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Drug Class Literature Scan: Substance Use Disorders, Opioid and Alcohol

Date of Review: October 2023

Date of Last Review: February 2023
Literature Search: 01/01/22 – 08/10/23

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

Plain Language Summary:

- The Food and Drug Administration (FDA) has approved these medicines to treat substance use disorders:
  - Lofexidine, methadone, buprenorphine, naloxone, and naltrexone for opioid use disorder.
  - Naltrexone, acamprosate, and disulfiram for alcohol use disorder.
- New evidence shows that methadone may be better than buprenorphine in helping people with opioid use disorder stay in treatment, but evidence is mixed. People with opioid use disorder have to go to their provider's office to take each dose of methadone, but this isn't required for buprenorphine tablets.
- Evidence shows that naltrexone may help people decrease gambling, but benefit is very uncertain.
- Naltrexone is probably more beneficial than baclofen for alcohol use disorder. Baclofen is a medicine that relaxes muscles, and we do not know if it will reduce alcohol use.
- 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 32 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.
- We do not recommend any changes to this policy.

Conclusions:

- A systematic review evaluating buprenorphine compared to methadone for treatment of adults with opioid use disorder (OUD) found similar rates of retention at 1 month, but slightly higher treatment retention with methadone compared to buprenorphine for other time points up to 24 months (relative risk [RR] 0.65; 95% confidence interval [CI] 0.51 to 0.84). [1] At 12 months, treatment retention was on average 43% (95% CI 39 to 47) with sublingual buprenorphine and 47% (95% CI 38 to 56) for methadone.[1] There were no apparent differences in adherence to treatment or extra-medical opioid use between groups, and there was insufficient evidence for other outcomes of interest including use of other drugs, cravings, withdrawal symptoms, global functioning, treatment satisfaction, engagement with criminal justice system, non-fatal opioid overdose, and serious adverse events.[1]
- A systematic review evaluating therapies for problematic gambling found some evidence that opioid antagonists, naltrexone and nalmefene, given over 10 to 16 weeks may reducing gambling symptom severity but may not improve response to treatment.[2] The magnitude of benefit remains uncertain and is likely to change with additional research.[2]

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- A systematic review found insufficient evidence to compare baclofen to naltrexone or acamprosate for treatment of alcohol use disorder. Baclofen may increase the risk of relapse compared to naltrexone (RR 2.50; 95% CI 1.12 to 5.56; n=60; 1 RCT; insufficient evidence), but evidence is very limited.[3]
- A systematic review evaluating efficacy of treatments for alcohol use disorder in low and middle-income countries found low quality evidence that combination use of pharmacologic and psychosocial interventions reduced harmful alcohol use and improved treatment remission compared to psychosocial interventions alone.[4] There was moderate quality evidence that combination treatment did not improve retention in treatment.[4] Limitations in the evidence precluded conclusions regarding pharmacologic treatment alone for outcomes of harmful alcohol use, remission, or relapse in low and middle-income countries.[4] Data from this review may be most applicable to Medicaid members who have immigrated to Oregon.
- The Food and Drug Administration (FDA) approved a new formulation of extended-release buprenorphine in 2023 based on results from a phase 3 randomized controlled trial (RCT) that demonstrated weekly or monthly subcutaneous injections were non-inferior to daily administration of sublingual buprenorphine.[5] The primary study outcomes were the proportion of opioid-negative urine drug screens from 1 to 24 weeks (35.1% vs. 28.4%; difference of 6.7%; 95% CI -0.1 to 13.6) and response to treatment based on opioid-negative urine drug screens at pre-specified times (17.4% vs. 14.4%; difference of 3.0%; 95% CI -4.0 to 9.9).[5]

Recommendations:
- No PDL changes are recommended based on new clinical evidence.
- After evaluation of costs in executive session, the P&T Committee recommended SUBLOCADE (buprenorphine) be voluntary non-preferred and BRIXADI (buprenorphine) be preferred based on supplemental rebate offers for 2024.

Summary of Prior Reviews and Current Policy
- Recent guidelines recommend either buprenorphine or methadone as first-line treatment options for opioid use disorder.[6] Methadone and injectable formulations of buprenorphine are administered in supervised settings and sublingual buprenorphine can be given in a non-supervised setting (e.g., dispensed by a pharmacy and taken by the member at home).
- For alcohol use disorder, recent guidelines from the Department of Veterans Affairs (VA) and Department of Defense (DoD) suggest naltrexone and topiramate for alcohol use disorder.[6] Acamprosate and disulfiram are suggested as first-line alternatives, and gabapentin is suggested as second-line therapy.[6]
- State law currently prohibits use of prior authorization (PA) within the first 30 days for drugs to treat substance use disorders. Multiple drugs for opioid or alcohol use disorder are currently preferred without PA in the fee-for-service (FFS) program including acamprosate tablets, buprenorphine/naloxone films and tablets (SUBOXONE, ZUBSOLV and generics), naltrexone tablets and injection (DEPADE, REVIA, VIVITROL and generics), and buprenorphine (SUBLOCADE) monthly injection. Prior authorization is required for sublingual buprenorphine formulations prescribed for more than 32 mg daily and for lofexidine which is non-preferred.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (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:

A 2023 systematic review evaluated efficacy of methadone compared to buprenorphine for treatment of adults with opioid use disorder.[1] The review excluded people who were pregnant and studies evaluating buprenorphine for detoxification. Primary outcomes for the systematic review included retention in treatment, adherence to treatment, and extra-medical opioid use. The review identified 32 RCTs (n=5,808) and 69 observational studies (n=323,340) comparing buprenorphine and methadone. Fifty-one RCTs (n=11,644) and 124 observational trials (n=700,035) evaluating treatment retention with buprenorphine were also included. The mean age of participants was 27 years and 66% of people identified as male. More than half of trials were conducted in North America (49 RCTs and 113 observational trials). Fifteen trials evaluated buprenorphine use during hospitalization, and 7 trials evaluated buprenorphine during incarceration or post-release from incarceration. Sublingual formulations of buprenorphine were studied in all except one trial. All observational trials had some risk of bias concerns, primarily due to confounding. About 25% of observational trials had serious concerns. There were some risk of bias concerns, primarily due to the randomization process, for more than half of RCTs. There was high risk of bias for about 25% of RCTs based on missing outcome data. Authors noted potential for publication bias, bias derived from *post-hoc* analyses, and selective outcome reporting. Sensitivity analyses were conducted based on trial quality and outcomes did not appear to differ based on study quality. Primary results are outlined below.

- Retention in treatment: There was no difference between methadone and buprenorphine at 1 month for observational studies or RCTs. In both RCTs and observational studies, methadone had better treatment retention at subsequent time points up to 24 months (RR 0.65; 95% CI 0.51 to 0.84) compared to buprenorphine. At 12 months treatment retention was on average 43% (95% CI 39 to 47%) with sublingual buprenorphine and 47% (95% CI 38 to 56) for methadone. Data was limited by high heterogeneity (I^2 of 57% to 99%). Sensitivity analyses indicated that buprenorphine retention at 1 month varied based on publication date which may be an indicator of changing clinical practice over time. Publication date was not a significant factor for other outcomes. Retention also varied by location (with lower retention with buprenorphine in studies done in Australasia and higher retention rates in eastern European studies). Individuals recruited from clinic sites also had higher retention rates with buprenorphine compared to individuals identified via databases which generally included a broader population.
- Adherence to treatment: Only 3 RCTs and 2 observational studies evaluated adherence to treatment. Adherence was evaluated using pill count in 3 studies, visits attended in 2 studies and biological methods in one study. Buprenorphine and methadone had similar adherence rates.
- Extra-medical opioid use: In 3 RCTs, extra-medical opioid use evaluated via urinalysis was lower for people treated with buprenorphine, but there were no apparent differences in observational studies or when evaluating extra-medical opioid use by self-report.
- Secondary outcomes were rarely evaluated in more than a few trials. Outcomes included use of other drugs, cravings, withdrawal symptoms, global functioning, treatment satisfaction, engagement with criminal justice system, non-fatal opioid overdose, and serious adverse events. Overall, there was insufficient evidence of differences between buprenorphine and methadone for these outcomes.

Authors noted other areas where there was insufficient published evidence including: outcomes for people dependent on fentanyl, extended-release buprenorphine compared to methadone, effects of dose on treatment retention, needs of different populations and how these might impact outcomes, supervised versus unsupervised dosing, and data on clinically relevant outcomes like non-fatal overdose, criminal justice system engagement, and global functioning.

A 2023 Cochrane review evaluated efficacy and safety of interventions to treat alcohol use disorder in low and middle-income countries.[4] Generally, harms related to alcohol use are disproportionally higher in low and middle-income countries compared to high-income countries. Studies note similar trends related to harmful alcohol use for people with lower socioeconomic status who live in high-income countries. While prevalence of any drinking tends to be lower among low socioeconomic groups, people who report drinking tend to have a more harmful pattern of drinking. Both pharmacologic and psychosocial interventions were included in this review. Of the 66 RCTs included, 6 studies evaluated pharmacological treatment alone and 8 evaluated combined pharmacologic and psychosocial treatment. Drugs included disulfiram, naltrexone, acamprosate, ondansetron, topiramate, gabapentin, baclofen, mirtazapine, and amitriptyline. The primary outcome was harmful alcohol use; secondary outcomes included retention in treatment and adverse effects. Trials were most commonly conducted in India (n=14), Brazil (n=12), Thailand (n=9), South Africa (n=5), and Kenya (n=4). They predominantly included male patients (median enrollment of 89% for trials that recruited both men and women). Data was limited by substantial heterogeneity in study design. Risk of bias was high for all interventions primarily from lack of blinding, high attrition rates, and selective outcome reporting. Duration of trials was relatively short (6 months for most trials) and many outcomes were evaluated using measures that have not been validated. Data may be most applicable to Medicaid members who have immigrated to Oregon. Results from the analysis are outlined here:

- There is low quality evidence that combination use of pharmacologic and psychosocial interventions are more effective at reducing harmful alcohol use compared to psychosocial interventions alone (standardized mean difference [SMD] = -0.43, 95% CI -0.61 to -0.24; I^2= 0%; n=475, 4 RCTs). Drugs evaluated in this analysis included naltrexone, disulfiram, ondansetron, and topiramate. Remission was slightly improved with combination pharmacological and psychosocial treatment compared to psychosocial interventions alone (RR=1.19, 95% CI 1.01 to 1.40; I2=18%; n = 462, 4 RCTs).
- There is insufficient evidence to determine if pharmacologic treatment alone reduces harmful alcohol use. No RCTs evaluating pharmacologic treatments assessed this outcome compared to placebo or another active treatments.
- Two trials compared acamprosate to another active therapy (baclofen, naltrexone, or disulfram). These studies found higher rates of relapse and lower rates of remission for members receiving acamprosate compared to another pharmacologic treatment (RR = 0.58, 95% CI 0.42 to 0.79; I^2=15%, 2 RCTs, n=171, insufficient evidence).
- Retention in treatment did not differ with acamprosate or gabapentin compared to placebo (RR 1.13; 95% CI 0.89 to 1.44; I^2=46%; n=247; 3 RCTs, low quality evidence) or with the combination of pharmacologic therapy and psychosocial interventions compared to psychosocial interventions alone (RR = 1.15, 95% CI 0.95 to 1.40, n=363, 3 RCTs, moderate quality evidence).

A 2023 Cochrane review evaluated efficacy of baclofen for alcohol use disorder.[3] Of the 17 RCTs included in the review, baclofen was compared to acamprosate or naltrexone in only 2 studies each.[3] Overall authors found insufficient evidence that baclofen may increase the risk of relapse (RR 2.50; 95% CI 1.12 to 5.56; n=60; 1 RCT) and decrease the number of people with an adverse event (RR 0.35; 95% CI 0.15 to 0.80; n=80; 2RCTs) compared to naltrexone.[3] There was no difference in any efficacy or safety outcomes when comparing baclofen to acamprosate based on one small RCT (n=60).[3] Baclofen tablets are available as a preferred muscle relaxant in FFS. Guidelines updated in 2021 from the VA/DOD recommend against use of baclofen for alcohol use disorder based on evidence from 2 RCTs which provided low quality evidence for efficacy but had inconsistent results for alcohol consumption outcomes.[6]

A 2022 Cochrane review evaluated treatments for management of disordered and problem gambling.[2] Treatments evaluated in this review included mood stabilizers, antidepressants, antipsychotics, and opioid antagonists. Studies were excluded if they evaluated efficacy of combination pharmacotherapy and psychosocial therapy. The primary outcome was reduction in severity of gambling symptoms. This summary focuses on data for opioid antagonists, which are included in this PDL class. Oral naltrexone was evaluated in 4 studies and 2 studies evaluated nalmefene. Most studies had risk of bias concerns, and there was a large amount of statistical heterogeneity across studies.[2] Duration of trials was on average 10 to 16 weeks and symptom severity was evaluated using a variety of clinician or self-reported measures.[2] Compared to placebo, opioid antagonists reduced mean gambling severity symptoms (SMD 0.46; 95% CI 0.74 to 0.19;

n=259; 3 RCTs; low quality evidence). A standardized mean difference of 0.46 generally represents a medium effect size.[2] However, there was no difference in responder status (assessed by gambling abstinence or improvement on other various measures) with opioid antagonists compared to placebo (RR 1.65; 95% CI 0.86 to 3.14; n=562; 4 RCTs; very low quality evidence).[2] Low quality evidence from a single RCT (n=77) also showed opioid antagonists improved depressive symptoms (SMD 0.76; 95% CI 1.29 to 0.23), anxiety symptoms (SMD 1.36; 95% CI 1.96 to 0.83), and functional impairment (SMD 0.53; 95% CI 1.06 to 0.01) at 18 weeks compared to placebo.[2] There was no studies assessing gambling expenditure, gambling frequency, or time spent gambling. There was insufficient information to compare nalmefene and naltrexone, to explore effects of different doses, or examine long-term outcomes. Authors of the review concluded that there is preliminary support for opioid antagonists for reducing gambling symptom severity, but not response to treatment in the short-term.[2] The magnitude of benefit remains uncertain and is likely to change with additional research.[2]

After review, 7 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
No new high quality guidelines were identified.

New Formulations:
In May 2023, the FDA approved Brixadi™, an extended-release subcutaneous buprenorphine injection that can be administered monthly or weekly. RCTs evaluating efficacy and safety of this formulation are detailed in **Table 1**. The primary phase 3 trial used for FDA approval evaluated subcutaneous buprenorphine compared to sublingual buprenorphine/naloxone tablets for outcomes of opioid-negative urine drug screens, self-reported opioid use, and retention in treatment.[5] Outcomes were assessed at a variety of time points that were defined *a priori* in conjunction with regulatory authorities.[5] Subcutaneous buprenorphine was non-inferior to sublingual buprenorphine/naloxone for all primary and key secondary endpoints including response rate, mean percent of opioid-negative urine drug screens from weeks 1 to 24, and treatment retention.[5] Of the participants randomized, 69% of people given subcutaneous buprenorphine and 72.6% of people given sublingual buprenorphine/naloxone completed the 24 week randomized period. For efficacy outcomes, missing data was imputed as a positive urine drug screen.

Safety outcomes included severe adverse events, overdose, hospitalization, and discontinuation due to adverse events. People randomized to sublingual buprenorphine had a numerically higher rate of severe adverse events (7% vs. 2.8%), nonfatal serious events (6% vs. 2.3%), hospitalizations (5.6% vs. 1.4%), and drug overdoses (2.3% vs. 0%) when compared to people receiving subcutaneous buprenorphine.[5] People randomized to subcutaneous buprenorphine had numerically more treatment discontinuations due to adverse events (3.3% vs. 1.4%) compared to sublingual buprenorphine.[5] The most common adverse events included injection-site reactions (pain, pruritus, erythema), headache, constipation, and nausea.

A long-term observational study also evaluated safety and tolerability of extended-release buprenorphine over 12 months.[7] Of the 227 people enrolled, 84% (n=190) switched from sublingual buprenorphine treatment.[7] Patients with OUD were excluded if they had comorbid substance use disorder for a different substance other than opioids or had comorbid chronic pain requiring opioid therapy. About 56% of people enrolled were in the United States, and about 26% were previously arrested.[7] Heroin was the primary opioid of use for 59% of patients.[7] Serious adverse events occurred in 5% (n=12) of participants and 2% (n=5) of patients discontinued treatment due to an adverse event.[7] The most common adverse events were injection site reactions.

An open-label RCT conducted in Australia evaluated patient-reported outcomes associated with extended-release subcutaneous buprenorphine compared to daily sublingual therapy (**Table 1**).[8] The trial primarily enrolled participants with OUD, primarily people who were already on therapy with sublingual buprenorphine and were willing to continue with treatment for the duration of the trial. The primary outcome was treatment satisfaction at 24 weeks using the Treatment Satisfaction Questionnaire for Medication (TSQM) Global Satisfaction Score (range 0-100 with higher scores indicating more satisfaction).[8] The TSQM score evaluates 3 categories including effectiveness, side effects and convenience. The minimum clinically important difference for this score was not reported. Average satisfaction scores were 71 and 74 points at baseline for subcutaneous and sublingual groups, respectively.[8] After 24 weeks, scores had increased to 82 points for extended-release subcutaneous buprenorphine compared to 73 points with sublingual buprenorphine (MD 8.2 points; 95% CI 1.7-14.6; p=0.01).[8] This difference was driven primarily by the subcategory evaluating convenience. Secondary outcomes included treatment satisfaction using a variety of other scales, treatment retention and illicit opioid use evaluated by UDS. However, the study was not powered to determine differences in these secondary outcomes.

New FDA Safety Alerts:
No new FDA safety alerts were identified.

References:

1. Degenhardt L, Clark B, Macpherson G, et al. Buprenorphine versus methadone for the treatment of opioid dependence: a systematic review and meta-analysis of randomised and observational studies. *The lancet Psychiatry.* 2023;10(6):386-402.
2. Dowling N, Merkouris S, Lubman D, Thomas S, Bowden-Jones H, Cowlishaw S. Pharmacological interventions for the treatment of disordered and problem gambling. *The Cochrane database of systematic reviews.* 2022;9:CD008936.
3. Agabio R, Saulle R, Rosner S, Minozzi S. Baclofen for alcohol use disorder. *The Cochrane database of systematic reviews.* 2023;1:CD012557.
4. Greene MC, Kane J, Alto M, et al. Psychosocial and pharmacologic interventions to reduce harmful alcohol use in low- and middle-income countries. *The Cochrane database of systematic reviews.* 2023;5:CD013350.
5. Lofwall MR, Walsh SL, Nunes EV, et al. Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder: A Randomized Clinical Trial. *JAMA Intern Med.* 2018;178(6):764-773.
6. The Department of Veterans Affairs and the Department of Defense. VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF SUBSTANCE USE DISORDERS. 2021.
7. Frost M, Bailey GL, Lintzeris N, et al. Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM2038) in the treatment of adult out-patients with opioid use disorder. *Addiction (Abingdon, England).* 2019;114(8):1416-1426.
8. Lintzeris N, Dunlop AJ, Haber PS, et al. Patient-Reported Outcomes of Treatment of Opioid Dependence With Weekly and Monthly Subcutaneous Depot vs Daily Sublingual Buprenorphine: A Randomized Clinical Trial. *JAMA network open.* 2021;4(5):e219041.
9. Jutras-Aswad D, Le Foll B, Ahamad K, et al. Flexible Buprenorphine/Naloxone Model of Care for Reducing Opioid Use in Individuals With Prescription-Type Opioid Use Disorder: An Open-Label, Pragmatic, Noninferiority Randomized Controlled Trial. *The American journal of psychiatry.* 2022;179(10):726-739.
10. Brixadi (buprenorphine) extended-release injection for subcutaneous use. [package labeling]. Plymouth Meeting, PA: Braeburn Inc; May 2023.

Appendix 1: Current Preferred Drug List

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

Appendix 2: New Comparative Clinical Trials

A total of 165 citations were manually reviewed from the initial literature search. After further review, all except 3 randomized controlled trials were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). These remaining 3 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome(s)	Results	Notes/Limitations
Jutras-Aswad, et al, 2022.[9] NCT03033732 Phase 4, OL, MC, NI, RCT N=272	1. Buprenorphine/ naloxone, flexible dosing from 4 to 24 mg/day (n=138) 2. Methadone, flexible dosing from 30 mg to 120 mg/day (n=134)	Adults with prescription OUD People with pain requiring opioids or people who primarily used heroin were excluded.	Proportion of opioid-free urine drug screens over 24 weeks (NI margin of 15%)	Proportion of opioid-free UDS 1. 24% (SD 34.4) 2. 18.5% (SD 30.5) MD 5.6%; 95% CI -0.3 to ∞ P=0.040 NI established	Internal Validity An accidental protocol deviation affected allocation at 4 sites (14.7% of enrolled participants). High and differential attrition between groups (41% methadone and & 49% buprenorphine/naloxone groups). Missing data from UDS prior to March 2020 were

<table>
<tr><td>24 weeks</td><td>Take home doses were allowed after 2-3 months of supervised ingestion for methadone and after 2 weeks for buprenorphine/ naloxone</td><td>Canada
Enrollment from October 2017 to March 2020. Follow-up ended July 2020.</td><td></td><td>Various sensitivity analyses with different populations had similar results.</td><td>considered positive. After the pandemic, visits were conducted by telephone and no UDS were performed. Values were considered missing at random.

<u>Applicability:</u> Follow-up visits occurred every 2 weeks and participants were compensated $40 per visit. Protocols for take home medications may differ between Canada and the United States.</td></tr>
<tr><td>Lofwall, et al.[5]

NCT02651584

DB, double-dummy, NI, phase 3 RCT

N=428

24 weeks</td><td>1. buprenorphine SC weekly for 12 weeks then monthly
2. buprenorphine/naloxone SL tablets daily

Patients who tolerated one 4mg SL buprenorphine dose were randomized</td><td>Adults with moderate to severe OUD
- 61% male
- Mean age: 34 years
- Primarily heroin use: 70-71%
- COWS score: 12
- SOWS score: 31-32
- Fentanyl positive UDS:
o SC: 29%
o SL: 23%

35 sites in the US from December 2015 to October 2016

Exclusion criteria:
- MOUD in prior 60 days
- Chronic pain requiring opioids
- AIDS
- Suicidal ideation or behavior
- Prolonged QTc or risk of torsades de pointes
- ALT/AST >3x ULN
- Bilirubin or serum creatinine >1.5x ULN</td><td><u>Primary (NI margin)</u>
- Response rate* (10%)
- Mean percent of opioid-negative UDS at 1-24 weeks (11%)
<u>Secondary</u>
- Mean percent of opioid-negative samples examined by CDF** at 4-24 weeks (5%)
- Study retention (15%)</td><td><u>Response rate</u>
1. 37 (17.4%)
2. 31 (14.4%)
Difference: 3.0% (95% CI -4.0 to 9.9); p<0.001 for NI

<u>Mean % Negative UDS at 1-24 weeks</u>
1. 35.1% (SD 2.5)
2. 28.4% (SD 2.5)
Difference: 6.7% (95% CI -0.1 to 13.6); p<0.001 for NI

<u>Retention</u>
1. 147 (69%)
2. 156 (72.6%)
Difference -3.5% (95% CI -12.2 to 5.1); p=0.006 for NI

<u>Mean % negative (CDF) at 4-24 weeks</u>
1. 35.1% (SE 2.5)</td><td>Non-inferiority established for primary endpoints.

<u>Internal Validity</u>
Randomization via a central system, but baseline characteristics differed for:
<table><tr><td></td><td>SL</td><td>SC</td></tr><tr><td>male</td><td>66%</td><td>57%</td></tr><tr><td>employment</td><td>33%</td><td>35%</td></tr><tr><td>history of arrest</td><td>67%</td><td>61%</td></tr><tr><td>non-opioid drug use</td><td>69%</td><td>73%</td></tr><tr><td>Fentanyl use</td><td>23%</td><td>29%</td></tr></table>Staff administering SC injections were unblinded as appearance of the injection was not identical to placebo.
Attrition: ITT analysis used. 26% of UDS were missing and imputed as positive for illicit opioids.

<u>Applicability</u>
Frequent provider visits (e.g., weekly) and attendance stipends provided to patients may increase adherence and treatment retention and may not be reflective of current clinical practice. Adherence to sublingual tablets was not assessed. Only one treatment site was primary-care based.</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td>2. 26.7% (SE 2.5)
P=0.009 for NI</td><td></td></tr>
<tr><td>Lintzeris, et al. 2021.[8]

OL, MC, RCT

N=119

Duration: 24 weeks</td><td>1. Buprenorphine SC up to 32 mg weekly or 160 mg monthly (n=60)
2. Buprenorphine SL (most commonly with naloxone) up to 32 mg daily (n=59)</td><td>Adults with opioid dependence who were established on SL buprenorphine treatment
- Baseline TSQM score: 71-74
- Illicit opioid use: 38-32%
- Age: 44-45 yrs
- Duration of OUD: 19-20 yrs

Australia
October 2018 to September 2019</td><td><u>Primary</u>
Treatment satisfaction score at 24 weeks (TSQM Global Satisfaction Score; range 0-100 with higher scores indicating more satisfaction)

<u>Select secondary</u>
Treatment retention

Illicit opioid use by UDS</td><td>Treatment satisfaction at week 24 (baseline score 71-73)
1. 82.5 (SD 2.3)
2. 74.3 (SD 2.3)
MD 8.2 (95% CI 1.7-14.6) p=0.01

Treatment retention
1. 53 (88.3%)
2. 56 (93.3%)

Illicit opioid use by UDS
1. 69.9% (95% CI 60.6%-79.3%)
2. 73.5% (95%CI 64.1%-82.9%)
Not significant</td><td>Higher global treatment satisfaction with SC forms of buprenorphine compared to SL forms. The minimum clinically important difference for TSQM score was not reported.

<u>Internal Validity</u>
OL study design may increase risk of performance bias. Differences in study groups at baseline may increase risk of selection bias.
<table><tr><td></td><td>SL</td><td>SC</td></tr><tr><td>Heroin use</td><td>54%</td><td>73%</td></tr><tr><td>Hepatitis C</td><td>36%</td><td>57%</td></tr><tr><td>Amphetamine use</td><td>20%</td><td>40%</td></tr><tr><td>Depression</td><td>61%</td><td>48%</td></tr></table>
<u>Applicability</u>
Provider visits monthly and psychosocial interventions were provided in accordance with local guidelines. Possible differences in study setting between Australia & the United States.</td></tr>
</table>

*Responder defined as no illicit opioid use by UDS and self-report at pre-specified time points which included at least 2 of 3 assessments from 9 to 11 weeks, at week 12, and at least 5 of 6 assessments from 12 to 24 weeks including weeks 21 to 24.

**The cumulative distribution function of the percent of negative opioid assessments included data from urine drug screens and self-reports for negative illicit opioid use.[10] This type of analysis is often used when there is a lack of consensus on a responder threshold. It is intended to evaluate and show a graphical representation of a variety of responder thresholds. Treatment groups generally differentiated themselves at lower responder thresholds. If treatment response was defined as ≥80% negative opioid assessments, there was no difference between groups.[10]

Abbreviations: AIDS = acquired immunodeficiency syndrome; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CDF = cumulative distribution function; CI = confidence interval; COWS = clinical opiate withdrawal scale; DB = double-blind; ITT = intention to treat; MC = multicenter; MD = mean difference; MOUD = medication for opioid use disorder; OL = open label; OUD = opioid use disorder; NI = non-inferiority; RCT = randomized controlled trial; SC = subcutaneous; SD = standard deviation; SE = standard error; SL = sublingual; SOWS = subjective opiate withdrawal scale; TSQM = Treatment Satisfaction Questionnaire for Medication; UDS = urine drug screen; ULN = upper limit of normal; yrs = years

Appendix 3: Abstracts of Comparative Clinical Trials

Jutras-Aswad D, Le Foll B, Ahamad K, et al. Flexible Buprenorphine/Naloxone Model of Care for Reducing Opioid Use in Individuals With Prescription-Type Opioid Use Disorder: An Open-Label, Pragmatic, Noninferiority Randomized Controlled Trial. *The American journal of psychiatry.* 2022;179(10):726-739.

OBJECTIVE: Extensive exposure to prescription-type opioids has resulted in major harm worldwide, calling for better-adapted approaches to opioid agonist therapy. The authors aimed to determine whether flexible take-home buprenorphine/naloxone is as effective as supervised methadone in reducing opioid use in prescription-type opioid consumers with opioid use disorder.

METHODS: This seven-site, pan-Canadian, 24-week, pragmatic, open-label, noninferiority, two-arm parallel randomized controlled trial involved treatment-seeking adults with prescription-type opioid use disorder. Participants were randomized in a 1:1 ratio to treatment with sublingual buprenorphine/naloxone (target dosage, 8 mg/2 mg to 24 mg/6 mg per day; flexible take-home dosing) or oral methadone (=60-120 mg/day; closely supervised). The primary outcome was the proportion of opioid-free urine drug screens over 24 weeks (noninferiority margin, 15%). All randomized participants were analyzed, excluding one who died shortly after randomization, for the primary analysis (modified intention-to-treat analysis).

RESULTS: Of 272 participants recruited (mean age, 39 years [SD=11]; 34.2% female), 138 were randomized to buprenorphine/naloxone and 134 to methadone. The mean proportion of opioid-free urine drug screens was 24.0% (SD=34.4) in the buprenorphine/naloxone group and 18.5% (SD=30.5) in the methadone group, with a 5.6% adjusted mean difference (95% CI=-0.3, +). Participants in the buprenorphine/naloxone group had 0.47 times the odds (95% CI=0.24, 0.90) of being retained in the assigned treatment compared with those in the methadone group. Overall, 24 drug-related adverse events were reported (12 in the buprenorphine/naloxone group [N=8/138; 5.7%] and 12 in the methadone group [N=12/134; 9.0%]) and mostly included withdrawal, hypogonadism, and overdose.

CONCLUSIONS: The buprenorphine/naloxone flexible model of care was safe and noninferior to methadone in reducing opioid use among people with prescription-type opioid use disorder. This flexibility could help expand access to opioid agonist therapy and reduce harms in the context of the opioid overdose crisis.

Lofwall MR, Walsh SL, Nunes EV, et al. Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder: A Randomized Clinical Trial. *JAMA Intern Med.* 2018;178(6):764-773.

Importance: Buprenorphine treatment for opioid use disorder may be improved by sustained-release formulations.

Objective: To determine whether treatment involving novel weekly and monthly subcutaneous (SC) buprenorphine depot formulations is noninferior to a daily sublingual (SL) combination of buprenorphine hydrochloride and naloxone hydrochloride in the treatment of opioid use disorder.

Design, Setting, and Participants: This outpatient, double-blind, double-dummy randomized clinical trial was conducted at 35 sites in the United States from December 29, 2015, through October 19, 2016. Participants were treatment-seeking adults with moderate-to-severe opioid use disorder.

Interventions: Randomization to daily SL placebo and weekly (first 12 weeks; phase 1) and monthly (last 12 weeks; phase 2) SC buprenorphine (SC-BPN group) or to daily SL buprenorphine with naloxone (24 weeks) with matched weekly and monthly SC placebo injections (SL-BPN/NX group).

Main Outcomes and Measures: Primary end points tested for noninferiority were response rate (10% margin) and the mean proportion of opioid-negative urine samples for 24 weeks (11% margin). Responder status was defined as having no evidence of illicit opioid use for at least 8 of 10 prespecified points during weeks 9 to 24, with 2 of these at week 12 and during month 6 (weeks 21-24). The mean proportion of samples with no evidence of illicit opioid use (weeks 4-24) evaluated by a cumulative distribution function (CDF) was an a priori secondary outcome with planned superiority testing if the response rate demonstrated noninferiority.

Results: A total of 428 participants (263 men [61.4%] and 165 women [38.6%]; mean [SD] age, 38.4 [11.0] years) were randomized to the SL-BPN/NX group (n = 215) or the SC-BPN group (n = 213). The response rates were 31 of 215 (14.4%) for the SL-BPN/NX group and 37 of 213 (17.4%) for the SC-BPN group, a 3.0% difference (95% CI, -4.0% to 9.9%; P < .001). The proportion of opioid-negative urine samples was 1099 of 3870 (28.4%) for the SL-BPN/NX

group and 1347 of 3834 (35.1%) for the SC-BPN group, a 6.7% difference (95% CI, -0.1% to 13.6%; P < .001). The CDF for the SC-BPN group (26.7%) was statistically superior to the CDF for the SL-BPN/NX group (0; P = .004). Injection site adverse events (none severe) occurred in 48 participants (22.3%) in the SL-BPN/NX group and 40 (18.8%) in the SC-BPN group.

Conclusions and Relevance: Compared with SL buprenorphine, depot buprenorphine did not result in an inferior likelihood of being a responder or having urine test results negative for opioids and produced superior results on the CDF of no illicit opioid use. These data suggest that depot buprenorphine is efficacious and may have advantages.

Trial Registration: ClinicalTrials.gov Identifier: NCT02651584.

Lintzeris N, Dunlop AJ, Haber PS, et al. Patient-Reported Outcomes of Treatment of Opioid Dependence With Weekly and Monthly Subcutaneous Depot vs Daily Sublingual Buprenorphine: A Randomized Clinical Trial. *JAMA network open.* 2021;4(5):e219041.

Importance: Patient-reported outcomes in the treatment of opioid dependence may differ between subcutaneously administered depot buprenorphine and daily sublingual buprenorphine.

Objective: To compare patient satisfaction between depot buprenorphine and sublingual buprenorphine in adult outpatients with opioid dependence.

Design, Setting, and Participants: This open-label, randomized clinical trial was conducted among adult patients with opioid dependence at 6 outpatient clinical sites in Australia from October 2018 to September 2019. Data analysis was conducted from October 2019 to May 2020.

Interventions: Participants were randomized to receive treatment with weekly or monthly depot buprenorphine or daily sublingual buprenorphine over 24 weeks.

Main Outcomes and Measures: The primary end point was the difference in global treatment satisfaction, assessed by the Treatment Satisfaction Questionnaire for Medication (TSQM) version 1.4 (range, 0-100; higher score indicates greater satisfaction) at week 24. Secondary end points included other patient-reported outcomes, including quality of life, treatment burden, and health-related outcomes, as well as measures of opioid use, retention in treatment, and safety.

Results: A total of 119 participants (70 [58.8%] men; mean [SD] age, 44.4 [10.5] years) were enrolled, randomized to, and received either depot buprenorphine (60 participants [50.4%]) or sublingual buprenorphine (59 participants [49.6%]). From the initial sample of 120, a participant (0.8%) in the sublingual buprenorphine group withdrew consent and did not receive study treatment. All participants were receiving sublingual buprenorphine when enrolled. The mean TSQM global satisfaction score was significantly higher for the depot group compared with the sublingual group at week 24 (mean [SE] score, 82.5 [2.3] vs 74.3 [2.3]; difference, 8.2; 95% CI, 1.7 to 14.6; P = .01). Improved outcomes were also observed for several secondary end points after treatment with depot buprenorphine (eg, mean [SE] treatment burden assessed by the Treatment Burden Questionnaire global score, on which lower scores indicate lower burden: 13.2 [2.6] vs 28.6 [2.5]; difference, -15.4; 95% CI, -22.6 to -8.2; P < .001). Thirty-nine participants (65.0%) in the depot buprenorphine group experienced 117 adverse drug reactions, mainly injection site reactions of mild intensity following subcutaneous administration, and 12 participants (20.3%) in the sublingual buprenorphine group experienced 21 adverse drug reactions. No participants withdrew from the trial medication or the trial due to adverse events.

Conclusions and Relevance: In this study, participants receiving depot buprenorphine reported improved treatment satisfaction compared with those receiving sublingual buprenorphine. The results highlight the application of patient-reported outcomes as alternative end points to traditional markers of substance use in addiction treatment outcome studies.

Trial Registration: anzctr.org.au Identifier: ANZCTR12618001759280.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to August 10, 2023

1	acamprosate.mp. or exp Acamprosate/	988
2	lofexidine.mp.	225
3	exp buprenorphine/ or exp buprenorphine, naloxone drug combination/	7391
4	exp Naltrexone/	8676
5	exp Disulfiram/	3735
6	exp substance-related disorders/ or alcoholism/	311045
7	exp Alcohol Deterrents/	13140
8	exp Prescription Drug Misuse/	17229
9	1 or 2 or 3 or 4 or 5	19973
10	6 or 7 or 8	320659
11	9 and 10	17117
12	limit 11 to yr="2022 -Current"	1197
13	limit 12 to (english language and humans)	1085
14	limit 13 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)	165

Appendix 5: Key Inclusion Criteria

Population	People with substance use disorder
Intervention	Drugs in Appendix 1
Comparator	Drugs in Appendix 1
Outcomes	Quality of life, function, maintenance in treatment, abstinence, hospitalizations, mortality, non-fatal overdose
Setting	Outpatient

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 32 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 32 mg (e.g., >32 mg/day or >64 mg every other day)?	**Yes:** Go to #4	**No:** Go to #8
4. Is there documentation of inadequate symptom improvement with 32 mg daily?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is there recent documentation (within past month) from a urine drug screen indicating that buprenorphine is being taken?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Has the prescriber evaluated the PDMP in the past 3 months?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Does the member have access to naloxone?	**Yes:** Approve for 30 days. Subsequent requests for continuation of therapy will require documentation of objective clinical benefit with higher doses (e.g. improved management of OUD), documentation of a comprehensive treatment plan for OUD, and ongoing monitoring plan for safety risks.	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the requested medication a preferred agent?	**Yes:** Approve for 6 months. Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.	**No:** Go to #9
9. 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 6 months. Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.

P&T/DUR Review: *10/23; 8/23 (SS); 2/23; 12/22; 12/20;11/19; 1/19; 1/17; 9/16; 1/15; 9/09; 5/09*
Implementation: *9/1/23; 1/1/2020; 3/1/2019; 4/1/2017; 9/1/13; 1/1/10*