
- Level of motivation for abstinence
- Health Status (medical and psychiatric history, and allergies)
- Contraindications for medications
- Safety profile of medication and drug-to-drug interactions between medication and drugs of abuse
- History of medication compliance

± For patients with comorbid substance use and psychiatric disorders, pharmacotherapy should be initially directed at treating the co-occurring psychiatric symptoms and disorders (See Robinson Z, Riggs PD: Co-occurring Psychiatric and Substance Use Disorders, in this issue).

Key Points

1. Pharmacotherapy, when used in conjunction with psychosocial substance treatment interventions, may improve outcomes compared to psychosocial treatment alone.
2. Compared to ample research in adults, relatively few randomized controlled medication trials have been conducted in adolescents with SUD.
3. Results suggest that a number of medications may improve adolescent substance treatment outcomes including nicotine replacement therapy (NRT) and bupropion SR (tobacco use disorder), n-acetylcysteine (cannabis use disorder), and buprenorphine-naloxone (opioid use disorder).

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Table 1

Pharmacotherapy for Adolescent Substance Use Disorders

Drug	Sample(s)	Study design(s)	Intervention dosing and duration	Outcome measures	Level of Evidence[a]
Alcohol Withdrawal Syndrome					
Benzodiazepines		Consensus Guidelines; there are no controlled treatment studies examining pharmacotherapy for adolescent AW or AWS.			Grade C (level 3 evidence) for AWS
Alcohol Use Disorder					
Naltrexone (oral)	Outpatient, treatment-seeking, adolescents (mean age = 13.2 years); Non-treatment-seeking heavy drinkers (ages 15–19); 2 studies, n= 27 total subjects	6-week, open-label, clinical study; 4-week double-blind, placebo controlled cross-over study using EMA	Naltrexone, oral, flexible dose, 25–50 mg daily; Naltrexone, oral, fixed dose, 50 mg daily	Self-report alcohol use (time-line follow-back methods and EMA); A-OCDS; alcohol craving; subjective-response to alcohol	Grade C (level 3 evidence) for AUD
Disulfiram	Post-detoxification, outpatient, treatment-seeking adolescents (ages 16–19); 1 study, n= 26 subjects	90-day, randomized double-blind, placebo controlled study	Disulfiram, oral, fixed dose, 200 mg daily	Self-report alcohol use	Grade C (level 3 evidence) for AUD
Ondansetron	Outpatient, treatment-seeking, adolescents (ages 14–20); 1 study, n= 12 subjects	8-week, open-label, clinical study	Ondansetron, oral, fixed dose, 4 micrograms/kg two times per day	Self-report alcohol use; adverse events	Grade C (level 3 evidence) for AUD
Topiramate	Non-treatment seeking, heavy drinkers (mean age = 19 years); 1 study, n= 13 subjects	5-week, randomized, placebo controlled, pilot study using EMA	Topiramate, oral, escalating dose, up to 200 mg per day	Self-report alcohol use (EMA); alcohol craving; subjective-response to alcohol	Grade C (level 3 evidence) for AUD
Tobacco Use Disorder					

Drug	Sample(s)	Study design(s)	Intervention dosing and duration	Outcome measures	Level of Evidence[a]
Nicotine Replacement Therapy (patch, gum, nasal spray)	Outpatient, treatment-seeking adolescents (ages 12–19), smoking ≥ 5 CPD[b]; 5 studies, n= 728 total subjects	Meta-analysis, 12-week randomized double-blind, double-placebo controlled study comparing nicotine patch to nicotine gum; 10-week randomized double-blind placebo-controlled study of nicotine patch; 6-to-9-week randomized, double-blind placebo controlled study of nicotine patch; 8-week open-label clinical study of nicotine nasal spray	Nicotine patch, fixed dose 21 mg (participants smoking ≥ 20 CPD) or 14 mg (< 20 CPD). Nicotine patch, fixed-taper dosing, starting dose 21 mg (participants smoking > 15 CPD) or 14 mg (10–14 CPD) tapered over 10-weeks. Nicotine gum, 4 mg (participants smoking ≥ 24 CPD) or 2 mg (< 24 CPD). Nicotine nasal spray, 1 mg dosing as needed.	CO–confirmed PPA at EOT; cotinine-confirmed PPA at EOT; nicotine craving; nicotine withdrawal	Nicotine patch: Grade B (level 2 evidence) for TUD Nicotine gum and nasal spray: Grade C (level 3 evidence) for TUD
Varenicline	Outpatient, treatment-seeking adolescents (ages 14–20), smoking ≥ 5 CPD; 1 study, n= 29 subjects	8-week, randomized double-blind controlled study comparing Varenicline to Buproprion XL	Varenicline, oral, 1 mg two times per day or Buproprione XL, oral, 300 mg daily	Self-report smoking reduction; cotinine confirmed PPA at EOT	Grade B (level 2 evidence) for TUD
Buproprion	Outpatient, treatment-seeking adolescents (ages 12–21), smoking ≥ 5 CPD[b]; 4 studies, n= 688 total subjects	Meta-analysis, 8-week, randomized, double-blind, placebo controlled add-on to nicotine patch; 6-week, randomized, double-blind, placebo controlled dose comparison study (150 mg vs. 300 mg) study; 6-week, randomized double-blind, placebo controlled study with added +/− CM; 8-week, randomized double-blind comparison to Varenicline	Buproprion SR, oral, fixed dose, 150 mg daily or 300 mg daily	Cotinine-confirmed PPA at EOT; CO-confirmed PPA at EOT; self-report smoking reduction	Grade B (level 2 evidence) for TUD
Cannabis Use Disorder					
N-acetylcysteine (NAC)	Outpatient, treatment-seeking, adolescents (ages 15–21); 2 studies, n= 134 total subjects	8-week, randomized, double-blind, placebo controlled study added to brief cessation counseling and CM; 4-week open-label pilot study	NAC, oral, fixed dose, 1200 mg two times per day (2400 mg/day)	Negative urine cannabinoid test, self-report cannabis use, cravings for cannabis	Grade B (level 2 evidence) for CUD
Topiramate	Outpatient, treatment-seeking,	6-week, randomized, double-blind, placebo	Topiramate, oral, fixed dose, titrated to 200 mg daily over	Positive urine cannabinoid test, self-	Grade C (level 3 evidence) for CUD

Drug	Sample(s)	Study design(s)	Intervention dosing and duration	Outcome measures	Level of Evidence[a]
	youth (ages 15–24); 1 study, n = 66	controlled pilot study medication added to 3 sessions of motivational enhancement therapy (MET)	4 weeks and maintained at 200 mg/day over 2 weeks	report cannabis use (% days of cannabis use, grams of cannabis use per day), treatment retention, adverse events, neurocognitive functioning	
Opioid Withdrawal Syndrome					
Buprenorphine and Buprenorphine-naloxone	Outpatient detoxification, treatment-seeking, adolescents (ages 13–18); 2 studies, n= 188 total subjects	Systematic review; 28-day randomized, double-blind, double-placebo, controlled study comparing clonidine and buprenorphine detoxification regimens; 12-week randomized multisite clinical trial comparing 2-week detoxification to 12-week maintenance	Buprenorphine, sublingual, fixed-taper dosing, starting dose 8 mg or 6 mg (age based); Buprenorphine-naloxone (2 mg/0.05 mg ratio), oral, fixed-taper dosing, up to 24 mg daily	Opiate negative urine tests, treatment retention, self-report HIV-risk behavior, opiate withdrawal symptoms	Grade B (level 2 evidence) for OWS
Clonidine (patch)	Outpatient detoxification, treatment-seeking, adolescents (ages 13–18); 1 study, n= 36 subjects	28-day randomized, double-blind, double-placebo, controlled study comparing clonidine and buprenorphine detoxification regimens	Buprenorphine, sublingual, fixed-taper dosing, starting dose 8 mg or 6 mg (age based); Clonidine, transdermal patch, fixed-taper dosing, starting dose 0.1–0.3 mg daily	Opiate negative urine tests, treatment retention, self-report HIV-risk behavior, opiate withdrawal symptoms	Grade B (level 2 evidence) for OWS
Opioid Use Disorder					
Methadone	Inpatient detoxification and Specialized Opioid Treatment Programs, treatment-seeking, adolescents, heroin users (ages ≤ 20); 9 studies, n= 6,263 total subjects	Systematic review; naturalistic study comparing methadone maintenance, detoxification, therapeutic community, and abstinence-based treatments; naturalistic studies of methadone maintenance or methadone detoxification treatment without comparator groups; methadone-based short-term detoxification (30-days) versus long-term detoxification (up to 6-	Methadone, oral, flexible dosing, for 30-day detoxification or up to 6-month maintenance treatment	Treatment retention, self-report opioid use	Grade C (level 3 evidence) for OUD

Drug	Sample(s)	Study design(s)	Intervention dosing and duration	Outcome measures	Level of Evidence[a]
		months)			
Buprenorphine-naloxone	Outpatient, treatment-seeking, adolescents (ages 15–21); 1 study, n= 152 subjects	Systematic review; 12-week, randomized, multisite, controlled study comparing 2-week buprenorphine-naloxone detoxification to 12-week buprenorphine-naloxone maintenance/extended treatment	Buprenorphine-naloxone (2 mg/0.05 mg ratio), oral, fixed-taper dosing, up to 24 mg daily	Opiate positive urine tests	Grade B (level 2 evidence) for OUD
Extended-release injectable Naltrexone (intramuscular)	Residential treatment transitioning to outpatient treatment, treatment-seeking, adolescents (ages 16–20); 1 study, n= 16 subjects	Retrospective, open-label, case series	XR-naltrexone, intramuscular injection, 380 mg once every 4 weeks	Treatment retention, abstinence, opioid use (chart abstraction of self-report and urine drug screen data)	Grade C (level 3 evidence) for OUD
Opioid Overdose					
Naloxone (intranasal)		Consensus guidelines; there have been no studies examining pharmacotherapy for opioid overdose in adolescents.	Naloxone, intranasal, 2mg/2ml pre-filled luer-lock needle-less syringe		Grade C (level 3 evidence) for Opioid Overdose

Abbreviations: A-OCDS = Alcohol Obsessive Compulsive Drinking Scale, AW = alcohol withdrawal, AWS = alcohol withdrawal syndrome, AUD = alcohol use disorder, Buproprion SR – sustained release buproprion, Buproprion XL – extended release buproprion, CM = contingency management, CO = carbon monoxide, Cotinine = urine cotinine level (ng/dl), CUD = cannabis use disorder, EMA = ecological momentary assessment, EOT = end of treatment, HIV = human immunodeficiency virus, NAC = n-acetyl-cysteine, NRT = nicotine replacement therapy, OUD = Opioid Use Disorder, OWS = Opioid Withdrawal Syndrome, PPA = point prevalence abstinence, TUD = tobacco use disorder, XR-naltrexone = Extended-release injectable Naltrexone

[a]Levels of evidence presented are based upon the US Preventative Services Task Force (USPSTF) Strength of Recommendation Taxonomy (SORT) approach to grading evidence in medical literature.[103] Levels of evidence include: Level 1: good-quality, patient-oriented evidence including systematic reviews, meta-analyses, and well-designed randomized controlled trials with consistent findings. Level 2: limited-quality, patient-oriented evidence including lower-quality/less consistent systematic reviews, meta-analyses, or clinical trials as well as cohort and case-control series. Level 3: other evidence in the form of consensus guidelines, disease-oriented evidence, and case series. These levels of evidence are used to determine a strength of recommendation grade, which include A (good-quality, patient-oriented evidence); B (limited-quality, patient-oriented evidence); C (other evidence); and no recommendation.

[b]For the adolescent TUD pharmacotherapy studies, and specifically the 5 NRT and 4 bupropion studies, all studies had CPD-based inclusionary criteria which ranged from ≥ 5 to ≥ 10 CPD.