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Drug Class Literature Scan: Substance Use Disorders

Date of Review: February 2023

Date of Last Review: December 2020
Literature Search: 01/01/20 – 11/18/2022

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- Is there any new data for medicines that are used to treat substance use disorders that would change how these medicines are covered under the Oregon Health Plan fee-for-service (Open Card) program?
- The Food and Drug Administration (FDA) has approved these medicines to treat substance use disorders:
  - Lofexidine, methadone, buprenorphine, naloxone, and naltrexone to assist with treating opioid use disorder.
  - Naltrexone, acamprosate, and disulfiram to assist with treating alcoholism.
  - Currently, no medicines are approved to assist with treating cocaine or methamphetamine use disorder.
- Studies show that both methadone and buprenorphine help people with opioid use disorder stay in treatment.
  - Methadone may be better than buprenorphine in helping people stay in opioid use disorder treatment, but evidence is mixed. One study found no difference between methadone and buprenorphine in the number of people who stay in treatment.
  - Buprenorphine probably keeps more people in treatment than naltrexone injection or counseling alone.
  - The Veterans Affairs/Department of Defense recommend buprenorphine/naloxone or methadone for opioid use disorder. They suggest naltrexone injection as an alternative medicine if buprenorphine or methadone do not have benefit or are not appropriate for the specific person.
  - In people who are pregnant and dependent on opioids that are not prescribed by a provider, methadone and buprenorphine may have similar benefit. In one study, buprenorphine improved birthweight, longer length of the baby at birth, and decreased risk of the baby being born too early compared with methadone. But there were important flaws in this evidence, so the results should be considered with caution and may not be true for all people. Another study showed methadone and buprenorphine may be similar in effectiveness in reducing adverse outcomes in people who are pregnant and their newborns.
- The Agency of Healthcare Research and Quality found evidence that both methadone and buprenorphine help reduce or stop use of substances in teen-agers and young adults 12 to 25 years of age with substance use disorder. Methadone was more effective for helping young adults to stay in treatment and reduce self-reported substance use.
- Most of the medicines studied in people who had both cocaine and opioid use disorder were ineffective.

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- The Department of Veterans Affairs and Department of Defense recommends oral naltrexone to treat alcohol use disorder. Providers may consider use of acamprosate or disulfiram if naltrexone had no benefit or is not appropriate for the specific person.
- The Oregon Health Plan covers nearly all medicines used to treat substance use disorder. Providers must explain to the Oregon Health Plan if they prescribe lofexidine or more than 24 mg per day of buprenorphine before the Oregon Health Plan will pay for the medicine. This process is called prior authorization. The goal of prior authorization is to make sure these medicines are used in a safe and effective way.

Conclusions:

- Since the last class update, 6 systematic reviews,[1-6] one meta-analysis,[5] and one guideline[7] have been published.
- A 2022 Cochrane Review assessed medication-assisted treatment with buprenorphine or methadone for the treatment of opioid use disorder (OUD) in people dependent on prescription opioids.[1] Methadone and buprenorphine did not differ on some outcomes such as positive urine drug screens at the end of treatment (moderate quality of evidence [QoE]) or the rate of adverse events (low QoE), although result favored methadone for retention and self-reported substance use (low QoE). There was moderate-certainty evidence from 4 studies that showed that buprenorphine monotherapy resulted in higher treatment retention rates over non-opioid treatments (detoxification, extended-release naltrexone injection, or psychological treatment without opioid agonist treatment).[1]
- A 2022 systematic review and meta-analysis evaluated comparative evidence for methadone and buprenorphine to determine the optimal opioid substitution agent to reduce adverse maternal and neonatal outcomes in pregnant individuals using illicit opioids.[2] Data from 16 observational cohort studies and 3 randomized controlled trials (RCTs) showed that buprenorphine was consistently associated with improved birthweight, longer length at birth, and lower risk of prematurity in neonates compared to methadone (low QoE for all outcomes).[2] In 4 RCTs that compared buprenorphine with methadone on improving maternal outcomes, there was a greater risk of maternal adverse effects with methadone and lower treatment retention rates with buprenorphine (low QoE).[2]
- A November 2020 Cochrane Review assessed the effectiveness of medication assisted treatment (MAT) for pregnant patients with OUD.[3] Medication assisted treatments, alone or in combination with a psychosocial intervention, were compared to no intervention, other pharmacological intervention or psychosocial interventions alone.[3] Methadone and buprenorphine may be similar in efficacy and safety for both the patients and their infants (low QoE).[3] There is insufficient evidence to make conclusions for the comparison between methadone and slow-release morphine in this population.[3] More evidence is needed to adequately compare different MAT options for pregnant individuals with OUD.[3]
- A 2020 systematic review by the Agency of Healthcare Research and Quality (AHRQ) reviewed pharmacologic interventions for adolescents and young adults 12 to 25 years of age with substance use disorder (SUD).[4] Evidence was insufficient for most interventions.[4] Most studies enrolled individuals with mixed use of opioids, alcohol, and cannabis.[4] For short-term treatment of OUD in adolescents and young adults, low-quality evidence showed that buprenorphine or buprenorphine-naloxone was more effective in achieving abstinence than clonidine (in one study), was more effective when augmented by memantine (in one study), and was more effective when tapered over longer rather than shorter durations (in 2 studies).[4] There is insufficient evidence of long-term efficacy of pharmacologic or behavioral treatment of OUD in adolescents and young adults.[4] The literature guiding medications for adolescents and young adults with OUD is limited, and more research is needed to evaluate optimal pharmacologic treatment duration and the benefit of adjunctive behavioral interventions.[4]
- A 2021 meta-analysis collated treatment retention rates reported by RCTs and observational studies that compared methadone to buprenorphine or buprenorphine-naloxone for treatment of adults with OUD.[5] The meta-analysis of RCTs and meta-analysis of observational studies both suggest retention rates are similar between methadone and buprenorphine products, based on low-quality evidence.[5]
- A systematic review and meta-analysis of medications for stimulant use disorders (cocaine, methamphetamine) in patients with co-occurring opioid use disorders was published in 2020.[6] Thirty-four trials focused on cocaine use disorder in patients with OUD met inclusion criteria.[6] Twenty-two medications

including anticonvulsants, antidepressants, antipsychotics, methadone, buprenorphine, and psychostimulants were studied.[6] Only 1 medication, a naltrexone implant (not available in the United States [U.S.]) was studied in people with methamphetamine abuse and OUD in Russia.[6] Low-strength evidence from 3 RCTs (n=115) showed that psychostimulants (dexamphetamine or mazindol) may reduce cocaine use, though the difference was not statistically significant (standard mean difference 0.35; 95% Confidence Interval [CI] -0.05 to 0.74).[6] Most of the medications studied for cocaine use compared to placebo were ineffective, although psychostimulants may warrant further study.[6]

- The Department of Veterans Affairs (VA) and Department of Defense (DoD) updated guidance for the management of SUDs in 2021.[7] Naltrexone and topiramate are recommended for alcohol use disorder.[7] Acamprosate and disulfiram are suggested as first-line alternatives and gabapentin is suggested as second-line therapy.[7] For OUD, buprenorphine/naloxone and methadone are recommended, and extended-release naltrexone is suggested as a first-line alternative.[7] There is insufficient evidence to recommend for or against the use of any pharmacotherapy for the treatment of cannabis use disorder, cocaine use disorder or amphetamine/methamphetamine use disorder.[7]
- In 2022, the Food and Drug Administration (FDA) issued a drug safety communication warning of dental problems associated with buprenorphine products that are dissolved in the mouth (i.e., sublingual, buccal).[8] Reported dental problems include tooth decay, cavities, oral infections, and loss of teeth, which can be serious and have been reported even in patients with no previous history of dental issues.[8]

Recommendations:

- No changes to the preferred drug list (PDL) are recommended.
- Since there has no utilization of lofexidine in the past year, retire prior authorization (PA) criteria for lofexidine. Requests for lofexidine will be addressed through non-preferred PA criteria.
- After evaluation of costs in executive session, no changes were made to the PDL.

Summary of Prior Reviews and Current Policy

- A literature scan of drugs to treat opioid and alcohol use disorders was last presented at the December 2020 P&T Committee meeting. Based on the review of recently published evidence, no changes to the PDL or PA criteria were made by the Committee.
- Currently, buprenorphine sublingual tablets and disulfiram tablets are designated as voluntary non-preferred. Buprenorphine injection (SUBLOCADE), naltrexone formulations, acamprosate, and buprenorphine/naloxone formulations are available as preferred products on the PDL. New products in this class are designated as voluntary non-preferred due to legislation designed to ensure open access to SUD treatments.
- A drug use evaluation (DUE) which assessed utilization of sublingual buprenorphine for off-label prescribing indications after removal of buprenorphine PA criteria for MAT in 2020 was presented to the Pharmacy and Therapeutics (P&T) Committee at the June 2022 meeting.[9] Based on the DUE evidence, no policy changes were implemented. A cohort of fee-for-service (FFS) patients who had paid claims for sublingual buprenorphine from 1/1/19 to 6/30/19 (control group) was compared to a similar group who had paid claims for sublingual buprenorphine from 1/1/20 to 6/30/20 (intervention group).[9] The conclusions from the DUE were as follows:
    - The number of patients prescribed sublingual buprenorphine over the 6-month study period increased by over 20% (from 364 patients to 472 patients after removal of the PA) indicating increased prescribing for sublingual buprenorphine.[9] During this same timeframe the average monthly fee-for-service enrollment increased by about 5% from 2019 to 2020.[9]
    - The proportion of patients prescribed sublingual buprenorphine formulations with a diagnosis of OUD was similar before and after the PA removal (89% vs. 87%, respectively).[9]
        - Similar rates were observed for the subgroup of patients prescribed combination buprenorphine/naloxone.[9]

- In a subgroup of patients with paid claims for sublingual buprenorphine monotherapy, the proportion of patients without a diagnosis of OUD increased after removal of the PA from 6.5% to 20.6%. However, this group still represents a small proportion of the overall population with claims for sublingual buprenorphine (4.4%).[9]

- In the third quarter of 2022 (July through September 2022), most of the Oregon Health Plan (OHP) FFS pharmacy claims for SUD medications were for oral buprenorphine/naloxone (63%), followed by sublingual buprenorphine (21%), and oral naltrexone (13%). In the second quarter of 2022 (April through June 2022) most of the physician administered SUD claims were for oral buprenorphine/naloxone (65%) and oral buprenorphine (33%). Physician administered claims include physician offices and MAT clinics.
- **Appendix 1** lists the current PDL status for drugs used in treat SUD. Doses of buprenorphine and buprenorphine/naloxone that exceed 24 mg per day, in addition to lofexidine, are subject to the clinical PA criteria outlined in **Appendix 5**.

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
<u>Opioid Agonist Treatment for People Dependent on Prescription Opioids</u>
A 2022 Cochrane Review assessed opioid agonist treatment with buprenorphine or methadone for the treatment of opioid use disorder (OUD) in people dependent on prescription opioids.[1] Literature was searched through January 2022 for RCTs of adults and adolescents with OUD that compared: 1) full opioid agonist (methadone, morphine, oxycodone, or codeine) versus a different full opioid agonist or partial opioid agonist (buprenorphine) for maintenance treatment; and 2) full or partial opioid agonist versus non-opioid agonist treatments (detoxification, extended-release naltrexone injection, or psychological treatment without opioid agonist treatment).[1]

Eight RCTs met inclusion criteria (n=709).[1] Four studies compared methadone and buprenorphine in people with dependence on prescription opioids. Four studies compared buprenorphine to either a buprenorphine taper (in addition to psychological treatment; 3 studies) or extended-release naltrexone injection (1 study).[1] Seven studies were conducted in an outpatient setting.[1] One study recruited participants who were admitted to hospital, with one group randomized to initiate buprenorphine as an inpatient while the other 2 groups offered a brief intervention and treatment referral information.[1] People with chronic non-cancer pain and OUD were recruited for the studies, and one study specifically recruited participants who misused buprenorphine by injecting it.[1] Seventy percent of the people in the studies were male. The average age was 32 years.[1] The average duration of the 4 studies that compared methadone and buprenorphine was 21 weeks; and the average duration of the 4 studies that compared buprenorphine to detoxification, extended-release naltrexone injection, or psychological treatment was 14 weeks.[1] Seven of the 8 studies were conducted in the U.S.; one study was conducted in Iran.[1] The primary outcomes were continued opioid

use, treatment retention, and adverse effects.[1] Overall, the evidence was of low quality.[1] All studies were randomized and open-label, which posed risk for performance and detection bias.[1] There was also meaningful amounts of missing data that posed high risk of attrition bias because patient attrition rates were high and varied between groups.

Low-certainty evidence from 3 studies showed a difference that favored methadone versus buprenorphine for the outcome of overall self-reported opioid use at end of treatment (risk ratio (RR) 0.49, 95% CI 0.28 to 0.86; n=165). Moderate-certainty evidence from one study did not find a difference in days of self-reported opioid use between methadone and buprenorphine (mean difference (MD) 1.41 days, 95% CI 3.37 lower to 0.55 days higher; n=129).[1] Low-certainty evidence from 4 studies also showed a difference in favor of methadone versus buprenorphine for retention in treatment (RR 1.21, 95% CI 1.02 to 1.43; n=379).[1] Low-certainty evidence from 3 studies showed no difference between methadone and buprenorphine with substance use as measured with urine drug screens at end of treatment (RR 0.81, 95% CI 0.57 to 1.17; n=206). There was low-certainty evidence from 3 studies that did not find a difference in adverse events between methadone and buprenorphine (RR 1.13, 95% CI 0.66 to 1.93; n=206).[1]

When buprenorphine monotherapy was compared to non-opioid treatment, low-certainty evidence from 4 studies showed that buprenorphine resulted in fewer opioid positive urine drug tests at end of treatment (RR 0.66, 95% CI 0.52 to 0.84; n=270). However, 4 studies did not find a difference in self-reported opioid use in the 30 days prior to the end of treatment period between buprenorphine and non-opioid treatment (RR 0.63, 95% CI 0.39 to 1.01; n=276).[1] There was low-certainty evidence from 3 studies that did not find a difference in the number of days of unsanctioned opioid use between buprenorphine and non-opioid treatment (MD −0.19, 95% CI −0.47 to 0.09; n=205).[1] There was moderate-certainty evidence from 4 studies that showed that buprenorphine resulted in higher treatment retention rates over non-opioid treatment (RR 3.02, 95% CI 1.73 to 5.27; n=333).[1] There was moderate-certainty evidence from 3 studies that buprenorphine and non-opioid treatments may not differ in adverse events (RR 0.50, 95% CI 0.07 to 3.48; n=252).[1]

In summary, methadone or buprenorphine did not differ on some outcomes such as positive urine drug screens at the end of treatment (moderate QoE) or the rate of adverse events (low QoE), although on the outcomes of retention and self-reported substance use some results favored methadone (low QoE).[1] However, treatment with buprenorphine appears more effective treatment retention rates then non-opioid treatments like detoxification, extended-release naltrexone injection, or psychological treatment (moderate QoE).[1] Patient preference, availability of treatment clinics, and the clinical assessment of the provider will help determine which MAT will result in higher odds of patient success.

<u>Buprenorphine versus Methadone in Pregnancy</u>

A 2022 systematic review and meta-analysis evaluated comparative evidence for methadone and buprenorphine to determine the optimal opioid substitution agent to reduce adverse maternal and neonatal outcomes in pregnant individuals using illicit opioids.[2] Few RCTs studied this population, so observational cohort studies were included.[2] Case-reports, case-series, and case-control studies were excluded.[2] Twenty studies (4 RCTs and 16 cohort studies) met inclusion criteria and included 7251 patients (methadone; n=4146, buprenorphine; n=3105).[2] Study locations included Europe (8), North America (10) and Oceania (2).[2] Maternal outcomes of interest included adverse associated with treatment, retention in treatment, illicit drug use, death, and mode of delivery (vaginal or cesarean section).[2] Neonatal outcomes were stillbirth, birthweight, growth (total body length at birth and small for gestational age), premature birth, opioid withdrawal treatment, and congenital anomalies.[2] All the studies were at high risk of bias.[2]

Data from 16 cohort studies and 3 RCTs showed that compared to methadone, buprenorphine was associated with greater newborn birth weight (weighted mean difference [WMD] 343 grams; 95% CI 40 to 645 in RCTs and WMD and 184 grams; 95% CI 121 to 247 in cohort studies); longer body length at birth (WMD 2.28 cm; 95% CI 1.06 to 3.49 in RCTs and WMD, 0.65 cm; 95% CI 0.31 to 0.98 in cohort studies); and reduced risk of prematurity (RR 0.41; 95% CI 0.18 to 0.93 in

RCTs and RR 0.63; 95% CI 0.53 to 0.75 in cohort studies; low QoE for all outcomes).[2] Neonatal abstinence syndrome, congenital anomalies, and stillbirths were similar between methadone and buprenorphine (low QoE).[2]

One RCT (n=175) documented maternal adverse effects associated with treatment.[2] There were 14 (16%) serious adverse effects and 83 (93%) adverse effects in the methadone arm, and 8 (9%) serious adverse effects, and 66 (77%) adverse effects in the buprenorphine arm (low QoE).[2] Three RCTs reported treatment retention.[2] The risk of early withdraw from treatment was higher with buprenorphine (32%) compared with methadone (32% vs. 20%; RR 1.60; 95% CI 1.00 to 2.55; low QoE).[2] Two cohort studies reported measures of additional opioid use throughout pregnancy.[2] One study reported 15/90 (17%) of patients used heroin in the buprenorphine group versus 20/45 (44%) in the methadone group.[2] In the other cohort study, 14/16 (88%) patients used additional opioids in the buprenorphine group, and 128/136 patients (94%) of patients in the methadone group.[2] When the results of these two studies were pooled, there was no difference between groups (RR 0.61; 95% CI 0.25 to 1.49; low QoE).[2] The rate of cesarean section was measured in 11 studies (8 cohort studies and 3 RCTs).[2] Buprenorphine was associated with lower cesarean sections versus methadone in cohort studies (RR 0.90; 95% CI 0.84 to 0.98; low QoE).[2] However, no differences in cesarean sections were observed in the RCTs (RR 0.84; 95% CI 0.52 to 1.36; low QoE).[2] No maternal deaths were reported in any studies.[2]

In summary, this systematic review concluded that compared to methadone, buprenorphine was consistently associated with improved birthweight, longer length at birth, and lower risk of prematurity in neonatal offspring based on data from 15 low-quality observational cohort studies and 3 RCTs with a high risk of bias.[2] In the 4 RCTs with high risk of bias, there was a greater risk of maternal adverse effects with methadone and lower treatment retention rates with buprenorphine.[2] However, given high risk of biases in these studies, the results should be interpreted with caution.

<u>Maintenance Agonist Treatments for Opiate-Dependent Pregnant Women</u>

A 2020 Cochrane Review assessed the effectiveness of MAT for pregnant individuals with OUD.[3] Medication-assisted treatment, alone or in combination with a psychosocial intervention, was compared to no intervention, other pharmacological intervention or psychosocial interventions alone.[3] The prevalence of opioid use among pregnant individuals can range from 1% to 2%, to as high as 21%.[3] Neonatal complications of opioid use include opioid withdrawal, postnatal growth deficiency, microcephaly, neuro-behavioral problems, increased neonatal mortality, and a 74-fold increase in sudden infant death syndrome.[3] Pregnancy is recognized as an opportunity to change lifestyle behaviors, and while abstinence from opioids during pregnancy is ideal, withdrawal from opioids during pregnancy is not recommended.[10]

Literature was searched through February 2020 for RCTs which evaluated the efficacy of MAT pregnant individuals with OUD.[3] Studies starting after delivery were excluded.[3] Four RCTs including 271 pregnant patients met inclusion critieria.[3] Three trials compared methadone with buprenorphine (n=223) and one trial compared methadone with oral slow-release morphine (n=43).[3] Two RCTs were from Austria (outpatients), one from the US (inpatients) and a fourth multicenter, international study was conducted in Austria, Canada and the US.[3] The trials continued for 15 to 18 weeks.[3] Three studies had adequate allocation concealment and were double-blind.[3] A major flaw of the studies was attrition bias: 3 out of 4 had a high dropout rate (30% to 40%), which was unbalanced between groups.[3] In the studies that compared methadone with buprenorphine, the quality of the evidence ranged from very low to moderate because of inconsistency in some outcomes between studies, high attrition, and small sample sizes.[3] The quality of the evidence was low in the single trial that compared methadone with slow-release morphine because of the small sample size studied.[3]

Outcomes of interest included child health status, neonatal mortality, treatment retention, and substance use.[3] There was no evidence of a difference in the dropout rate from treatment between methadone and buprenorphine (RR 0.66, 95% CI 0.37 to 1.20, 3 studies; n=223; moderate QoE).[3] No difference in the use of primary substances between methadone and buprenorphine was found (RR 1.81, 95% CI 0.70 to 4.68; 2 studies; n=151; low QoE).[3] Birth weight was higher

with buprenorphine versus methadone in the 2 trials that reported data (MD -530 g, 95% CI -662.78 to -397.22; n=19 and MD -215 g, 95% CI -238.93 to -191.07; n=131) although the results could not be pooled due to very high heterogeneity (very low QoE).[3] The number of newborns treated for neonatal abstinence syndrome did not differ between groups (RR 1.19, 95% CI 0.87 to 1.63; 3 studies; n=166; low QoE).[3] Only one study that compared methadone with buprenorphine reported adverse events.[3] In mothers, there were 14/89 (16%) serious adverse events in the methadone group and 8/86 (9%) in the buprenorphine group, with no difference in the number of mothers with serious adverse events (RR 1.69; 95% CI 0.75 to 3.83; n=175; low QoE). In newborns, there were more serious adverse events (6/73; 8%) in the methadone group than in the buprenorphine group (1/58; 2%), with no difference in the number of newborns with serious adverse effects (RR 1.22; 95% CI 1.07 to 1.39; n=131; low QoE).[3]

In the methadone versus slow-release morphine RCT there were no dropouts in either treatment group.[3] Slow-release morphine was superior to methadone for abstinence from heroin use during pregnancy (RR 2.40, 95% CI 1.00 to 5.77; n=48 participants; low QoE).[3] No adverse effects were reported for the pregnant patients. One child in the methadone group had central apnea and one child in the morphine group had obstructive apnea.[3]

In summary, methadone and buprenorphine may be similar in efficacy and safety for the treatment of OUD in pregnant patients and their neonates.[3] There is insufficient evidence to adequately compare methadone and slow-release morphine.[3] There is a need for more RCTs of adequate sample size that compare MAT in pregnant individuals with OUD.[3]

Agency Of Healthcare Research and Quality: Interventions for Substance Use Disorders in Adolescents and Young Adults

An AHRQ systematic review of interventions for adolescents and young adults aged 12 to 25 years with substance use disorder (SUD) was published in 2020.[4] Both behavioral and pharmacological interventions used for adolescents or young adults with SUD, excluding tobacco, were evaluated.[4] In studies that assessed relapse or reduction in substance use, RCTs with a minimum of 10 patients per arm, and nonrandomized comparative studies or single group studies enrolling at least 100 patients per arm were included.[4] Pharmacologic interventions were divided into those used primarily for SUD or primarily to manage psychiatric comorbidities.[4] One hundred eighteen studies met inclusion criteria.[4] The most commonly reported outcomes included frequency of substance use and abstinence.[4] Evidence was described for 3 major categories of interventions: 1) brief behavioral interventions (consisting of 1 or 2 encounters), typically targeted at adolescents with problematic use; 2) intensive (i.e., 3 or more encounters) behavioral interventions; and 3) pharmacological treatments used to treat OUD.[4] For the purposes of this literature scan, the evidence for medications used to treat OUD will be highlighted.

Most studies enrolled some combination of individuals with mixed use of alcohol, cannabis, opioids, and occasionally other drugs.[4] Two studies evaluated users of methamphetamine, cocaine or ecstasy.[4] However these 2 studies only evaluated behavioral interventions and had methodological concerns including incomplete blinding, incomplete outcome data and poor compliance with interventions.[4] Studies often combined different types of interventions, making comparisons of specific interventions difficult.[4] The available studies did not consistently report a common set of outcomes, which limited the ability to combine information from potentially relevant studies.[4] For most outcomes, individual studies were deemed to have a high risk of bias due to incomplete outcome data, poor compliance, and lack of blinding.[4]

Four comparative studies assessed pharmacologic or combination pharmacologic and behavioral interventions to reduce opioid use in a total of 330 individuals with OUD.[4] Risk of bias was high for all studies.[4] The most significant areas of potential bias across the 4 trials included incompleteness of outcome data reporting and low compliance with the interventions.[4] Participants in the studies were on average 17 to 23 years of age (range across studies 14 to 25 years).[4] In the studies, 59% of participants were male (range across studies 39–66%) and 80% were White (range 70–97%).[4] In addition, 52% reported heroin as the primary substance of use (range from 21 to 91%) and 44% reported injection or intravenous opioid use (range from 24 to 70%).[4] All studies reported on co-use of at least

one other substance: including alcohol, cannabis, cocaine, and amphetamines.[4] All 4 studies assessed sublingual buprenorphine-naloxone or buprenorphine monotherapy combined with behavioral interventions for short-term opioid detoxification.[4] One study compared buprenorphine with clonidine and another study augmented buprenorphine-naloxone treatment with 15 or 30 mg of memantine.[4] No studies of methadone or naltrexone were identified.[4] A meta-analysis was not feasible due to the small number of participants and study heterogeneity.[4] Primary outcomes were reduction of opioid use and maintenance of abstinence. Treatment retention was a secondary outcome in 1 study.[4]

An extended course (12 weeks) of buprenorphine led to a more than greater likelihood of opioid abstinence at 3 months (measured as percent of patients with negative urine screens) compared to a short course (2 weeks) of buprenorphine (1 RCT; n=154; odds ratio [OR] 2.4; 95% CI 1.0 to 5.9; low QoE).[4] Another study (n=53) showed a slow buprenorphine taper over 56 days was more effective than a rapid buprenorphine taper over 28 days in maintaining abstinence at 2 months (OR 2.59; 95% CI 0.73 to 9.18; low QoE).[4] A third study found that buprenorphine performed better for abstinence at 1 month compared to clonidine, although the confidence interval was very wide (OR 4.00, 95% CI 1.00 to 16.0; 1 study; n=36; low QoE).[4] This study reported treatment retention as a secondary outcome.[4] The study retained 72% of participants in the buprenorphine group compared with 39% in the clonidine group (p=0.04).[4] A fourth study compared buprenorphine-naloxone plus memantine 15 mg, buprenorphine-naloxone plus memantine 30 mg, and buprenorphine-naloxone plus placebo in 80 individuals with OUD.[4] Participants in the buprenorphine-naloxone-memantine 30 mg group had improved abstinence at 3 months compared with participants who received buprenorphine-naloxone-memantine 15 mg (OR 9.20, 95% CI 2.62 to 32.28) or placebo (OR 9.20, 95% CI 2.69 to 31.46; moderate QoE for both outcomes).[4]

In summary, for short-term treatment of OUD in adolescents and young adults, low-quality evidence showed that buprenorphine or buprenorphine-naloxone was more effective in achieving abstinence than clonidine (in one study), was more effective when augmented by memantine (in one study), and was more effective when tapered over longer rather than shorter durations (in 2 studies).[4] There is insufficient evidence of long-term efficacy of pharmacologic or behavioral treatment of OUD in adolescents and young adults.[4] The literature guiding medications for adolescents and young adults with OUD is limited, and more research is needed to evaluate optimal pharmacologic treatment duration and the benefit of adjunctive behavioral interventions.[4]

Treatment Retention of Adults with Opiate Use Disorder Who Received Medication Assisted Treatment

A 2021 meta-analysis summarized treatment retention rates reported by RCTs and observational studies which compared oral methadone to buprenorphine or buprenorphine-naloxone for treatment of adults with OUD.[5] Studies with a behavioral focus or placebo comparisons were excluded.[5] Data were extracted separately for two different definitions of treatment retention: length of time retained in the study and presence on the final day of a study.[5] Separate random effects meta-analyses were performed for RCTs and controlled observational studies.[5] Among 7603 studies reviewed, 10 RCTs and 3 observational studies met inclusion criteria (n=5065).[5] All RCTs were found to have low or unclear risk of bias due to incomplete outcome data.[5] There was an unclear or high risk of bias relating to blinding of outcome assessments, allocation concealment, and random sequence generation.[5] For observational studies, 2 studies were had moderate risk of bias and one study had low risk of bias based on the 8-item tool derived from the Joanna Briggs Institute (JBI) Cohort Study Critical Appraisal Instrument for observational studies.[11] The JBI tool considered studies on the following criteria: selection of the study groups, comparability of the groups, addressing bias and confounding factors, and ascertainment of the outcome of interest.[5]

Across studies, the average treatment retention rate was highly variable (RCTs: buprenorphine 20.0 to 82.5% and methadone 30.7 to 83.8%; and observational studies: buprenorphine 20.2 to 78.3% and methadone 48.3 to 74.8%; low QoE).[5] No difference in treatment retention was observed between buprenorphine and methadone in RCTs based on the time period retained in the study (standardized mean difference [SMD] -0.07; 95% CI -0.35 to 0.21; p=0.63; 4 RCTs; n=334; I^2= 37%; low QoE).[5] A meta-analysis was not feasible for observational studies where treatment retention was measured as the length of time retained in the

study.[5] No difference between buprenorphine and methadone was observed where treatment retention was defined as presence on the final study day in RCTs (RR 0.89; 95% CI 0.73 to 1.08; p=0.24; 8 RCTs; n=718; I^2= 56%; low QoE) or in observational studies (RR = 0.75; 95% CI 0.36 to 1.58; 3 studies; n=3498; I^2= 98%; p=0.45; low QoE).[5] In summary, studies suggest treatment retention may be similar for methadone and buprenorphine (or buprenorphine-naloxone), with wide variation across studies.[5]

Stimulant Use Disorders in Patients with Co-Occurring Opioid Use Disorders

A systematic review and meta-analysis of medications for stimulant use disorders in patients with co-occurring opioid use disorders was published in 2020.[6] The 2020 systematic review is part of a larger 2018 report commissioned by the U.S. Veterans Health Administration (VHA) that examined the benefits and harms of medications for cocaine and methamphetamine use disorders.[12] Among treatment-seeking people with OUD, reports of past-month methamphetamine use nearly doubled from 18.8% to 34.2% between 2011 and 2017.[13] Similarly, amongst people with prescription OUD in 2015, 31.5% reported cocaine use disorders in the prior year.[14]

The literature search for randomized controlled trials in multiple databases was conducted through April 2019.[6] Thirty-four trials that focused on cocaine use disorder in patients with OUD met inclusion criteria.[6] Twenty-two medications including anticonvulsants, antidepressants, antipsychotics, methadone, buprenorphine, and psychostimulants were studied.[6] Only 1 medication, a naltrexone implant (not available in the U.S.) was studied in people with methamphetamine abuse and OUD in Russia.[6] Most studies enrolled participants stabilized on opioid maintenance therapy, generally methadone.[6] Primary outcomes were abstinence defined as stimulant-negative urine screens for 3 or more consecutive weeks; overall use defined as the proportion of stimulant-negative urine specimens; and retention defined as the proportion of participants who completed treatment.[6]

None of the 6 studies that assessed abstinence found significant differences between groups.[6] Moderate-strength evidence from 10 RCTs (n=1006) showed that antidepressants (desimpramine, bupropion, and fluoxetine) worsened retention compared to placebo (RR of dropout, 1.22; 95% CI 1.05 to 1.41).[6] Combined retention data from 3 RCTs (n=292) show moderate-strength evidence of worse retention with anticonvulsants compared with placebo (RR 0.86, 95% CI 0.76 to 0.97), and low-strength evidence for no effect on cocaine use or abstinence in cocaine users with comorbid OUD.[6] Two RCTs provide insufficient-strength evidence for treating cocaine use disorder with antipsychotics (risperidone or aripiprazole) in people with comorbid OUD.[6] There was moderate-strength evidence that disulfiram worsened treatment retention (6 RCTs, n=605, RR 0.86, 95 % CI 0.77 to 0.95).[6] Low-strength evidence from 3 RCTs showed that psychostimulants (dexamphetamine or mazindol) may reduce cocaine use, though the difference was not statistically significant (n=115; standard MD 0.35; 95 % CI -0.05 to 0.74).[6] Three trials compared buprenorphine directly with methadone in people with cocaine use disorder, and moderate strength of evidence showed no significant difference in treatment retention when all three studies were pooled (N = 309, RR 1.17, 95 % CI 0.91 to 1.51).[6] There was only 1 trial for methamphetamine use disorder, which showed insufficient-strength evidence for a naltrexone implant in treating methamphetamine use disorder.[6] Most of the medications studied for cocaine use were ineffective, although psychostimulants warrant further study.[6]

After review, 18 systematic reviews were excluded due to poor quality,[15-18] wrong study design of included trials (e.g., observational only),[19-21] comparator (e.g., no control or placebo-controlled),[22,23] or outcome studied (e.g., non-clinical).[24-33]

New Guidelines:

Veterans Affairs/Department of Defense: Management of Substance Use Disorders

The VA/DoD Evidence-Based Practice Work Group published updated guidance for the management of substance use disorders in August 2021.[7] This guideline is designed to assist providers in screening, assessing, and treating patients with SUD.[7] For amphetamine, cocaine or methamphetamine use disorder, cognitive

behavioral therapy combined with contingency management has proven to be most effective.[7] Contingency management refers to treatment approaches that provide incentives (such as desirable times with monetary value) for achieving specific treatment goals.[7] For the purposes of this literature scan, key pharmacologic recommendations for OUD and alcohol use disorder (AUD) will be summarized.

Opioid Use Disorder

Patients who are provided medically supervised withdrawal, particularly those who do not receive formal, structured non-pharmacotherapy treatment, have high risk of relapse with resultant morbidity and mortality.[7] Furthermore, evidence suggests opioid agonist treatment (OAT) is more effective than other pharmacotherapies over time and improves safety.[7] Long-term methadone treatment has decades of demonstrated effectiveness.[7] Studies have also shown buprenorphine to be used successfully in office-based settings over increasingly longer periods.[7] Additionally, patients utilizing buprenorphine to assist with opioid discontinuation demonstrate positive patient outcomes when used for longer-term treatment versus a quick taper.[7]

There are situations where medically supervised withdrawal from opioids may be preferred over long-term OAT.[7] Examples include a taper of opioids using methadone, buprenorphine, or other symptom-treatment medications if patients: 1) are entering an environment that requires abstinence from any opioids (e.g., prison, court-ordered abstinence-based treatment programs), 2) wish to receive non-opioid treatment (e.g., treatment with injectable naltrexone), and 3) are in a profession that prohibits opioids (e.g., military, healthcare provider, air traffic controller).[7] Buprenorphine can provide relatively short, safe, medically supervised withdrawal treatment.[7] There is no consensus on the treatment duration for short-term medically supervised withdrawal from opioids.[7] Opioid withdrawal management is only indicated under certain circumstances (e.g., for patients with OUD who will be treated with extended-release naltrexone or because a patient chooses not to be treated with OAT).[7] If medically supervised opioid withdrawal is indicated, the preferred approach is initial stabilization with methadone or buprenorphine followed by a short or extended taper.[7]

Treatment retention is a metric of success utilized by some studies.[7] One study concluded that there are no statistically significant differences in treatment retention between methadone and buprenorphine; one study found methadone was superior to placebo; and three RCTs concluded buprenorphine may be more effective than methadone.[7] Buprenorphine and methadone have both been found to be more effective than clonidine.[7] No evidence was identified to support the addition of clonidine to a regimen of buprenorphine or methadone.[7] The quality of the evidence was low due to small sample sizes, high attrition rates, and imprecision.[7]

Recommendations to Manage Opioid Use Disorder:

- Recommend *against* withdrawal management without MAT due to high risk of relapse and overdose (strong recommendation; low QoE).[7]
- For patients with OUD for whom opioid withdrawal management is indicated:
    - Buprenorphine/naloxone in any setting; or
    - Methadone or buprenorphine/naloxone provided through an accredited Opioid Treatment Program (weak recommendation; low QoE).[7]
    - If methadone and buprenorphine is contraindicated or unavailable, clonidine or lofexidine are reasonable second-line agents (weak recommendation; low QoE).[7]
- For patients with OUD for whom MAT is recommended:
    - Buprenorphine/naloxone in any setting or methadone or buprenorphine/naloxone provided through an accredited Opioid Treatment Program (strong recommendation; high QoE); or
    - Extended-release intramuscular naltrexone (weak recommendation; low QoE).[7]
- There is insufficient evidence to recommend any specific FDA-approved formulation or routes of delivery of buprenorphine (without naloxone).[7]
- There is insufficient evidence to recommend for or against oral naltrexone.[7]

Pregnant Individuals with Opioid Use Disorder

In 2012, the incidence of maternal opioid use at delivery had increased more than 4-fold in the previous 10 years.[7] Similarly, the incidence of neonatal abstinence syndrome identified at delivery increased almost 3-fold during the same time period.[7] Methadone is the most common medication to treat pregnant women with OUD and has been associated with positive maternal and neonatal outcomes.[7] Since the advent of buprenorphine to treat OUD, there has been increased interest in using it to treat OUD in pregnancy.[7] Buprenorphine has been found to improve maternal and infant outcomes among pregnant patients with OUD, particularly with incidence and severity of neonatal abstinence syndrome and opioid-use related outcomes.[7] One RCT showed that treatment with buprenorphine was associated with similar maternal and infant outcomes compared with methadone.[7] There is currently no evidence to suggest that buprenorphine/naloxone carries additional risk compared to buprenorphine alone in pregnancy.[7]

The workgroup did not issue specific recommendations for managing pregnant individuals with OUD. However the guidance states that patient choice is an important factor in deciding between methadone and buprenorphine in pregnancy.[7] Providers should consider the availability of medication, as buprenorphine is more widely available in some settings than methadone.[7]

Alcohol Use Disorder

Moderate-quality evidence showed that naltrexone improved alcohol consumption outcomes (e.g., percent heavy drinking days, number of drinks per day, return to heavy drinking, and percent drinking days) for the treatment of AUD.[7] A 2014 meta-analysis found topiramate improved combined abstinence and heavy drinking outcomes and may decrease alcohol reinforcement and the propensity to drink by reducing craving for alcohol through antagonism of glutamate receptors and inhibition of dopamine release.[34] While topiramate is not approved for AUD by the FDA, there is moderate-quality evidence that the drug significantly reduces heavy drinking and improves abstinence.[7] Side effects associated with naltrexone, including initial transient nausea, tend to be minimal, and there are options for monthly injection or once-daily dosing.[7] In contrast, topiramate may cause dizziness, negative cognitive effects, or weight loss. In the absence of contraindications, there is insufficient evidence to recommend one of these medications over the other and treatment should be individualized.[7]

Acamprosate and disulfiram may reduce alcohol consumption when used for the treatment of AUD, based on low-quality evidence.[7] Acamprosate may act by normalizing central glutamatergic dysregulation in AUD, thereby relieving symptoms of prolonged alcohol withdrawal.[7] Numerous European trials found acamprosate effective in improving consumption outcomes; however, some US trials have failed to show such benefits.[7] Two meta-analyses found acamprosate improved alcohol consumption outcomes relative to placebo, most notably return to drinking after abstinence.[7] Moderate-quality evidence of significantly elevated rates of certain adverse events (e.g., anxiety, diarrhea, and vomiting) suggests there is some level of harm associated with acamprosate.[7] The frequent daily dose administration required and large tablet size presents a challenge to many patients and can negatively affect treatment adherence.[7] Acamprosate may be considered for patients with AUD who are also taking prescribed opioids or who have significant hepatic damage/impairment since it is not subject to hepatic clearance.[7] Patients who are highly motivated, abstinent before initiation, and not discouraged by the burden of three-times daily dosing are well suited for acamprosate.[7]

A meta-analysis of 22 RCTs showed statistically significant efficacy of disulfiram for AUD compared to a variety of control conditions.[7] Because the action of disulfiram depends on the expectation of adverse effects, it should not be given to patients who are unable to consider the consequences of alcohol consumption while taking disulfiram.[7] Low-quality evidence suggests there are potential harms associated with disulfiram, including increased risk of adverse events.[7] Disulfiram should only be used when abstinence is the goal, established with patient concurrence, and when initiated with addiction-focused counseling.[7] There was low-quality evidence for all reported disulfiram outcomes as a result of very serious limitations for overall abstinence outcomes and serious limitations for other consumption outcomes (i.e., return to drinking, percent drinking days).[7]

The effects of gabapentin likely occur through modulation of gamma-aminobutyric acid (GABA) activity in the amygdala associated with AUD.[7] The need for frequent daily dosing may make adherence difficult for some patients. There are increased concerns regarding the misuse potential of gabapentin. [7] Low-quality evidence from one RCT showed that gabapentin in combination with counseling significantly improved rates of abstinence and heavy drinking in individuals with alcohol dependence; however, the single-site setting and high dropout rate raised concerns regarding its potential for bias and limited generalizability.[7] Another RCT demonstrated the addition of gabapentin to oral naltrexone improved drinking outcomes relative to naltrexone alone in the first 6 weeks after drinking cessation.[7] Gabapentin may be an option for patients with AUD and co-occurring neuropathic pain, or for some with sleep disorders.[7] Also, since gabapentin is eliminated renally, it may be an option for patients with clinically significant hepatic disease.[7] More research is needed on the safety and effectiveness of gabapentin for AUD.[7]

Recommendations to Manage Alcohol Use Disorder:

- For patients with moderate or severe AUD:
  - Naltrexone (oral or extended-release) or topiramate (strong recommendation; moderate QoE).[7]
  - Acamprosate or disulfiram (weak recommendation; low QoE).[7]
- For patients with moderate or severe AUD for whom naltrexone, topiramate, acamprosate or disulfiram is contraindicated or ineffective:
  - Gabapentin (weak recommendation; low QoE).[7]

After review, one guideline was excluded due to poor quality.[35]

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts[36]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Buprenorphine	BUPRENEX	06/17/2022	Warnings	Buprenorphine may prolong the QT interval by 15 msec or more. This QTc prolongation effect does not appear to be mediated by hERG channels and is unlikely to be pro-arrhythmic when used alone in patients without risk factors. The risk of combining buprenorphine with other QT-prolonging agents is not known. Consider these observations in clinical decisions when prescribing buprenorphine to patients with risk factors such as hypokalemia, bradycardia, recent conversion from atrial fibrillation, congestive heart failure, digitalis therapy, baseline QT prolongation, subclinical long-QT syndrome, or severe hypomagnesemia.
Methadone	DOLOPHINE METHADOSE	06/02/2021	Use in Specific Populations: Pregnancy	Most available data on methadone use in pregnancy do not indicate an increased risk of major malformations. Pregnant individuals in a methadone treatment program have improved prenatal care leading

				to reduced incidence of obstetric and fetal complications and neonatal morbidity and mortality when compared to pregnant individuals who use illicit drugs.

Buprenorphine Sublingual and Buccal Administration: FDA Drug Safety Communication

The FDA issued a drug safety communication in January 2022 regarding transmucosal administration of buprenorphine.[8] Dental problems have been reported with buprenorphine products dissolved in the mouth.[8] The dental problems include tooth decay, cavities, oral infections, and loss of teeth.[8] They can be serious and have been reported even in patients with no history of dental issues.[8] Three hundred five cases of dental problems have been identified (131 cases classified as serious) with buprenorphine products dissolved in the mouth.[8] These only include cases reported to FDA or published in the medical literature, so there may be additional cases. The average age of the patients was 42 years, but those as young as 18 years were also affected.[8] Most cases were in patients using the medicines for OUD; however, 28 cases of dental problems occurred in patients using it to treat pain.[8] In 26 cases, patients had no prior history of dental problems.[8] Some cases reported dental problems occurring as soon as 2 weeks after treatment began, with the median time to diagnosis being approximately 2 years after starting treatment.[8] Many cases were reported by health care professionals and provided documentation of extensive dental adverse events. Of the 305 cases, 113 mentioned two or more teeth were affected.[8] The most common treatment for these dental problems was tooth extraction/removal, which was reported in 71 cases.[8]

The FDA advises practitioners to refer their patients to a dentist as soon as possible after starting transmucosal buprenorphine.[8] Counsel patients about the potential for dental problems and the importance of taking extra steps after the medicine has completely dissolved, including to gently rinse their teeth and gums with water and then swallow.[8] Patients should be advised to wait at least 1 hour before brushing their teeth. Dentists treating someone taking a transmucosal buprenorphine product should perform a baseline dental evaluation and caries risk assessment, establish a dental caries preventive plan, and encourage regular dental checkups.[8]

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
naltrexone microspheres	VIVITROL	INTRAMUSC	SUS ER REC	Y
acamprosate calcium	ACAMPROSATE CALCIUM	ORAL	TABLET DR	Y
buprenorphine	SUBLOCADE	SUBCUT	SOLER SYR	Y
buprenorphine HCl/naloxone HCl	BUPRENORPHINE-NALOXONE	SUBLINGUAL	FILM	Y
buprenorphine HCl/naloxone HCl	SUBOXONE	SUBLINGUAL	FILM	Y
buprenorphine HCl/naloxone HCl	BUPRENORPHINE-NALOXONE	SUBLINGUAL	TAB SUBL	Y
buprenorphine HCl/naloxone HCl	ZUBSOLV	SUBLINGUAL	TAB SUBL	Y
naltrexone HCl	DEPADE	ORAL	TABLET	Y
naltrexone HCl	NALTREXONE HCL	ORAL	TABLET	Y
naltrexone HCl	REVIA	ORAL	TABLET	Y
disulfiram	DISULFIRAM	ORAL	TABLET	V
buprenorphine HCl	BUPRENORPHINE HCL	SUBLINGUAL	TAB SUBL	V
lofexidine HCl	LUCEMYRA	ORAL	TABLET	N

Appendix 2: New Comparative Clinical Trials

A total of 181 citations were manually reviewed from the initial literature search. After further review, 180 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Trivedi MH, et al[37] DB, MC, PC, RCT	1. Naltrexone ER 380 mg IM every 3 weeks and Bupropion ER 450 mg po once daily Vs. 2. Placebo IM and PO once daily 2 stages lasting 6 weeks each	Adults aged 18 to 65 yo with moderate or severe methamphetamine use disorder Stage 1: n=403 Stage 2: n=225 (Sequential parallel comparison study design: Participants who did not respond to placebo in Stage 1 were re-	Response: defined as at least 3 methamphetamine-negative urine samples out of 4 samples obtained at 6 and 12 weeks	Percent of Responders in Stage 1 1. 18/109 (16.5%) 2. 10/294 (3.4%) Percent of Responders in Stage 2 1. 13/114 (11.4%) 2. 2/111 (1.8%) Weighted treatment effect (both stages combined) 1. 13.6% 2. 2.5% Difference: 11.1 $\pm$ 2.5% 95% CI: not calculated	Low attrition and high adherence to trial regimen may limit generalizability to general population 69% of participants were men, which limits applicability to women 71% of participants were White Sequential parallel study design may be difficult to replicate

	Total duration: 12 weeks	randomized 1:1 to treatment or placebo in Stage 2)		Wald z-test statistic: 4.53; P<0.001	Use of weighted combination for response analysis enhanced he likelihood of detecting treatment efficacy
Abbreviations: DB = double-blind; ER = extended release; IM = intramuscular; MC = multi-center; PC = placebo-controlled; PO = oral; RCT = randomized clinical trial; SL = sublingual; YO = years old					

Appendix 3: Abstracts of Comparative Clinical Trials

Bupropion and Naltrexone in Methamphetamine Use Disorder[37]

BACKGROUND: The use of naltrexone plus bupropion to treat methamphetamine use disorder has not been well studied.

METHODS: We conducted this multisite, double-blind, two-stage, placebo-controlled trial with the use of a sequential parallel comparison design to evaluate the efficacy and safety of extended-release injectable naltrexone (380 mg every 3 weeks) plus oral extended-release bupropion (450 mg per day) in adults with moderate or severe methamphetamine use disorder. In the first stage of the trial, participants were randomly assigned in a 0.26:0.74 ratio to receive naltrexone–bupropion or matching injectable and oral placebo for 6 weeks. Those in the placebo group who did not have a response in stage 1 underwent rerandomization in stage 2 and were assigned in a 1:1 ratio to receive naltrexone–bupropion or placebo for an additional 6 weeks. Urine samples were obtained from participants twice weekly. The primary outcome was a response, defined as at least three methamphetamine-negative urine samples out of four samples obtained at the end of stage 1 or stage 2, and the weighted average of the responses in the two stages is reported. The treatment effect was defined as the between-group difference in the overall weighted responses.

RESULTS: A total of 403 participants were enrolled in stage 1, and 225 in stage 2. In the first stage, 18 of 109 participants (16.5%) in the naltrexone–bupropion group and 10 of 294 (3.4%) in the placebo group had a response. In the second stage, 13 of 114 (11.4%) in the naltrexone–bupropion group and 2 of 111 (1.8%) in the placebo group had a response. The weighted average response across the two stages was 13.6% with naltrexone–bupropion and 2.5% with placebo, for an overall treatment effect of 11.1 percentage points (Wald z-test statistic, 4.53; P<0.001). Adverse events with naltrexone–bupropion included gastrointestinal disorders, tremor, malaise, hyperhidrosis, and anorexia. Serious adverse events occurred in 8 of 223 participants (3.6%) who received naltrexone–bupropion during the trial.

CONCLUSIONS: Among adults with methamphetamine use disorder, the response over a period of 12 weeks among participants who received extended-release injectable naltrexone plus oral extended-release bupropion was low but was higher than that among participants who received placebo. (Funded by the National Institute on Drug Abuse and others)

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) 1996 to November Week 2 2022; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to November 18, 2022

1. acamprosate.mp.	844
2. exp DISULFIRAM/	1191
3. exp NALTREXONE/	5931
4. BUPRENORPHINE/	5779
5. BUPRENORPHINE, NALOXONE DRUG COMBINATION/	492
6. lofexidine.mp.	125
7. Methadone/	8047
8. Alcoholism/	37128
9. Substance-Related Disorders/	66270
10. Methamphetamine/	8265
11. Cocaine/	15321
12. Analgesics, Opioid/	54199
13. Cannabis/	8248
14. 1 or 2 or 3 or 4 or 5 or 6 or 7	19436
15. 8 or 9 or 10 or 11 or 12 or 13	177014
16. 14 and 15	8352
17. Limit 16 to (english language and humans and yr="2020 -Current" and (clinical trial, phase iii or meta-analysis or practice guideline or randomized controlled trial or "systematic review"))	181

Buprenorphine and Buprenorphine/Naloxone

Goals:

- Prevent use of high-dose transmucosal buprenorphine products for off-label indications.

Length of Authorization:

- Up to 6 months

Requires PA:

- Transmucosal buprenorphine products that exceed an average daily dose of 24 mg per day

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is the diagnosis funded by the OHP?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; not funded by OHP
2. Is the prescription for opioid use disorder (opioid dependence or addiction)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the prescription for a transmucosal formulation of buprenorphine (film, tablet) with an average daily dose of more than 24 mg (e.g., >24 mg/day or >48 mg every other day)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4

Approval Criteria		
4. Is the requested medication a preferred agent?	**Yes:** Approve for anticipated length of treatment or 6 months, whichever is less. Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.	**No:** Go to #5
5. Will the prescriber switch to a preferred product? Note: Preferred products are reviewed for comparative safety and efficacy by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for anticipated length of treatment or 6 months, whichever is less. Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.

P&T/DUR Review: *2/23 (DM); 12/22; 12/20;11/19; 1/19; 1/17; 9/16; 1/15; 9/09; 5/09*
Implementation: *1/1/2020; 3/1/2019; 4/1/2017; 9/1/13; 1/1/10*

Lofexidine - RETIRE

Goals:

- Encourage use of substance use disorder medications on the Preferred Drug List.
- Restrict use of lofexidine to medically appropriate use based on FDA-approved indications.

Length of Authorization:

- Up to 14 days

Requires PA:

- Lofexidine

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication? (mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults)	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for up to 14 days of total therapy. Note: FDA approved indication is for up to 14 days of therapy AND Notify prescriber concomitant naloxone is recommended if not present in claims history.

P&T/DUR Review: 2/23 (DM); 12/22 (DM); 12/20 (DM); 11/19; 1/19
Implementation: Retired 4/1/23; 3/1/19