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

**Date of Review:** November 2019

**Date of Last Review:** January 2019

**Literature Search:** 01/01/2018–06/20/2019

**Current Status of PDL Class:**

See **Appendix 1**.

**Conclusions:**

- Since the last class update on drugs used to manage substance use disorders (SUDs), two new systematic reviews were published and 2 new buprenorphine/naloxone formulations received FDA approval.
- The Canadian Agency for Drugs and Technologies in Health (CADTH) issued a Rapid Response Report in April 2019 focused on recently published evidence for the use of buprenorphine in management of opioid use disorder (OUD).<sup>1</sup> Although there were some instances where specific formulations of buprenorphine demonstrated statistically significant improvements in outcomes of interest (e.g., reduction in opioid consumption, prevention of relapse, maintenance of abstinence, and retention into treatment) compared to other formulations, no clear patterns emerged regarding the comparative clinical effectiveness of buprenorphine for the treatment of OUD.<sup>1</sup> With respect to the safety of various formulations, none of the included studies reported statistically significant differences in the safety profiles of buprenorphine formulations.<sup>1</sup>
- In May 2019, CADTH published a report evaluating the use of buprenorphine for management of OUD during pregnancy.<sup>2</sup> The report identified a lack of evidence regarding the comparative effectiveness and safety of various buprenorphine or buprenorphine-naloxone formulations for the treatment of opioid use disorders during pregnancy.<sup>2</sup>

**Recommendations:**

- Based on the review of recently published evidence, no changes to the preferred drug list (PDL) or prior authorization (PA) criteria are recommended.
- After evaluation of costs in executive session, buprenorphine sublingual tablets, disulfiram tablets, and buprenorphine/naloxone film (Bunavail®) were designated as voluntary non-preferred and buprenorphine injection (Sublocade®) was designated as preferred. The recommendation was made to designate new products in the class as voluntary non-preferred.

**Summary of Prior Reviews and Current Policy**

A class update focused on drugs used to manage substance use disorders (SUDs) was presented to the Pharmacy and Therapeutics (P and T) Committee in January 2019. Current guidelines from the Veterans Administration and Department of Defense primarily recommend utilization of methadone (in the context of a treatment program), or buprenorphine/naloxone for patients with OUD (strong recommendation).<sup>3</sup> Buprenorphine alone may be considered for patients who are pregnant (weak recommendation), and extended-release injectable naloxone is recommended as an option for patients for whom opioid agonist therapy is contraindicated, unacceptable, or unavailable, and who have established opioid abstinence for at least 7 days without acute withdrawal symptoms (strong

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recommendation).<sup>3</sup> Two unique therapies were included in the January 2019 class update. In November 2017, the FDA approved buprenorphine extended-release injection (Sublocade™) to treat patients with moderate-to-severe OUD who have first received treatment with a transmucosal buprenorphine-containing product for at least 7 days.<sup>4</sup> In May 2018, lofexidine (Lucemyra™) received FDA approval for short-term (up to 14 days) mitigation of severe opioid withdrawal symptoms in adults to facilitate abrupt opioid discontinuation.<sup>5</sup> Lofexidine, a centrally acting alpha2-adrenergic receptor agonist, is structurally and pharmacologically similar to clonidine.<sup>5</sup> There is poor quality evidence from one published trial that adults undergoing acute withdrawal from opioids or heroin experienced less symptoms with lofexidine compared to placebo as assessed by the mean Short Opioid Withdrawal Scale (SOWS)-Gossop on day 3 of treatment.<sup>6</sup> After reviewing the class update, the P and T committee recommended the following:

- Make lofexidine non-preferred on the Prioritized Drug List (PDL) and implement PA criteria to ensure appropriate utilization.
- Add extended release subcutaneous buprenorphine injection (Sublocade™) to PA criteria for buprenorphine and buprenorphine/naloxone products.

In January 2017, in order to minimize barriers to care and provide increased access to medications for the treatment of OUD, the P and T Committee recommended removal of PA criteria for naltrexone extended release injection and preferred buprenorphine/naloxone sublingual tablets and film (unless the daily dose of buprenorphine exceeds 24 mg). At the January 2019 P and T Committee meeting, a policy evaluation assessing the impact of removing prior authorization (PA) requirements for preferred MAT for treatment of OUD was also presented. It was reported that utilization of buprenorphine/naloxone and medical claims for MAT continue to increase. After removal of the PA criteria in January 2017, approximately 83% of patients prescribed MAT had an initial paid claim compared to 40% of patients in the year prior to the PA removal. Off-label use of MAT appears to be limited. Approximately 85% of patients had a diagnosis of OUD based on available diagnoses or presence of medical claims for OUD. Utilization of non-pharmacological psychosocial support or enrollment in SUD treatment programs was limited. Only 39-40% of patients had at least one claim for non-pharmacological substance use disorder (SUD) services, and approximately 34% of patients had long-term utilization of non-pharmacological therapy after 3 months of treatment with MAT.

In the Oregon Health Plan (OHP) Fee-For-Service (FFS) program, preferred agents on the Preferred Drug List (PDL) include: buprenorphine/naloxone film and sublingual tablets, acamprostate tablets, naltrexone extended-release injection, and naltrexone tablets. **Appendix 1** lists the current PDL status for medications used in treatment of SUD. Buprenorphine sublingual tablets are restricted for use in pregnant females and all buprenorphine monotherapy products require PA as outlined in the clinical PA criteria listed in **Appendix 6**. In the second quarter of 2019 (May through September 2019), 75% of OHP FFS claims for SUD medications were for buprenorphine/naloxone, 13% of claims were for naltrexone, 11% of claims were for buprenorphine, and 1% of claims were for acamprostate.

### **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.

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## **New Systematic Reviews:**

### *Buprenorphine for Management of Opioid Use Disorder*

The Canadian Agency for Drugs and Technologies in Health issued a Rapid Response Report in April 2019 focused on recently published evidence for the use of buprenorphine in management of OUD.<sup>1</sup> Several formulations of buprenorphine are available for the treatment of OUD in Canada, including the single ingredient buccal film, buprenorphine extended-release injection, subcutaneous implant, as well as the combination product of buprenorphine with naloxone in a sublingual tablet. The CADTH search was limited to English-language documents published between January 1, 2014 and March 20, 2019. Two systematic reviews and 3 RCTs were identified regarding the clinical effectiveness and safety of various buprenorphine formulations for the treatment of OUD.<sup>1</sup> A primary limitation of the RCTs was that participants and outcome assessors were not blinded to the treatment received.<sup>1</sup> Given that several of the outcomes reported in these trials were based on subjective measures (e.g., Subjective Opiate Withdrawal Scale [SOWS] scores, opioid craving visual analogue scale scores, or self-reported use of heroin), the findings of open-label studies may be at risk for bias in either direction depending on the perceptions and expectations of participants and clinicians involved.<sup>1</sup> Though there were some instances where specific formulations of buprenorphine demonstrated statistically significant improvements in outcomes of interest (e.g., reduction in opioid consumption, prevention of relapse, maintenance of abstinence, and retention into treatment) compared to other formulations, no clear patterns emerged regarding the comparative clinical effectiveness of buprenorphine for the treatment of OUD.<sup>1</sup> With respect to the safety of various formulations, none of the included studies reported statistically significant differences in the safety profiles of buprenorphine formulations.<sup>1</sup>

### *Buprenorphine for Opioid Use Disorders during Pregnancy*

In May 2019, CADTH published a report evaluating the use of buprenorphine for management of OUD during pregnancy.<sup>2</sup> The search was limited to English language documents published between January 1, 2014 and April 8, 2019. Three evidence based guidelines met the inclusion-criteria and were included in the report.<sup>2</sup> One guideline was from the British Columbia Ministry of Health, one from the Society of Obstetricians and Gynecologists of Canada, and one from the World Health Organization (WHO).<sup>2</sup> The included guidelines were also supported by evidence of limited quantity and quality.<sup>2</sup> The report identified a lack of evidence regarding the comparative effectiveness, safety, and cost-effectiveness of various buprenorphine or buprenorphine-naloxone formulations for the treatment of opioid use disorders during pregnancy.<sup>2</sup> Two of three guidelines contained relevant recommendations that reflected this lack of high-quality comparative evidence.<sup>2</sup> These two guidelines recommended buprenorphine treatment in preference to the buprenorphine-naloxone formulation for opioid use disorders during pregnancy.<sup>2</sup> One other Canadian guideline cited the same evidence to support the use of buprenorphine-naloxone as a safe and effective alternative to buprenorphine alone during pregnancy.<sup>2</sup> No additional recommendations for various buprenorphine or buprenorphine-naloxone formulations during pregnancy were identified.

After review, 1 systematic review was 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).<sup>7</sup>

**New Guidelines:** No new guidelines were identified.

## **New Formulations:**

Cassipa® a new dosage strength of buprenorphine/naloxone (16mg/4mg) sublingual film received Food and Drug Administration (FDA) approval September 2018. The drug is indicated for maintenance treatment of opioid dependence and was approved through an abbreviated approval pathway based on previous evidence for buprenorphine/naloxone safety and efficacy.

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Brixadi™, an extended-release formulation of buprenorphine for subcutaneous administration weekly and monthly received tentative FDA approval December 2018. It is indicated for the treatment of moderate-severe OUD in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. The FDA provided tentative approval pending patent considerations (potential market entry in 2020). The drug must be administered only by healthcare providers in a healthcare setting.

**New FDA Safety Alerts:** No new FDA safety alerts have been issued.

#### References:

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3. Clinical Practice Guideline for Substance Use Disorders (2015). U.S. Department of Veterans Affairs/Department of Defense <http://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPGRevised22216.pdf> Accessed April 10, 2019.
4. Sublocade™ (buprenorphine extended-release) Injection Prescribing Information. North Chesterfield, VA; Indivior Inc. November 2017.
5. Lucemrya™ (Lofexidine) Prescribing Information. Louisville, KY; US WorldMeds, May 2018.
6. Gorodetzky CW, Walsh SL, Martin PR, Saxon AJ, Gullo KL, Biswas K. A phase III, randomized, multi-center, double blind, placebo controlled study of safety and efficacy of lofexidine for relief of symptoms in individuals undergoing inpatient opioid withdrawal. *Drug and alcohol dependence*. 2017;176:79-88.
7. Rahimi-Movaghar A, Gholami J, Amato L, Hoseinie L, Yousefi-Nooraie R, Amin-Esmaeili M. Pharmacological therapies for management of opium withdrawal. *Cochrane Database Syst Rev*. 2018;6:CD007522.
8. Bisaga A, Mannelli P, Yu M, et al. Outpatient transition to extended-release injectable naltrexone for patients with opioid use disorder: A phase 3 randomized trial. *Drug & Alcohol Dependence*. 2018;187:171-178.
9. 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.
10. Sullivan MA, Bisaga A, Pavlicova M, et al. A Randomized Trial Comparing Extended-Release Injectable Suspension and Oral Naltrexone, Both Combined With Behavioral Therapy, for the Treatment of Opioid Use Disorder. *Am J Psychiatry*. 2019;176(2):129-137.

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**Appendix 1: Current Preferred Drug List**

<u>Generic</u>	<u>Brand</u>	<u>Route</u>	<u>Formulation</u>	<u>PDL</u>
acamprosate calcium	ACAMPROSATE CALCIUM	ORAL	TABLET DR	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
naltrexone microspheres	VIVITROL	INTRAMUSC	SUS ER REC	Y
buprenorphine	SUBLOCADE	SUB-Q	SOLER SYR	N
buprenorphine HCl	BUPRENORPHINE HCL	SUBLINGUAL	TAB SUBL	N
buprenorphine HCl/naloxone HCl	BUNAVAIL	BUCCAL	FILM	N
disulfiram	ANTABUSE	ORAL	TABLET	N
disulfiram	DISULFIRAM	ORAL	TABLET	N
lofexidine HCl	LUCEMYRA	ORAL	TABLET	N
buprenorphine HCl	PROBUPHINE	IMPLANT	IMPLANT	

## Appendix 2: New Comparative Clinical Trials

A total of 30 citations were manually reviewed from the initial literature search. After further review, 27 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 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	Results																
<p>Bisaga, et al<sup>8</sup></p> <p>DB, MC, RCT</p> <p>N=378</p> <p>19 sites</p> <p>7 days</p>	<p>PO NTX + SL BUP</p> <p>Vs.</p> <p>PO NTX + PBO</p> <p>Vs.</p> <p>PBO</p> <p><i>To determine the efficacy, of oral NTX used in with BUP prior to the first dose of XR-NTX for detoxification.</i></p>	<p>-Patients aged 18-60 yo with diagnosis of OUD</p> <p>-Use of opioids &gt; 3 mos</p> <p>-Mild withdrawal (COWS ≥6)</p>	<p>Proportion of patients who received and tolerated an XR-NTX injection, as demonstrated by COWS score ≤12 or SOWS score ≤10 one hour following XR-NTX administration.</p>	<table border="1"> <thead> <tr> <th>Outcome</th> <th>NTX/BUP (n=124)</th> <th>NTX/PBO (n=126)</th> <th>PBO (n=124)</th> </tr> </thead> <tbody> <tr> <td>Received XR-NTX (%)</td> <td>46.8%</td> <td>40.5%</td> <td>46.8%</td> </tr> <tr> <td>Received and tolerated XR-NTX</td> <td>N = 57 (46%)</td> <td>N=51 (40.5%)</td> <td>N=57 (46%)</td> </tr> <tr> <td>P value</td> <td>0.94</td> <td>0.383</td> <td>N/A</td> </tr> </tbody> </table> <p><i>A 7-day detoxification protocol with NTX alone or NTX with BUP provided similar rates of induction onto XR-NTX as placebo (no differences).</i></p>	Outcome	NTX/BUP (n=124)	NTX/PBO (n=126)	PBO (n=124)	Received XR-NTX (%)	46.8%	40.5%	46.8%	Received and tolerated XR-NTX	N = 57 (46%)	N=51 (40.5%)	N=57 (46%)	P value	0.94	0.383	N/A
Outcome	NTX/BUP (n=124)	NTX/PBO (n=126)	PBO (n=124)																	
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P value	0.94	0.383	N/A																	
<p>Lofwall, et al<sup>9</sup></p> <p>DB, NI, MC, RCT</p> <p>N=428</p> <p>35 sites</p> <p>24 weeks</p>	<p>SC BUP + SL PBO</p> <p>Vs.</p> <p>SL BUP-NX + SC PBO</p> <p><i>To determine whether treatment with weekly and monthly SC BUP depot formulations is noninferior to a daily SL BUP-NX in treatment of OUD.</i></p>	<p>Patients aged 18-65 yo with moderate-to-severe OUD</p>	<p>Mean percentage of urine samples with test results negative for illicit opioids for weeks 1 to 24 and percent of responders.</p>	<p>Table 2.</p> <table border="1"> <thead> <tr> <th>Outcome</th> <th>SL BUP-NX</th> <th>SC-BUP</th> <th>Treatment differences</th> </tr> </thead> <tbody> <tr> <td>Opioid negative urine sample</td> <td>28.4 (2.5%)</td> <td>35.1 (2.5%)</td> <td>6.7 (95% CI: -0.1 to 13.6) P&lt;0.001 for NI</td> </tr> <tr> <td>% of responders</td> <td>31 (14.4%)</td> <td>37.0 (17.4%)</td> <td>3.0 (95% CI: -4.0 to 9.9) P&lt;0.001 for NI</td> </tr> </tbody> </table> <p><i>Compared with SL buprenorphine, depot buprenorphine was noninferior for both primary outcomes.</i></p>	Outcome	SL BUP-NX	SC-BUP	Treatment differences	Opioid negative urine sample	28.4 (2.5%)	35.1 (2.5%)	6.7 (95% CI: -0.1 to 13.6) P<0.001 for NI	% of responders	31 (14.4%)	37.0 (17.4%)	3.0 (95% CI: -4.0 to 9.9) P<0.001 for NI				
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<p>Sullivan, et al.<sup>10</sup></p> <p>OL, PG, RCT</p> <p>N=60</p> <p>24 weeks</p>	<p>PO NTX</p> <p>Vs.</p> <p>IM XR-NTX</p> <p><i>Compare the outcomes of patients with OUD treated with XR-NTX or oral NTX</i></p>	<p>Patients aged 18-60 yo with opioid dependence</p>	<p>The primary aim of this study was to compare the retention (time to dropout) of participants across the two treatment arms during 24 weeks of treatment</p>	<table border="1"> <thead> <tr> <th>Outcome</th> <th>XR-NTX</th> <th>PO NTX</th> <th>P value</th> </tr> </thead> <tbody> <tr> <td>Treatment retention</td> <td>N=28 (57.1%)</td> <td>N=9 (28.1%)</td> <td>HR=2.19 95% CI = 1.07 to 4.43</td> </tr> </tbody> </table> <p><i>Patients receiving XR-naltrexone had twice the rate of treatment retention at 6 months compared with those taking oral naltrexone.</i></p>	Outcome	XR-NTX	PO NTX	P value	Treatment retention	N=28 (57.1%)	N=9 (28.1%)	HR=2.19 95% CI = 1.07 to 4.43								
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Treatment retention	N=28 (57.1%)	N=9 (28.1%)	HR=2.19 95% CI = 1.07 to 4.43																	

Abbreviations: BUP=buprenorphine; COWS=Clinical Opiate Withdrawal Scale; DB=double blind; HR=hazard ratio; IM=intramuscular; MC=multicenter; Mos=months; NI=non-inferiority; NTX=oral naltrexone; NX=naloxone; OL=open label; OUD=opioid use disorder; PBO=placebo; PG=parallel group; PO=oral; RCT=randomized clinical trial; SC=subcutaneous; SL=sublingual; SOWS=Subjective Opiate Withdrawal Scale; XR-NTX=extended-release naltrexone; YO=years old

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## Appendix 3: Abstracts of Comparative Clinical Trials

### 1. Outpatient transition to extended-release injectable naltrexone for patients with opioid use disorder: A phase 3 randomized trial.<sup>8</sup>

#### BACKGROUND:

Injectable extended-release naltrexone (XR-NTX), approved to prevent relapse to opioid dependence, requires initial abstinence. This multisite outpatient clinical trial examined the efficacy and safety of low-dose oral naltrexone (NTX), combined with a brief buprenorphine (BUP) taper and standing ancillary medications, for detoxification and induction onto XR-NTX.

#### METHODS:

Patients (N = 378) were randomized, stratified by primary short-acting opioid-of-use, to one of three regimens: NTX + BUP; NTX + placebo BUP (PBO-B); placebo NTX (PBO-N) + PBO-B. Patients received 7 days of ascending NTX or placebo, concurrent with a 3-day BUP or placebo taper, and ancillary medications in an outpatient setting. Daily psychoeducational counseling was provided. On Day 8, patients passing a naloxone challenge received XR-NTX.

#### RESULTS:

Rates of transition to XR-NTX were comparable across groups: NTX/BUP (46.0%) vs. NTX/PBO-B (40.5%) vs. PBO-N/PBO-B (46.0%). Thus, the study did not meet its primary endpoint. Adverse events, reported by 32.5% of all patients, were mild to moderate in severity and consistent with opioid withdrawal. A first, second, and third XR-NTX injection was received by 44.4%, 29.9%, and 22.5% of patients, respectively. Compared with the PBO-N/PBO-B group, the NTX/BUP group demonstrated higher opioid abstinence during the transition and lower post-XR-NTX subjective opioid withdrawal scores.

#### CONCLUSIONS:

A 7-day detoxification protocol with NTX alone or NTX + BUP provided similar rates of induction to XR-NTX as placebo. For those inducted onto XR-NTX, management of opioid withdrawal symptoms prior to induction was achieved in a structured outpatient setting using a well-tolerated, fixed-dose ancillary medication regimen common to all three groups.

### 2. Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine with Naloxone for Treatment of Opioid Use Disorder: A Randomized Clinical Trial.<sup>9</sup>

#### 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.

### **3. A Randomized Trial Comparing Extended-Release Injectible Suspension and Oral Naltrexone, Both Combined With Behavioral Therapy, for the Treatment of Opioid Use Disorder.<sup>10</sup>**

#### OBJECTIVE:

The oral formulation of the opioid antagonist naltrexone has shown limited effectiveness for treatment of opioid use disorder due to poor adherence. Long-acting injection naltrexone (XR-naltrexone), administered monthly, circumvents the need for daily pill taking, potentially improving adherence, and has been shown to be superior to placebo in reducing opioid use over 6 months of treatment. This open-label trial compared the outcomes of patients with opioid use disorder treated with XR-naltrexone or oral naltrexone in combination with behavioral therapy.

#### METHOD:

Sixty opioid-dependent adults completed inpatient opioid withdrawal and were transitioned to oral naltrexone. They were stratified by severity of opioid use (six or fewer bags versus more than six bags of heroin per day) and randomly assigned (1:1) to continue treatment with oral naltrexone (N=32) or XR-naltrexone (N=28) for 24 weeks. The first dose of XR-naltrexone (380 mg) was administered prior to discharge, with monthly doses thereafter, and oral naltrexone was given in a 50-mg daily dose. All participants received weekly behavioral therapy to support treatment and adherence to naltrexone.

#### RESULTS:

A Cox proportional hazards model adjusting for race, gender, route of use, and baseline opioid use severity indicated that significantly more patients were retained in treatment for 6 months in the XR-naltrexone group (16 of 28 patients, 57.1%) than in the oral naltrexone group (nine of 32 patients, 28.1%) (hazard ratio=2.18, 95% CI=1.07, 4.43).

#### CONCLUSIONS:

Patients receiving XR-naltrexone had twice the rate of treatment retention at 6 months compared with those taking oral naltrexone. These results support the use of XR-naltrexone combined with behavioral therapy as an effective treatment for patients seeking opioid withdrawal and nonagonist treatment for preventing relapse to opioid use disorder.

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#### Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to June Week 3 2019 Ovid MEDLINE(R) In-Process & Other Non-Indexed Citation June 20, 2019

1 exp Buprenorphine/	3591
2 exp Buprenorphine, Naloxone Drug Combination	217
3 exp Naltrexone/	4693
4 Lofexidine.mp	103
5 Substance-Related Disorders	51433
6 1 or 2 or 3 or 4	8251
7 6 and 5	374
8 limit 5 to (English language and humans and yr="2018 -Current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	7

Ovid MEDLINE(R) without Revisions 1996 to June Week 3 2019; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citation June 20, 2019

1acamprostate.mp.	768
2 exp Disulfiram/	3405
3 exp Naltrexone/	7577
4 exp Alcoholism/	73266
5 exp Substance-Related Disorders/	266719
6 exp Alcohol Deterrents/	11669
7 1 or 2 or 3	11331
8 4 or 5 or 6	274338
9 7 and 8	11308
10 limit 9 to (English language and humans and yr="2018 -Current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	23

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**Appendix 5: Key Inclusion Criteria**

<b>Population</b>	Patients with opioid or alcohol use disorder
<b>Intervention</b>	Various formulations of buprenorphine (e.g., extended-release subcutaneous injection, sublingual, implant, transdermal, intramuscular) or buprenorphine-naloxone combinations or naltrexone
<b>Comparator</b>	Various formulations of buprenorphine (e.g., extended-release subcutaneous injection, sublingual, implant, transdermal, intramuscular) or buprenorphine-naloxone combinations or naloxone
<b>Outcomes</b>	1. Clinical effectiveness (e.g., reduction in opioid consumption, prevention of relapse, maintenance of abstinence, retention into treatment, and adherence to medication.) 2. Safety (e.g., reduction in misuse and diversion, reports or evidence of abuse, urine drug screening results, overdose, all-cause mortality)
<b>Timing</b>	Up to 24 weeks
<b>Setting</b>	Outpatient