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Psychotropics for Treatment of Substance Use Disorders in Adolescents: A Brief Review

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Review Article

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Abstract

Substance use disorders (SUD) remain a long-standing problem for adolescents. Medication assisted treatment (MAT) is now standard treatment for adult SUD but less common in adolescents. This article provides a brief summary of the available psychotropics used to treat SUD in adolescent patients; psychotropics should be considered as one part of a multi-disciplinary approach to treatment of SUD. Due to the growing impact of the opioid public health crisis in the adolescent population, pediatricians have an expanding role in identifying and treatment of opioid use disorders, in addition to other substance use disorders. Pediatricians and adolescent medicine physicians are critically important in the solution to the addiction problem. There is expanding evidence that treatment of SUDs must be integrated into multiple parts of the delivery care system, including primary care settings.

Medications Used to Treat Opioid Use Disorders (OUD): Methadone and buprenorphine are the two primary methods of MAT available to treat OUD. Methadone is highly regulated and only available to patients over age 18 in the United States. Buprenorphine/naloxone is FDA-approved for patients age ≥16, with the American Academy of Pediatrics Committee on Substance Use and Prevention (2016) recommending improved pediatrician access to buprenorphine training and MAT consideration for adolescents.

Buprenorphine/Naloxone (Suboxone) and Buprenorphine (Subutex): Buprenorphine is a schedule III drug, requiring additional prescriber trainings and requirements. Buprenorphine is a mu-opioid partial agonist with greater safety margins than full agonists and less withdrawal. It is often combined 4:1 with naloxone, an antagonist; Alho, et al. found that this combination reduced "street value", likely decreasing abuse potential.

Keywords: Treatment of SUDs; Buprenorphine/Naloxone; Buprenorphine

Abbreviations: SUD: Substance Use Disorders; MAT: Medication Assisted Treatment; OUD: Opioid Use Disorders; NOWS: Neonatal Opioid Withdrawal Syndrome; NTRIs: Nucleoside Reverse Transcriptase Inhibitors; CM: Contingency Management; AUD: Alcohol Use Disorder; UCD: Cannabis Use Disorder; NAC: N-Acetylcysteine; OTC: Over-The-Counter; NP: Nicotine Patch; NG: Nicotine Gum; NNS: Nicotine Nasal Spray; ACS: Acute Coronary Syndrome; PAHs: Polycyclic Aromatic Hydrocarbons; ICS: Inhaled Corticosteroids; CO: Carbon Monoxide.

Induction

Prior to induction, providers should consider type of opioid dependence, time since last use, and degree of dependence. To avoid precipitating withdrawal, initial dose

should be started only with objective signs of moderate withdrawal present (i.e., 48 hours after use). For patients in withdrawal from short-acting opioids: on day 1, administer 5mg/0.5mg buprenorphine/naloxone, titrating in 2-4 mg increments of buprenorphine at supervised two-hour intervals up to 8 mg/2 mg buprenorphine/naloxone based on withdrawal symptoms. On day 2, administer up to 16 mg/4 mg buprenorphine/naloxone as a single dose. Naloxone absorption is higher with buccal vs sublingual administration, necessitating sublingual administration during induction to minimize precipitated withdrawal.

Maintenance

For maintenance, administer buccal or sublingual buprenorphine/naloxone. Dosage from day 3 onwards should be progressively adjusted in 2 mg/0.5 mg or 4 mg/1 mg buprenorphine/naloxone increments to a level which suppresses withdrawal symptoms as early as possible. After stabilization, maintenance dose is generally between 4 mg/1mg and 24 mg/6mg daily. Recommended maintenance is 16 mg/4mg buprenorphine/naloxone daily as a single dose. Dosages higher than 24 mg/6 mg daily have not demonstrated clinical advantage and should involve addiction specialists.

Method of Administration

Buprenorphine/naloxone is available as dissolvable tablets or film. For sublingual administration, the film/tablet is placed under the tongue, close to the base on a lateral side. It must be kept under the tongue until completely dissolved. For buccal administration, place film inside either cheek until completely dissolved, ~10 minutes. Oral buprenorphine/naloxone has poor absorption and greater gastrointestinal disturbances.

Clinical Supervision

Treatment is ideally comprehensive, including therapy, and should be initiated with supervised progressing to unsupervised administration. Buprenorphine/naloxone requires regular follow-up (i.e., initially weekly) based on individual circumstances. Once urine drug screens (UDS) do not indicate illicit drug use and at stable dosage, less frequent visits may be appropriate (i.e., monthly).

Warnings and Precautions

Buprenorphine is subject to diversion and abuse. Respiratory depression and death have been associated with buprenorphine particularly when taken intravenously with concomitant depressants (i.e., benzodiazepines, alcohol). Buprenorphine can cause severe, possibly fatal respiratory depression in children and must be stored securely. Neonatal opioid withdrawal syndrome (NOWS) is a treatable outcome of opioid use in pregnancy. Adrenal insufficiency is reported with prolonged opioid use. Avoid if known hypersensitivity to buprenorphine/naloxone. Chronic administration produces physical dependence, with rapid tapering resulting in opioid withdrawal syndrome. Buprenorphine is not an appropriate analgesic; deaths are reported in opioid naïve individuals receiving 2 mg doses. Liver functions should be monitored as moderate-to-severe hepatic impairment are relative contraindications. Caution patients about risks of driving or operating machinery.

Adverse Reactions

Adverse events commonly observed with sublingual/buccal buprenorphine/naloxone were oral hypoesthesia, glossodynia, mucosal erythema, headache, nausea, vomiting, hyperhidrosis, constipation, withdrawal symptoms, insomnia, pain, and peripheral edema.

Drug Interactions

Prescribe with caution in patients receiving CNS depressants and warn against concomitant misuse. Monitor dosing if starting or ending CYP3A4 inhibitors/inducers or using nucleoside reverse transcriptase inhibitors (NRTIs) or atazanavir. Concomitant use with serotonergic drugs may cause serotonin syndrome, discontinue if suspected.

Reports of Interest

- **Buprenorphine in the Detoxification of Adolescents with OUD**

Marsch, et al. [1] studied buprenorphine in opioid-dependent adolescents, randomly assigning adolescents to 28-day outpatient, MAT-withdrawal with either buprenorphine or clonidine, enrolling 36 youth ages 13-18. Both treatment arms received medication, placebo, counseling, and contingency management (CM). Participants successfully completing detoxification were offered continued treatment with naltrexone. Subjects in the buprenorphine arm received 6-8 mg of buprenorphine, decreased by 2 mg weekly. The clonidine group received transdermal patches 0.1-0.3 mg for the first 7 days, decreased weekly, and replaced with a placebo clonidine patch by day 21. UDS was collected thrice weekly. At study conclusion, more adolescents receiving buprenorphine vs clonidine were retained in treatment, 72% vs 39%, ($p<.05$) and had more opiate-negative UDS, 64% vs 32% ($p= .01$). All participants experienced withdrawal relief and fewer risky behaviors. At study conclusion, 61% of buprenorphine vs 5% of clonidine participants initiated naltrexone.

- **Buprenorphine/Naloxone in Adolescents with OUD**

Woody, et al. [2] conducted a multicenter outpatient comparison trial of buprenorphine-naloxone in 12-week treatment vs short term detoxification with patients aged 14-21; only 16% of participants (n=156) were under 18. The detox treatment arm received 14 mg of buprenorphine, tapered off by day 14. Patients in the 12-week group received 24 mg of buprenorphine daily, tapering weeks 9-12. Patients were also enrolled in counseling. Primary outcomes were opioid-positive UDS at weeks 4, 8, and 12. Secondary outcomes were dropout from assigned condition, self-reported use, injecting, other drug use, and enrollment in outside treatment. Follow-up visits were conducted at months 6, 9, and 12, assessing self-reported injecting, outside treatment, and substance use. Opioid-positive results in detox vs 12-week patients were 61% vs 26%, 54% vs 23%, 51% vs 43%, respectively, at weeks 4, 6, and 8, as well as higher proportions at 6-, 9-, and 12-month follow-up. The 12-week group also had better retention at 70% vs 20.5% (p<.001), reporting less opioid use, injecting, and outside treatment. Follow-up opiate-positive UDS rates remained high, at 83% in the detox group and 71% in the 12-week group.

Warden, et al. [3] analyzed data from Woody, et al. [2] for predictors of attrition, finding 36% study-dropout rates in the detox group between weeks 2-4 vs only 8% in the 12-week group by week 4. Retention in the 12-week group was associated with early adherence to buprenorphine/naloxone, early opioid-negative urines, use of any medication in the month prior to treatment, and lifetime non-heroin opioid use; prior 30-day hallucinogen use was associated with attrition. In the detox group, only sleep medications were associated with retention but not as independent predictors.

- **Use of Buprenorphine/Naloxone for Long Term Outpatient Treatment in Adolescents**

A retrospective case review by Matson, et al. [4] reviewed 103 charts of opioid-dependent adolescents in an outpatient buprenorphine/naloxone clinic. Opioid abstinence and buprenorphine/naloxone compliance were assessed by UDS at each visit, and were overall high (85.2% and 86.6%, respectively). Retention was 75% at the second visit, yet only 45% at 60 days, and 9% at one year. Female sex (p<0.05), opioid-negative (p<0.001), tetrahydrocannabinol-negative (p<0.001), and buprenorphine/naloxone-positive UDS (p<0.001) were associated with longer retention.

Mutlu, et al. [5] completed a retrospective case review of adolescents in eight-week inpatient treatment where buprenorphine/naloxone was started, followed by one year of outpatient treatment. This study found that inpatient treatment improved retention at one year (24%) in contrast to Matson, et al. [4] (9%).

Extended-Release Naltrexone (XR-NTX) / Vivitrol

Many providers hesitate initiating buprenorphine in adolescents, given their relatively short OUD history. Hammond, et al. [6] noted that opioid agonists are not considered primary intervention in youths due to stigma, dependence, and concerns on neurodevelopment; injectable XR-NTX may be more acceptable. Oral naltrexone has been available for many years to treat AUD and OUD, yet patients rarely adhere to daily naltrexone and frequently relapse; XR-NTX is as a monthly injection to improve adherence. XR-NTX is FDA-approved ages 18 for alcohol use disorder (AUD) and OUD and may be ordered by any prescriber.

Dosage and Administration

Patients are recommended to be off all opioid-containing medicines for 7-10 days before initiating XR-NTX, or up to two weeks if transitioning from buprenorphine or methadone, to diminish precipitated withdrawal.

Because negative UDS is not definitive for opioid abstinence, if there are concerns regarding occult opioid use, a naloxone challenge can be performed (although sensitivity remains limited): A naloxone challenge can assess dependence but should not be performed with symptoms of withdrawal or opioid-positive UDS. To perform a subcutaneous (SC) naloxone challenge, administer 0.8 mg of naloxone and monitor vitals and withdrawal symptoms for 20 minutes (i.e., irritability, anxiety, rhinorrhea, teary eyes, sweating, piloerection, yawning, myalgia, cramping, nausea, vomiting, diarrhea). An oral naltrexone challenge can alternatively be completed with 25-50 mg of oral naltrexone for 1-3 days. If no withdrawal symptoms occur, initiate XR-NTX. In settings without concern for occult opioids (i.e., juvenile detention), proceed directly with XR-NTX 380 mg.

Reports of Interest

Fishman, et al. [7] performed a retrospective case series of 16 adolescents and young adults (average age 18.5; 50% female) treated for OUD with outpatient XR-NTX. Four-month retention was 63%; mean number of XR-NTX doses was 2.5. At analysis, 69% of patients had substantial reductions in opioid use, 56% met “good outcome” criteria, and none reportedly overdosed.

- **Treatment for OUD in Adolescents**

It is important to ensure that youth are offered treatment for OUD immediately at the time of diagnosis. Treatment for include medications, behavioral interventions, and referral to mutual support groups. . In 2016, the American Academy

of Pediatrics released policy statement recommending that pediatricians offer medications for treatment of severe OUD. Although large, placebo-controlled trials are lacking in this age group, evidence can be interpreted from adult studies, including the 'gold standard' of medication use in OUD treatment.

- **Medications Used to Treat Cannabis Use Disorder (CUD)**

Cannabis is the most used illicit drug by adolescents in the United States, with recent legalization and medicinal approval in several states contributing to perceived safety. Currently no medications are FDA-approved to treat CUD.

Reports of Interest

- **N-Acetylcysteine (NAC)**

Gray, et al. [8] completed a double-blind trial of NAC, an over-the-counter (OTC) prodrug, in cannabis-dependent adolescents based on its modulation of intracellular and extracellular glutamate via the cysteine-glutamate exchanger. Adolescents were randomized to receive a double-blind 8-week course of NAC or placebo, along with CM and counseling. Urine was tested for cannabinoids at all visits. 116 subjects ages 15-21 were enrolled, with NAC dosed at 1200 mg twice daily. Participants receiving NAC had an odds ratio 2.4 times the placebo for negative UDS (95% CI=1.1-5.2), but posttreatment abstinence rates were not statistically different. NAC was well tolerated.

- **Medications Used to Treat AUD**

Although several medications treat AUD detoxification, adolescents with AUD often lack sufficient years to need medically assisted detoxification. No medications are FDA-approved for this in children/adolescents; refer to adult literature when appropriate.

Naltrexone

- **Reports of Interest**

Naltrexone is an FDA-approved opiate-receptor agonist for adults with AUD. Deas, et al. [9] conducted a six-week open-label clinical trial of naltrexone in five adolescents seeking AUD treatment, flexibly dosed at 25-50 mg daily. Youth were assessed with the Adolescent Obsessive Compulsive Drinking Scale (A-OCDS) and monitored with liver function tests. At 6 weeks, average daily drinks decreased from baseline by 7.61 standard drinks, with significant reduction in alcohol-related thoughts. Miranda, et al. [10] separately examined 28 adolescents who were heavy drinkers, using a double-blind, placebo-controlled crossover with randomization into naltrexone vs placebo for 8-10 days, with washout in-between. Adolescents ages 15-19 were given 50 mg of naltrexone or placebo daily. Results showed that naltrexone reduced heavy drinking ($p<0.04$) and changed subjective responses to alcohol ($p< 0.01$). The study found naltrexone well-tolerated with reduced cravings, heavy drinking, and drinking on study days.

Disulfiram (Antabuse)

- **Reports of Interest**

Disulfiram is FDA-approved for adults with AUD and is considered an alcohol-sensitizing/aversive agent via inhibition of alcohol dehydrogenase, leading to rapid increase in acetaldehyde with alcohol consumption and aversive symptoms including skin flushing, hypotension, reflex tachycardia, tachypnea, palpitations, anxiety, headache, nausea, and vomiting. Niederhofer, et al. [11] completed a randomized double-blind placebo-controlled study of disulfiram in adolescents ages 16-19 (n=49). Participants underwent 90-day alcohol detoxification and were randomized to either disulfiram 200 mg/day or placebo after 5 days of abstinence, then followed weekly for 90 days. Mean cumulative abstinence duration was significantly greater in the disulfiram group vs placebo (68.5 vs 29.7 days). On day 90, two placebo vs seven disulfiram patients had been abstinent continuously ($p=0.0063$). Disulfiram was well-tolerated.

Reports of Interest

- **Acamprosate (Campral)**

Acamprosate is FDA-approved for adults with AUD. It is an NMDA-glutamate antagonist which reduces cravings through mesolimbic dopaminergic effects, renally excreted without hepatic metabolization. Steady state is reached after 7 days. Only one study has investigated adolescent use: Niederhofer, et al. [12] in a double-blind, placebo-controlled trial of 26 patients ages 16-19. Patients were randomly treated with acamprosate at 1332 mg daily or placebo for 90 days, assessed by interview, self-report, questionnaire, and laboratory screening. At 90 days, 7 acamprosate and 2 placebo patients had been continuously abstinent ($p=0.0076$). Mean cumulative abstinence duration was 79.8 days in the acamprosate group vs 32.8 in placebo ($p=0.012$).

MAT for Adolescent Smoking Cessation

The CDC reported that, in 2015, 1/3 of high school seniors reported lifetime cigarette use with 6% as daily smokers. While historically improved, the Surgeon General estimated that 5.6 million children alive in 2014 would die early from smoking. Smoking-cessation interventions remain critical.

Three medication categories are FDA-approved for tobacco cessation in adults: nicotine replacement therapies (NRT), Zyban, and varenicline. Evidence in adolescents is less

clear.

Nicotine Replacement Therapies (NRT)

NRT provides nicotine to reduce cravings and withdrawal. Several products are approved in adults: nicotine patch (NP), nicotine gum (NG), nicotine lozenges, nicotine nasal spray (NNS), and nicotine inhaler. NP delivers steady-dose nicotine transdermally and is available in 7, 14, and 21 mg doses worn over 24 hours or 5, 10, and 15 mg doses over 16 hours. Nicotine gum and lozenges are available at doses of 2 or 4 mg; smokers should chew 1 piece every 1-2 hours (maximum 24 pieces daily). NNS is dosed as two sprays and equivalent to 1 mg of nicotine, recommending 1-2 doses hourly (maximum 5 doses hourly; 40 doses daily). Nicotine inhalers come in 10 mg/cartridge, dosing 6-16 cartridges daily.

While each cigarette contains 8-20 mg of nicotine, absorption is typically <1 mg. Smokers using 11 cigarettes daily should start at NP 21 mg for 4-6 weeks before tapering to 14 mg for 2-4 weeks, then 7 mg for 2-4 weeks. At 6-10 cigarettes daily, start with the 14 mg patch for 4-6 weeks, then 7 mg for 2-4 weeks. If using NG or lozenges and smoking 20 daily cigarettes, start at 4 mg, tapering as comfortable. NP, NG, and lozenges are available OTC, whereas NNS and inhaler are prescription-only.

Warnings/Precautions

Tobacco must be stopped when initiating NRT to avoid nicotine toxicity. Use caution in pregnancy, history of acute coronary syndrome (ACS), arrythmias, peptic ulcers, or age <18. Each specific NRT has additional contraindications. Discontinue if experiencing nausea, dizziness, weakness, vomiting, or irregular heartbeats.

Drug Interactions

Tobacco smoke contains polycyclic aromatic hydrocarbons (PAHs), potent inducers of cytochrome P450 isoenzymes 1A1, 1A2, and possibly 2E1. Many drugs are substrates for these cytochromes; active smokers may thus require higher doses of these drugs than after quitting. Kroon, et al. [13] described pharmaco*kinetic* interactions with smoking leading to reduced blood levels, most commonly: caffeine, clozapine, fluvoxamine, olanzapine, tacrine, thiothixene, thioridazine, selegiline, duloxetine, clomipramine, chlorpromazine, asenapine, mirtazapine, and theophylline. Insulin peaks faster and higher in smokers. Pharmaco*kinetic* interactions are caused by tobacco smoke, not by nicotine or NRT. Conversely, pharmaco*dynamic* interactions are largely due to nicotine and sympathetic nervous system activation, with nicotine affecting actions of certain drugs, primarily hormonal contraceptives and inhaled corticosteroids (ICS). Hormonal contraceptives are contraindicated in women 35 or older, smoking 15 cigarettes daily, due to risk of cardiovascular events. ICS are less efficacious in smokers.

Faber, et al. [14] studied CYP1A2 activity using caffeine clearance in 12 subjects who smoked 20 cigarettes daily. At steady state, CYP1A2 activity was reduced 36.1%. The authors recommended a 10% daily dose reduction of CYP1A2 substrates until day 4 following cessation. The roles of cigarette number vs individual variation affecting CYP1A2 induction are unknown.

Reports of Interest

The earliest trial of NRT in adolescent smokers was by Smith, et al. [15] using NP. Rates of abstinence are typically <10%, but reduced withdrawal and daily smoking was observed. Adverse effects were most commonly skin-related.

Hanson, et al. [16] conducted the first double-blind, placebo-controlled study of NRT. 100 participants received 10 weeks of NP or placebo patch, along with CBT and CM. The active NP group reported lower cravings and withdrawal scores but had no significant differences in biological verified abstinence at 7 or 30 days.

Moolchan, et al. [17] completed a double-blind, double-dummy, randomized 3-arm trial with 120 participants reporting 10 cigarettes daily for >1 year. They were randomized to NP with placebo gum, NG with placebo patch, or placebo patch and gum, with all participants receiving CBT. Abstinence was assessed through self-report and verified carbon monoxide (CO) levels. Intent-to-treat analyses showed CO-confirmed prolonged abstinence rates of 18% in the active NP group, 6.5% in the active NG group, and 2.5% in placebo, with statistically significant differences between active NP vs placebo groups. At 3-month follow-up, sustained abstinence was demonstrated but not group-specific. Both NP and NG were well-tolerated with adverse events resembling adults.

Rubinstein, et al. [18] conducted a pilot randomized trial of NNS in 40 adolescent smokers. Participants were assigned to either weekly group therapy for eight weeks (n=17) or eight weeks of therapy plus six weeks of NNS. Eight-week biologically verified abstinence was not significantly different between groups. Common side effects were nasal irritation, taste, and smell.

Scherphof, et al. [19] conducted a double-blind randomized controlled trial of NRT with 257 adolescents, focused on sustained abstinence from NP vs placebo at 2, 6, or 9 weeks after quitting, and at 6 and 12 months in

a continuation study [20]. The initial study found that use of NP predicted abstinence but was only true for the high-compliance group at treatment end. NRT was again deemed safe and well-tolerated.

Bupropion-SR/Zyban

Buproprion is an aminoketone-class or "atypical" antidepressant. Bupropion is believed to inhibit dopamine, serotonin, and norepinephrine CNS reuptake and may antagonize the nicotinic acetylcholine-receptor.

Bupropion is available as immediate-release, slow-release (SR; 12-hour) or extended-release (XL; 24-hour). It is approved to treat certain mood disorders; see the antidepressant chapter xx for details.

Only Zyban (a brand-name bupropion-SR) is approved for smoking cessation in adults. It should be initiated one week before "quit date" at 150 mg, 1 tablet, daily, increased after 3 days to 150 mg twice daily, then continued for 7-12 weeks. Combination treatment with NP may be prescribed.

Reports of Interest

Following early, underpowered studies, Upadhyahya, et al. [21] studied Zyban in 16 adolescent smokers, receiving bupropion-SR and counseling for 6 weeks. Limitations were numerous and conclusions were limited.

Niederhofer, et al. [22] randomized 22 participants to 90 days of 150 mg immediate-release bupropion vs placebo, following prior inpatient nicotine withdrawal. All participants received psychotherapy. At 90 days, continuous abstinence was 55% in the bupropion group vs 18% in placebo, with higher mean cumulative abstinence duration (78 ± 40 days vs 30 ± 19 days, respectively). Relapse definition varies from other studies, however, and abstinence CO level was unspecified.

Killen, et al. [23] examined bupropion-SR in adolescent smokers randomized to either 9 weeks of bupropion-SR 150 mg daily or placebo. All participants (n=211) received 8 weeks of NP and weekly skills-training. Differences were not statistically significant between treatment groups at either 10 or 26 weeks.

Muramoto, et al. [24] recruited 312 adolescents aged 14-17. Participants were randomized in a six-week double-blinded fashion into three groups: bupropion-SR 150 mg daily, 300 mg daily, or placebo, plus weekly counseling. The main outcome was 7-day abstinence at 6 weeks and 30-day prolonged abstinence. CO and urinary cotinine levels were obtained to verify abstinence. Week-6 seven-day point-prevalence abstinence rates were: placebo, 5.6%; 150 mg, 10.7%; 300 mg, 14.5% (P=0.03, 300 mg vs placebo). At 26 weeks, confirmed point-prevalence abstinence rates were: placebo, 10.3%; 150 mg, 3.1%; 300 mg, 13.9% (P=0.049) and were significantly higher for 300 mg vs placebo at every week during treatment except week 4. Relapse remained rapid following discontinuation.

Gray, et al. [25] studied bupropion-SR and concomitant CM in a double-blind, placebo-controlled design, enrolling 134 smokers ages 12-21 with numerous enrollment criteria. Subjects were randomized to 6 weeks of bupropion-SR + CM, bupropion-SR + non-CM, placebo + CM, or placebo + non-CM, with 12-week follow-up. Reported 7-day point-prevalence abstinence was confirmed with urine cotinine. Combined bupropion SR + CM treatment yielded significantly superior abstinence during active treatment vs placebo + non-CM treatment ($p<0.05$), appearing to have short-term superiority vs intervention alone.

Varenicline (Chantix)

In 2006, the FDA approved varenicline as a prescription-only treatment for adult smoking cessation. It is a nicotinic-acetylcholine-receptor partial antagonist, blocking cravings, withdrawal, and reinforcing effects. Adult studies show a superior efficacy vs bupropion-SR and NP.

Varenicline is a tablet available at 0.5 and 1 mg, taken after eating. Smokers begin varenicline one week prior to quitting, titrating from 0.5 mg on days 1-3 to 0.5 mg twice daily on days 4-7, then continued at 1 mg twice daily for 12-24 weeks.

Alternatively, a person can start varenicline while reducing smoking until abstinent by 12 weeks, continuing treatment for an additional 12 weeks. Consider dose reduction if adverse effects.

Warnings/Precautions

Serious neuropsychiatric events have been reported with varenicline, including mood changes, psychosis, paranoia, homicidal ideation, agitation, anxiety, panic, and suicide, occurring with and without preexisting psychiatric disease. Patients should be instructed to stop varenicline and contact their provider immediately if these changes occur; providers should consider dose reduction, closer monitoring, or discontinuation.

While a 2009 FDA Blackbox warning was placed on varenicline regarding neuropsychiatric events, the warning was removed in 2016 based on outcomes in the EAGLES study (Evaluating Adverse Events in a Global Smoking

Cessation Study).

Along with neuropsychiatric warnings, use caution in renal impairment, pregnancy, breastfeeding, and adolescents. Seizures, heightened effects of alcohol, somnolence, dizziness, and loss of consciousness are reported; patients should be cautioned if driving or operating machinery. Sleepwalking, hypersensitivities, angioedema, Stevens-Johnson Syndrome, and erythema multiforme have also been reported.

While a meta-analysis by Singh, et al. found that varenicline increased risk for serious cardiovascular morbidity following stable cardiovascular disease, subsequent studies and meta-analyses have found no significant difference or decreased risk with varenicline.

Adverse Events

In placebo-controlled studies, the most common adverse events with varenicline were nausea, vomiting, constipation, flatulence, and vivid or strange dreams.

Drug Interactions

Varenicline appears to have no clinically meaningful pharmacokinetic interactions. Smoking cessation, independently, however, affects various metabolisms (see discussion above).
Reports of Interest

Faessel, et al. [26] studied pharmacokinetics and safety of varenicline in a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. They enrolled smokers (≥3 cigarettes daily) ages 12-16 into high-body-weight (≥55 kg) and low-body-weight (≤55 kg) groups. Subject were randomized to 14 days of treatment with high-dose varenicline (1-2 mg/day), low-dose varenicline (0.5-1 mg/day), or placebo, monitoring renal clearance, volume of distribution, and adverse effects. Nausea, headache, vomiting, and dizziness were significantly higher in treatment groups than placebo, but 92% were mild intensity. Varenicline steady-state exposure in the high-body-weight group resembled adults. Pharmacokinetics in the low-body-weight group was adequate at half the adult dose.

Gray, et al. [27] examined the use of varenicline and bupropion-XL in older adolescent smokers (ages 15-20), randomized (double-blind) to varenicline (n=15) or bupropion-XL (n=14), with 1-week titration and 7-weeks active treatment. Tolerability and cotinine-confirmed abstinence were assessed weekly, with no serious adverse events. Over 7 weeks, varenicline-participants reduced from 14 to 1 cigarettes daily; bupropion-XL-participants reduced from 16 to 3 cigarettes daily with no statistically significant difference between groups [28-30].

Results of these studies support the feasibility and safety of conducting further adolescent varenicline trials.

Summary

Substance use disorders (SUD) have been a significant problem for adolescents and young adults for many years. Most recently the opioid epidemic has led to an increased emphasis on medication assisted treatment (MAT) to help treat SUD. The use of medication assisted treatment for adult opioid addicts has become the treatment standard. Its use in adolescents is less commonplace, but evidence-based treatments must be established for all age groups and patient populations. Due to the lack of large, double blinded, placebo-controlled trials in youth, it is a necessity to extrapolate gold standard treatments from adult studies and institute those in adolescent patients. This article may serve as a brief review for prescribers treating adolescent patients struggling with Substance Use Disorders. The use of psychotropic medications is a critical piece of a multi-disciplinary team approach and should be considered in combination with mutual supports, behavioral interventions, and community resources.

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References

1. Marsch LA, Bickel WK, Badger GJ, Stothart ME, Quesnel KJ, et al. (2005) Comparison of pharmacological treatments for opioid-dependent adolescents. Arch Gen Psychiatry 62: 1157-1164.

2. Woody GE, Poole SA, Subramaniam G, Dugosh K, Bogenschutz M, et al. (2008) Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth a randomized trial. JAMA 300(17): 2003-2011.

3. Warden D, Subramaniam GA, Carmody T, Woody GE, Minhajuddin A, et al. (2012) Predictors of attrition with buprenorphine/naloxone treatment in opioid dependent youth. Addict Behav 37(9): 1046-1053.

4. Matson SC, Hobson G, Abdel-Rasoul M, Bonny AE (2014) A retrospective study of retention of opioid-dependent adolescents and young adults in an outpatient buprenorphine/naloxone clinic. J Addict Med 8(3): 176-182.

5. Mutle C, Demirci AC, Yalcin O, Kilicoglu AG, Topal M,

et al. (2016) One-year follow-up of heroin-dependent adolescents treated with Buprenorphine/Naloxone for the first time in a substance treatment unit. Journal of substance abuse treatment 67: 1-8.

6. Hammond CJ, Gray KM (2016) Pharmacotherapy for substance use disorders in youths. J Child Adolesc Subst Abuse 25(4): 292-316.

7. Fishman MJ, Winstanley EL, Curran E, Garrett S, Subramaniam G (2010) Treatment of opioid dependence in adolescents and young adults with extended-release naltrexone: Preliminary case-series and feasiblity. Adduction 105(9): 1669-1676.

8. Gray KM, Carpenter MJ, Lewis AL, Klintworth EM, Upadhyaya HP (2012) Varenicline versus bupropion XL for smoking cessation in older adolescents: A randomized, double-blind pilot trial. Nicotine Tob Re 14(2): 234-239.

9. Deas D, May K, Randall C, Johonson N, Anton R (2005) Naltrexone treatment of adolescent alcoholics: An open-label pilot study. JJ Child Adolesc Psychopharmaco 15(5): 723-728.

10. Miranda R, Ray L, Blanchard A, Reynolds EK, Monti PM, et al. (2014) Effects of naltrexone on adolescent alcohol cue reactivity and sensitivity: An initial randomized trial. Addict Biol 19(5): 941-954.

11. Niederhofer H, Staffen W (2003) Comparison of disulfiram and placebo in treatment of alcohol dependence of adolescents. Drug Alcohol Rev 22(3): 295-297.

12. Niederhofer H, Staffen W (2003) Acamprosate and its efficacy in treating alcohol dependent adolescents. Eur Child Adolesc Psychiatry 12(3): 144-148.

13. Kroon LA (2007) Drug interactions with smoking. American Journal of Health-System Pharmacy 64(18): 1917-1921.

14. Faber MS, Fuhr U (2004) Time response of cytochrome P450 1A2 activity on cessation of heavy smoking. Clinical Pharmacology & Therapeutics 76(2): 178-1784.

15. Smith TA, House RF, Croghan IT, Gauvin TR, Colligan RC, et al. (1996) Nicotine patch therapy in adolescent smokers. Pediatrics 98(4Pt1): 659-667.

16. Karen H, Sharon A, Sue J, Dorothy H (2003) Treatment of adolescent smokers with the nicotine patch. Nicotine & Tobacco Research 5(4): 515-526.

17. Moolchan ET, Robinson ML, Ernst M, Cadet JL, Pickworth WB, Heishman SJ, et al. (2005) Safety and efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. Pediatrics 115(4): e407-e414.

18. Rubinstein ML, Benowitz NL, Auerback GM, Moscicki AB (2008) A randomized trial of nicotine nasal spray in adolescent smokers. Pediatrics 122(3): e595-600.

19. Scherphof CS, Van den Eijnden, Regina JJM, Engels RC, Vollebergh WA (2014) Short-term efficacy of nicotine replacement therapy for smoking cessation in adolescents: A randomized controlled trial. J Subst Abuse Treat 46(2): 120-127.

20. Scherphof CS, Van den Eijnden, Regina JJM, Engels RC, Vollebergh WA (2014) Long-term efficacy of nicotine replacement therapy for smoking cessation in adolescents: A randomized controlled trial. Drug Alcohol Depend 140: 217-220.

21. Upadhyaya HP, Brady KT, Wang W (2004) Bupropion SR in adolescents with comorbid ADHD and nicotine dependence: A pilot study. Journal of the American Academy of Child & Adolescent Psychiatry 43(2): 199-205.

22. Niederhofer H, Huber M (2004) Bupropion may support psychosocial treatment of Nicotine-Dependent adolescents: Preliminary results. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 24(11): 1524-1528.

23. Killen JD, Robinson TN, Ammerman S, Hayward C, Rogers J, et al. (2004) Randomized clinical trial of the efficacy of bupropion combined with nicotine patch in the treatment of adolescent smokers. J Consult Clin Psychol 72(4): 729.

24. Muramoto ML, Leischow SJ, Sherrill D, Matthews E, Strayer LJ (2007) Randomized, double-blind, placebo-controlled trial of 2 dosages of sustained-release bupropion for adolescent smoking cessation. Arch Pediatr Adolesc Med 161(11): 1068-1074.

25. Gray KM, Carpenter MJ, Baker NL, Hartwell KJ, Lewis AL, Hiott DW, et al. (2011) Bupropion SR and contingency management for adolescent smoking cessation. J Subst Abuse Treat 40(1): 77-86.

26. Faessel H, Ravva P, Williams K (2009) Pharmacokinetics, safety, and tolerability of varenicline in healthy adolescent smokers: A multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther 31(1): 177-189.

27. Gray KM, Carpenter MJ, Baker NL, DeSantis SM, Kryway E,

et al. (2012) A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents. Am J Psychiatry 169(8): 805-812.

28. Alho H, Sinclair D, Vuori E, Holopainen A (2007) Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. Drug Alcohol Depend 88(1): 75-78.

29. Committee on Substance Use and Prevention (2016) Medication-assisted treatment of adolescents with opioid use disorders. Pediatrics 138(3): e20161893.

30. Robinson CA, Wilson JD (2020) Management of opioid misuse and opioid use disorders among youth. Pediatrics 145(S2): S153-S164.