Extended-Release Opioid Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder: Effectiveness and Value

Evidence Report

October 25th, 2018

Prepared for

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The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/mat-stakeholder-list/.

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List of Acronyms Used in this Report

AATOD	American Association for the Treatment of Opioid Dependence
AE	Adverse event
AMCP	Academy of Managed Care Pharmacy
AHRQ	Agency for Healthcare Research and Quality
ASAM	American Society of Addiction Medicine
CADTH	Canadian Agency for Drugs and Technologies in Health
CDF	Cumulative distribution function
COWS	Clinical Opiate Withdrawal Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association
ED	Emergency department
FDA	United States Food and Drug Administration
HCV	Hepatitis C virus
HHS	United States Department of Health and Human Services
HIV	Human immunodeficiency virus
LCD	Local Coverage Determination
MAT	Medication for addiction treatment and/or medication-assisted treatment
NCD	National Coverage Determination
NIDA	National Institute on Drug Abuse
OLE	Open-label extension
OUD	Opioid use disorder
PCP	Primary care physician
PICOTS	Population, Intervention, Comparators, Outcomes, Timing, and Settings
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized clinical trial
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious adverse event
SAMHSA	US Substance Abuse and Mental Health Services Administration
SF-36	36-item Short Form Questionnaire
SOWS	Subjective Opiate Withdrawal Scale
TIP	Treatment Improvement Protocol
UHC	UnitedHealthcare
UMP	Utilization Management Policy
US	United States
USPSTF	United States Preventive Services Task Force
VAS	Visual analogue scale

Executive Summary

Background

Opioid use disorder (OUD) is an increasingly common public health concern that is central to the public health crisis in the US known as the opioid epidemic. In 2016, it was estimated that 2.1 million people suffered from an OUD in the US and 116 Americans died daily from opioid-related drug overdoses.[1] and overall life expectancy in the US decreased in 2015 due to the opioid epidemic.[2,3] On October 27, 2017, the Acting Secretary of Health and Human Services declared a nationwide public health emergency regarding the opioid crisis[4]. The Council of Economic Advisers estimates the overall economic cost of the opioid crisis to society to be $504 billion, or 2.8% of US gross domestic product.[5]

The diagnosis of OUD is based on criteria related to the following dimensions: impaired control, social impairment, risky use, increased tolerance, and withdrawal.[6] The diagnostic criteria for moderate to severe OUD roughly correspond to the concept of opioid addiction.[7] OUD is to be considered a chronic, treatable illness that requires long-term treatment and is marked by periods of "remission" (reduction in or elimination of signs and symptoms) and relapse.

Considering the chronic nature and behavioral impacts of OUD, the primary aim of treatment is recovery rather than cure. A person in recovery refers to an individual who abstains from further use, reduces their substance use to a safer level, or takes steps to mitigate the potential physical and emotional harm resulting from continued use.[8] Though some individuals enter and sustain recovery on their own, recovery is mostly achieved via access to evidence-based clinical treatment and recovery support services.[9]

Misuse of opioids occurs in many different patient subpopulations comprising patients who have followed many different paths to the disorder. In all age groups, medical use of prescription opioids can lead to OUD, but younger adults are more likely to abuse heroin and synthetic opioids, while older individuals are more likely to move from therapeutically-appropriate use of opioids for acute or chronic pain to misuse of those same opioids.[10] Overall, OUD patients do present with important psychiatric comorbidities, especially depression, post-traumatic stress disorder, and personality disorders.[11]

The use of medication for the treatment of OUD is called MAT, for "medication for addiction treatment" (MAT), also known as "medication-assisted treatment", and is considered as one of the essential elements for countering the opioid epidemic.[12]. The FDA has approved three medications (in various forms) for the treatment of OUD: methadone, buprenorphine, and naltrexone.[13] All three drugs are to be used in combination with counseling and psychosocial support[14], described as a "multipronged approach that can include counseling, vocational training, psychosocial therapy,

family support, and building connections to community resources,"[14] also including safe/supportive housing as an essential dimension for many patients. Table ES1 provides an overview of the three FDA-approved drugs for the treatment of OUD.

Table ES1. Comparison of Medications for OUD[15,16-18]

	Methadone	Buprenorphine	Naltrexone
Mechanism of Action at mu-Opioid Receptor	Agonist	Partial agonist	Antagonist
Phase of Treatment	Medically supervised withdrawal, maintenance	Medically supervised withdrawal, maintenance	Maintenance, following medically supervised withdrawal
Route of Administration	Oral	Sublingual buccal, subdermal implant, subcutaneous extended-release	Oral, intramuscular extended-release
Effective Dosage by Mouth	Usually 60mg–120mg daily	Usual sublingual/buccal stabilizing dose between 12 mg–16 mg daily	Limited effectiveness of oral naltrexone due to limited treatment retention
Regulation through Controlled Substances Act	Schedule II	Schedule III	Not regulated through Controlled Substances Act
Availability	Only available in opioid treatment programs with SAMHSA certification and DEA registration	Prescribed by physicians, nurse practitioners and physician assistants with a SAMHSA prescribing waiver	Available by prescription

In a recently published draft guidance document, the FDA recommends using a decrease in opioid use as a primary efficacy endpoint for demonstrating the effectiveness of drugs for OUD. The FDA further states that "sponsors and other stakeholders often mistakenly believe that using a change in drug use patterns as the endpoint always requires complete abstinence." Long-term studies should demonstrate that observed reductions in drug use predict clinical benefit, even if opioid use has not completely stopped.[19] By accepting and recommending a primary endpoint of a clinically relevant decrease in the use of opioids, rather than abstinence, the FDA endorses certain dimensions of "harm reduction strategies" that aim to minimize death, disease, and injury from continuing drug use, with a focus on improving daily social function and productivity.

Despite the essential role of MAT in treating OUD and in preventing harm, including death, an important gap persists between the need for and the availability of MAT. More than 30 million people live in US counties without a single prescriber for addiction treatment[20] and currently only

about 20% of patients with OUD are receiving treatment[21] Expanding access to OUD medications is considered an important public health strategy for countering the opioid epidemic.[12]

Populations in prisons and jails present a unique challenge for MAT, as regular use of heroin or other opioids is common prior to incarceration. The lack of access to MAT by incarcerated populations drives diversion for self-medication to control withdrawal and cravings. This diversion reinforces negative beliefs about opioid agonist therapy in correctional settings.[20] During imprisonment, tolerance of opioids is diminished and the risk for death from overdose is greatly increased upon release.

Extended-release formulations have generated clinical interest because of their potential to improve retention in treatment and circumvent some of the access challenges seen with current forms of MAT. These formulations are currently available only for buprenorphine and naltrexone. Table ES2 provides an overview of extended-release medications for OUD that are currently available or under consideration by the FDA.

Table ES2. Extended-Release Formulations for OUD Medications

Substance	Name and Company	FDA Approval	FDA Recommended Dosing
Buprenorphine	Sublocade™, Indivior (Subcutaneous injection)	Nov 30, 2017	After at least seven days of treatment with a transmucosal buprenorphine-containing product delivering the equivalent of 8 to 24 mg of buprenorphine daily, Sublocade abdominal subcutaneous injections are initiated with 300 mg monthly for the first two months followed by a maintenance dose of 100 mg monthly. Maintenance dose can be increased up to 300mg monthly.
	Probuphine®, Titan Pharmaceuticals, Inc. (Subdermal implant)	May 26, 2016	For patients on maintenance treatment with a transmucosal buprenorphine-containing product delivering the equivalence of buprenorphine 8 mg or less per day. Four Probuphine implants inserted subdermally in the upper arm for six months of treatment, after a new insertion in the other arm, transitioned back to a transmucosal buprenorphine-containing product.
	CAM2038, Braeburn (Subcutaneous injection)	PDUFA date expected for December 26, 2018	N/A
Naltrexone	Vivitrol®, Alkermes (Intramuscular injection)	December 10, 2010 for OUD	After an opioid-free duration of a minimum of seven to 10 days. Administered 380 mg intramuscularly every four weeks or once a month.

After completed withdrawal, Vivitrol is administered by a healthcare provider as an intramuscular (IM) gluteal injection, alternating buttocks for each subsequent injection. As with all medications for OUD, treatment with Vivitrol should be accompanied by psychosocial support.[22] As naltrexone is not regulated by the Controlled Substances Act, Vivitrol can be prescribed without any specific requirements.

Treatment with Sublocade replaces a daily dose of buprenorphine with a transmucosal product with extended-release formulation of buprenorphine. For treatment to be initiated, patients need to be on a stable transmucosal dose of 8 to 24 mg buprenorphine for at least seven days. Sublocade is administered through abdominal subcutaneous injection and forms a solid mass upon contact with body fluids. If administered intravenously, it can cause life-threatening pulmonary emboli, as mentioned in a black box warning in the FDA label. Sublocade can only be prescribed by physicians, nurse practitioners, and physician assistants holding a SAMHSA waiver.

Treatment with Probuphine implants involves surgical subdermal insertion on the inside of the upper arm of a set of four rods, each 2.5 mm in diameter and 26 mm in length, each rod containing the equivalent of 80 mg of buprenorphine, at steady-state releasing the equivalent of an 8 mg daily transmucosal buprenorphine dose.[12] The implants must be removed after six months and a second set of rods can be placed in the other arm. After this second insertion, patients must transition back to a transmucosal buprenorphine-containing product.[23]

The CAM2038 buprenorphine injection is currently under regulatory review with an expected approval date in December 2018. In clinical studies, this subcutaneous injection has been administered weekly or monthly with multiple dose strengths, in any subcutaneous tissue. The manufacturer proposes to include treatment initiation in the indication for CAM2038.[24] If the FDA retains this proposal in the label to be approved, this would eliminate the need for prior treatment with transmucosal buprenorphine.

Insights Gained from Discussions with Patients and Patient Groups

As part of our review, we spoke with organizations working with individuals and families affected by OUD. There was a consensus that MAT is often difficult to access, in part because of the stigma attached to OUD. This stigma is rooted in a widespread belief that drug addiction is a moral failing rather than a medical condition that is best addressed through treatment.

OUD needs to be considered a chronic disease that can affect widely varying populations in terms of age, background, and other factors. The expression, "treatment is not one-size-fits-all," was used by several organizations to stress the importance of patients having access to different treatment options on their road to recovery; some patients enter recovery without the assistance of MAT, while others require MAT for long periods of time or even their entire lives.

Equal access to all types of medications is considered important. For example, we received comments that Vivitrol® (Naltrexone, Alkermes) is currently more easily available than other medications. Buprenorphine extended-release medications are considered important new treatment options that could improve recovery and should be widely available for consideration by patients and physicians.

It was also mentioned that peer support is particularly important for young people entering the recovery process, as they usually lack a strong existing social network compared to older adults.

Several organizations stressed that better daily functioning and well-being, and eventually recovery, are the most important outcomes of treatment. For some this may involve complete abstinence from non-medical opioid use, for others a reduced and controlled level of use. It was mentioned that this corresponds specifically to the discussions at the public meeting on Patient-Focused Drug Development for Opioid Use Disorder convened in April 2018 by the FDA.[25]

Comparative Clinical Effectiveness

Our review focused on the efficacy, safety, and effectiveness of extended-release medication versus each other and versus transmucosal formulations of buprenorphine/naloxone. We do recognize that methadone being used since the 1960s has a very strong evidence base. However, as a schedule II substance regulated through the Controlled Substances Act, it cannot be legally dispensed for MAT through community pharmacies or physician offices, but only as part of highly structured treatment programs. Due to this very different context of use, it has not been chosen in the present assessment as a comparator for the extended-release medications for OUD, but we have identified and summarized previous systematic reviews that are detailed in the report.

In this review of the comparative clinical effectiveness of newer, extended-release treatments for MAT (two buprenorphine injections, one buprenorphine implant, and a naltrexone injection), we systematically identified and synthesized the existing evidence from clinical studies. We evaluated studies of patients 16 years or older with OUD. For the comparison of the interventions of interest versus each other and versus transmucosal formulations of buprenorphine/naloxone, we extracted any relevant data, whether in published or unpublished form (e.g., conference abstracts or presentations, FDA review documents). Due to important differences in study characteristics and outcomes assessed, we did not compare the interventions of interest through direct or indirect quantitative assessments. We sought evidence on different outcomes as detailed in section 1.2 of the report. A detailed description of the methods is available in section 3.2.

Our literature search identified a total of 557 potentially relevant references. Among the 23 references included for the present analysis, 18 references report findings from 11 comparative trials. Five of these trials were identified as key trials evaluating the four drugs of interest and analysed for the comparability of evidence (Table ES3). In four of the key trials, three of the interventions of interest: CAM2038 (Braeburn), Probuphine® (Buprenorphine/Naloxone, Titan Pharmaceuticals Inc.) and Vivitrol were compared to buprenorphine/naloxone, while the remaining one key trial for Sublocade™ (Buprenorphine/Naloxone, Indivior) was placebo-controlled with no active comparator. We identified no head-to-head trials of the interventions of interest. The trials and their quality ratings are described in detail in the full report.

Table ES3. Comparability of Evidence: Key Trials Across the Interventions of Interest

	Trial	Study Design	Treatment Duration (Weeks)	Detoxification/ Induction Period	**Time of Randomization**	**Outcomes**
CAM2038	Lofwall 2018	Phase III RCT Non-inferiority	24	**Detoxification**: none **Induction**: one day of 4 mg bup/1 mg nal	At start of induction	• Urine samples used to assess abstinence • Outcome measured over 24 weeks
Sublocade	Trial 13-0001	Phase III RCT	24	**Detoxification**: none **Induction**: run-in induction phase with SL bup/nal film followed by open-label phase with 8 to 24 mg doses of buprenorphine/naloxone for four to 11 days	After induction	• Combination of urine samples and self-report used to assess abstinence • Outcome measured over 24 weeks
Probuphine	Rosenthal 2016	Phase III Non-inferiority	24	**Detoxification**: none **Induction**: stable dose of 8 mg/day or less of sublingual buprenorphine received for at least 24 weeks	After induction	• Urine samples and self-report used to assess abstinence • Outcome assessed over 24 weeks
Vivitrol	X-BOT	Phase IV		**Detoxification**: yes, protocols and length of time varied by site	Before induction	• Abstinence not reported • Time to relapse event reported
	Tanum 2017	Phase III RCT Non-inferiority	12	**Detoxification**: yes	After detoxification	• Urine samples used to assess abstinence • Outcome measured over 12 weeks

Clinical Benefits

Mortality

We sought evidence on the effect of the interventions of interest on reducing mortality. However, we found no relevant data on this outcome.

All-Cause Discontinuation

Discontinuation rates appeared similar with CAM2038, Probuphine, and Vivitrol compared with sublingual buprenorphine/naloxone. However, tests of statistical significance were not reported. Of note, significantly more patients discontinued before induction with Vivitrol compared to buprenorphine/naloxone. Results from the placebo-controlled trials of Sublocade and Probuphine showed substantially greater attrition in the placebo group than in the active treatment arms. The most common reasons for discontinuation were lack of efficacy, adverse events, withdrawing consent, being unable to complete induction, loss to follow-up, and withdrawal symptoms.

Abstinence and Relapse Outcomes

Abstinence from opioid use was variably defined in available trials. For most interventions, the number of opioid-negative urines did not statistically differ in comparison to sublingual buprenorphine/naloxone. Results from the Probuphine trials showed statistically significantly greater abstinence than buprenorphine/naloxone on various measurements. Participants on Sublocade treatment were also more likely to be abstinent, but in comparison to placebo. Relapse to opioid use was a measure specific to trials of Vivitrol; a statistically significantly higher rate of relapse was seen with Vivitrol versus buprenorphine/naloxone in the intent-to-treat group.

Diminishing Illicit Use of Opioids

Vivitrol was the only intervention with data on diminishing illicit use of opioids which was assessed in one key trial. That trial found that Vivitrol decreased use of heroin and other illicit opioids when compared to buprenorphine/naloxone over the duration of the trial.

Opioid craving – Visual Analog Scale

Opioid craving scores on CAM2038 and Probuphine were not statistically significantly different from those on buprenorphine/naloxone. Sublocade decreased opioid craving compared with placebo. One trial found numerically lower opioid craving scores with Vivitrol than buprenorphine/naloxone, but statistical significance was not reported.

Opioid Withdrawal

No significant differences were shown for CAM2038 and Probuphine each in comparison to buprenorphine/naloxone in the Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate

Withdrawal Scale (SOWS). Only the higher dose arm of Sublocade showed any significant difference from placebo. There were no COWS or SOWS data for Vivitrol.

Health-Related Quality of Life

Evidence on health-related quality of life and patient outcomes were reported only in trials of Vivitrol. Results showed an overall increase in quality of life in patients receiving Vivitrol compared with placebo. Patient satisfaction with treatment occurred more with Vivitrol than with buprenorphine/naloxone.

Healthcare Utilization

Limited data were reported on healthcare utilization, and only for Vivitrol. Evidence from available trials found no differences in healthcare utilization between Vivitrol and treatment as usual. Results from one observational study showed reduced inpatient admissions with Vivitrol.

Other outcomes

No data on incidence of infectious diseases, functional outcomes, employment-related outcomes, diversion, and accidental pediatric exposure were reported in the trials that met our inclusion criteria.

Harms

Serious adverse events were generally uncommon and similar in trials of CAM2038, Probuphine, and Vivitrol in comparison to buprenorphine/naloxone and in the Sublocade trial vs placebo. Low numbers of participants discontinued due to adverse events in the trials of CAM2038, Probuphine, and Vivitrol when compared to buprenorphine/naloxone. The most common adverse events reported in the trials were injection/implant site pain, gastrointestinal issues, headaches, and insomnia (see Table 3.5 in report).

Controversies and Uncertainties

As mentioned previously, differences in trial designs, population selection, comparators, and outcome measures precluded formal comparisons between the different extended-release formulations. All four formulations also differ in their labeled or potential treatment indications; for example, only CAM2038 has the possibility of starting OUD treatment directly after diagnosis. Sublocade and Probuphine must be preceded by daily transmucosal use of buprenorphine and Vivitrol by a period of medically supervised opioid withdrawal. Probuphine implants should be used for patients on maintenance treatment with a transmucosal buprenorphine-containing product delivering a low to moderate dose, the equivalent of buprenorphine 8 mg or less per day. The effective required buprenorphine dosage for most patients is between 12 and 16 mg daily, therefore only patients who can tolerate such doses may be suitable for Probuphine implants.

Various outcome measures were used in the trials of the interventions of interest. Outcome measures are based on different calculations of negative urine samples (Appendix Table D5), using the term relapse to designate a certain percentage of positive urine samples. However, the term relapse refers to a person with OUD who is being treated and is in remission experiences a loss of control. A relapse is different from a return to opioid use that is limited in scope and time and that does not involve the return of the signs or symptoms of OUD. It is not certain to which degree different rates of negative urine samples constitute a meaningful measure of success, even for the short duration of the trials.

The lack of any clear guidance on how to obtain the opioid-free state needed for starting Vivitrol makes comparisons between the evidence for the extended-release agonist formulations and the extended-release antagonist formulation very difficult. Head-to-head trials of agonist formulations should be possible, but have not yet been conducted.

In the real world, OUD patients often present with important psychiatric comorbidities, such as depression, post-traumatic stress disorder, and personality disorders.[11] Patients with psychiatric comorbidities are largely excluded from the trials (refer to Appendix Table D2), thus limiting their generalizability. This is not limited to the evidence on extended-release formulations, but present in the evidence base for all MATs.[26]

As noted by SAMHSA in the 2018 TIP, no evidence clearly predicts which patients are best treated with Vivitrol versus methadone or buprenorphine formulations.[12] The treatment sequences for different subpopulations with OUD cannot be based solely on the available evidence, but rather must be informed by clinical knowledge and the local context.

The evidence on the use of the extended-release formulations is subject to the same general limitations as for the other medications for OUD. It is not yet known if or when to best taper these medications, [12] and evidence is lacking on the added value of the different types of counseling and psychosocial support required by the FDA label the most recent clinical practice guideline.[12]

The available research focuses on short-term outcomes and does not provide any evidence of observed reductions or patient control of drug use that are of clinical and social benefit, even if opioid use has not completely stopped.[19,27] In addition, questions around the impact of extended-release formulations on critically important outcomes, such as overdose and other OUD-associated mortality, health-related quality of life, work productivity, educational attainment, and incarceration have largely gone unanswered by the evidence currently available.

Summary and Comment

Using the ICER Evidence Matrix shown in section 3.4 of the report, we assigned evidence ratings independently for each of the interventions of interest compared to transmucosal buprenorphine/naloxone for study participants with OUD being considered for MAT.

Table ES4. Evidence Ratings (Versus Transmucosal Buprenorphine/Naloxone)

Comparisons	Evidence Rating
CAM2038	C+
Sublocade	I
Probuphine	P/I
Vivitrol	C

CAM2038

Evidence for CAM2038 is comprised of one 24-week Phase III trial in comparison to buprenorphine/naloxone. Results showed CAM2038 to be non-inferior to buprenorphine, but not significantly different in abstinence, opioid craving, and opioid withdrawal. For participants with OUD being considered for MAT, we have moderate certainty that CAM2038 provides a small, or substantial net health benefit given the increased convenience and provider interaction associated with subcutaneous injections, but high certainty that it is at least comparable as it is a buprenorphine-containing treatment. Therefore, we consider the evidence on CAM2038 to be comparable or better (C+).

Sublocade

Evidence for Sublocade is limited to one 24-week Phase III trial compared to placebo. In the absence of a direct comparison of Sublocade to buprenorphine/naloxone, we consider the evidence on Sublocade compared to buprenorphine/naloxone to be insufficient (I).

Probuphine

Evidence for Probuphine compared to buprenorphine/naloxone comprises two 24-week Phase III trials. For participants with OUD being considered for MAT, we have moderate certainty of a comparable or small net health benefit for the trial populations. However, we have concerns that the study population may not be reflective of the more general population being considered for MAT. Therefore, we consider the evidence on Probuphine in comparison to buprenorphine/naloxone to be promising but inconclusive (P/I).

Vivitrol

Evidence for Vivitrol compared to buprenorphine/naloxone consists of data derived from two trials: one 24-week Phase IV trial, and one shorter 12-week Phase III trial. Results showed that Vivitrol is

non-inferior to buprenorphine/naloxone on a variety of abstinence outcomes. Vivitrol has the most mature evidence base of any of the treatments of focus for this review. Differences observed between Vivitrol and buprenorphine/naloxone are due at least in part to differences in treatment intent and goals. Therefore, we considered the evidence on Vivitrol in comparison to buprenorphine/naloxone to have high certainty of a comparable net health benefit (C).

Long-Term Cost Effectiveness

We conducted an economic evaluation to estimate the cost-effectiveness of the interventions of interest among adult patients considered for OUD treatment, from a U.S. health sector perspective. Costs and outcomes in the model were discounted at 3% annually, and the model had four-week cycle lengths and was run over a five-year time horizon.

Our model compared buprenorphine extended-release subcutaneous injections (CAM2038 [investigational]), extended-release injectable naltrexone (Vivitrol), and buprenorphine subdermal implant (Probuphine), to a transmucosal buprenorphine/naloxone, specifically generic sublingual (SL) buprenorphine/naloxone in the base case analysis; another extended-release subcutaneous injection (Sublocade) was compared to SL buprenorphine/naloxone in a scenario analysis. We developed a decision tree with pre-MAT initiation rules for each intervention of interest based on pre-treatment induction/detoxification protocols in the key clinical trials and FDA labels, in keeping with an intention-to-treat perspective. MAT-specific initial state probabilities in the subsequent Markov model were assigned based on pre-MAT initiation outcomes (Figure 4.1A) for each MAT. The Markov model comprised five health states, namely, "MAT with Illicit Use of Opioids", "MAT with NO Illicit Use of Opioids", "OFF MAT with Illicit Use of Opioids", "OFF MAT with NO Illicit Use of Opioids" and "Death" (Figure 4.1B). Patient flow through the model was unidirectional, in that once in a health state, patients could not move to a previously occupied health state. For patients treated with CAM2038, or Sublocade, and their respective comparators, those successful in the pre-MAT initiation started the model in the "MAT with Illicit Use of Opioids" health state, while those who were unsuccessful entered the model in the "OFF MAT with Illicit Use of Opioids" health state. With increasing abstinence over time, those successful transitioned to the "MAT with NO Illicit Use of Opioids" health state, where they could remain or transition over to permanent abstinence from illicit use ("OFF MAT with NO Illicit Use of Opioids") or relapse ("OFF MAT with Illicit Use of Opioids). Patients treated with Vivitrol, or Probuphine, and their respective comparators upon success with pre-treatment protocols entered the model in the "MAT with NO Illicit Use of Opioids" health state and could transition to a state of permanent abstinence from illicit use or relapse. Patients could die from all-cause mortality from any health state, or from opioid-related overdose while illicitly using opioids and not on MATs.

The modeled cohort focused on adult patients diagnosed with OUD seeking MATs and had a mean age of 36 years; 30% of the cohort were female and there was a 50:50 split of illicit use of prescription opioids and injection drugs. Some of the key modeling assumptions included:

- Return to pre-treatment choice of illicit use of opioids (prescription or injection), upon relapse following MAT
- 10% of all patients who remained abstinent from illicit use while on MATs for one year or more could transition to permanent abstinence from illicit use
- A single cost and utility were chosen for illicit use (by prescription or injection, and concurrent use of MATs); illicit use was not modeled according to different levels of use
- Constant mortality from opioid overdose irrespective of duration of illicit use
- Incidence of HIV and HCV infections only among persons who inject drugs (PWID) and not among those who illicitly used prescription opioids
- Serious adverse events of illicit use that were not related to overdose were not included

A detailed description of model choices, assumptions, and respective rationale for each can be found in Section 4, Table 4.3 of this report.

Treatment efficacy estimates, namely, abstinence from illicit use of opioids for CAM2038 and its comparator, and relapse to illicit use of opioids for Vivitrol and Probuphine and their respective comparators were derived from the respective key clinical trials. Treatment discontinuation was also derived from trials. Wherever Kaplan-Meier (KM) curves available, they were digitized and fit with parametric curves that fit the digitized data, and were extrapolated beyond the trial duration, for the modeled time horizon. Mortality in the model was a function of background mortality increased by overdose-related mortality among those who illicitly used opioids without MATs, as well as mortality from HCV or HIV infection among PWID. Health state utilities were sourced from a US-specific cross-sectional survey study where available, with calculations made to estimate utilities when on MATs and illicitly using opioids using data from a UK-specific study. We applied disutility multipliers in PWID with HIV or HCV to reflect these comorbidities and treatment associated with them. Due to a variation in reporting of adverse events (AE) among trials and their being reported by severity, and AE-related costs assumed to not impact overall costs substantially, we did not include AEs in the model.

MAT drug costs in the model were sourced from the Federal Supply Schedule database for all except Vivitrol, which was provided to us as a net price by the drug's manufacturer. For the SL buprenorphine/naloxone comparator, we used the undiscounted WAC in accordance with ICER's Reference Case. We included administration and monitoring costs for all interventions of interest as appropriate. Non-drug health care costs were sourced from a claims analysis and awarded to health states in the model as appropriate. We also included costs for specific HIV and HCV-related treatment as well as non-drug treatments costs for these co-morbidities. For the modified societal perspective, we included the costs of lost productivity, and the costs of criminal justice and incarceration that were applied to the percentage of patients assumed employed or involved in crime-related activities in this hypothetical patient cohort.

Details regarding inputs, sensitivity analyses, and scenario analyses are available in Section 4 of the report. We ran scenario analyses for a Sublocade vs. SL buprenorphine/naloxone comparison that included separate threshold analyses for drug price and efficacy for Sublocade to achieve cost-effectiveness threshold of up to $150,000 per QALY, and one where we assumed treatment efficacy and adherence the same as those seen in the CAM2038, with Sublocade's FSS price and also a favorable assumption reflecting 100% success with pre-Sublocade treatment induction.

Base-Case Results

Treatment with any of the interventions of interest resulted in higher costs relative to SL buprenorphine/naloxone, while QALY gains were seen only for CAM2038 and Probuphine. We do not report the incremental costs of CAM2038 relative to its comparator since CAM2038 does not yet have a known price, and any incremental cost is only based on non-drug costs. All interventions and their respective comparators showed similar life-year outcomes (4.62 years).

Table ES5. Incremental Cost Effectiveness Results of the Interventions of Interest Versus Respective SL Generic Buprenorphine/Naloxone Comparators

Intervention	Incremental Costs	Incremental QALYs	Incremental Cost-Effectiveness Ratio (Cost per QALY gained)
CAM2038	-	0.06	-
Vivitrol	$10,300	(0.03)	More costly, less effective (Dominated)
Probuphine	$2,700	0.01	$265,000

QALY: Quality-Adjusted Life Year

All incremental results are versus each interventions respective SL buprenorphine/naloxone comparator, over a 5-year time horizon.

Sensitivity Analyses

One-way sensitivity analyses showed that results were generally most sensitive to intervention discontinuation rate (relapse to illicit use of opioids), the incidence of HCV, and intervention costs. Results of our probabilistic analyses showed that none of the 1,000 simulations resulted in incremental cost-effectiveness ratios that were at or below the $150,000 per QALY threshold for Vivitrol, while only 12.4% of simulations resulted in incremental cost-effectiveness ratios that were at or below the same threshold for Probuphine. We do not report probabilistic results for CAM2038 since we have no price for this treatment and cannot calculate an incremental cost-effectiveness ratio.

In the Sublocade vs. generic SL buprenorphine/naloxone scenario, a threshold analysis for price showed per cycle Sublocade costs similar to that of CAM2038's, assuming Sublocade's efficacy to be the same as CAM2038's. The second threshold analysis examining the efficacy required for Sublocade to reach a $150,000 per QALY cost-effectiveness threshold showed that even if patients treated with Sublocade achieved complete abstinence from illicit use of opioids with 100% treatment adherence, at its current price the cost-effectiveness of Sublocade would still exceed $215,000 per QALY. A third scenario comparing Sublocade to generic SL buprenorphine/naloxone that assumed Sublocade's efficacy to be the same as CAM2038's, using Sublocade over a five-year time horizon resulted in an incremental cost-effectiveness ratio of approximately $577,000 per QALY gained.

Modeling interventions from a societal perspective resulted in higher total costs, with incremental results directionally similar to the base case findings. All other scenario analyses produced results similar to the base-case analyses, except for when Vivitrol was analyzed using a "per protocol" approach, which resulted in its cost-effectiveness being approximately $1 million per QALY.

Threshold Analyses

We could not calculate threshold prices for Vivitrol based on the base case estimates since it was less effective relative to its comparator. Threshold analyses for Cam2038 and Probuphine were calculated at the $50,000, $100,000 and $150,000 per QALY willingness-to-pay (WTP) thresholds (Table ES6)

Table ES6. Threshold Analysis Results

	WAC per Unit	Net Price per Unit	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY
CAM2038*	-	-	$219†	$313†	$406†
Probuphine	$4,950‡	$3,640‡	$1,165‡	$1,741‡	$2,318‡

*No list or net prices for CAM2038 were available as of the date of this report.

†Price per four-week dose

‡Price per implant lasting six months

Summary and Comment

Our analyses indicate that all the interventions of interest generate similar life years, with only marginal differences in QALYs relative to their respective comparators. Only CAM2038 and Probuphine produce incremental QALYs relative to the respective comparators while Vivitrol does not. Recognizing that Vivitrol is used in a population with specific treatment goals and intent that are different from those associated with the other MATs, we analyzed its cost-effectiveness in a "per protocol" scenario which resulted in an incremental cost-effectiveness ratio of approximately $1 million per QALY, well above commonly accepted cost-effectiveness thresholds of $100,000 to $150,000 per QALY. The findings remained robust in most sensitivity and scenario analyses. While evidence was inadequate to compare Sublocade to SL buprenorphine/naloxone, even under extremely favorable assumptions its cost effectiveness exceeded commonly accepted thresholds.

We were limited by the lack of data for effective modeling around patients cycling though multiple MATs and intervention re-use. We lacked treatment-specific quality-of-life estimates and robust data on diversion and switching to other opioids, and differences in trial designs prevented the use of a comparator with normalizable efficacy estimates.

The findings of our analysis suggest that the interventions of interest result in only marginal changes in QALYs relative to generic SL buprenorphine/naloxone, but universally higher costs, with resulting ratios when calculable, well above commonly-cited thresholds of $50,000 to $150,000 per QALY gained.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Potential Other Benefits

Table ES7. Potential Other Benefits

Other Benefits	Description
This intervention offers reduced complexity that will significantly improve patient outcomes.	Extended-release formulations are important additional treatment options that could improve long term recovery by lowering the constraints of daily adherence to transmucosal buprenorphine formulations.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	In correctional settings extended-release formulations offer the potential of decreasing diversion and may diminish negative beliefs about opioid agonist therapy and improve general access to MAT for inmates. Regulator could consider not to subject extended-release formulations to waivers in the future, thus increasing overall and regional access to MAT
This intervention will significantly reduce caregiver or broader family burden.	n/a
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	n/a
This intervention will have a significant impact on improving return to work and/or overall productivity.	n/a
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	Administration by a health professional can contribute to prevent accidental poisoning in children that currently occurs with transmucosal products.

Contextual Considerations

Table ES8. Potential Contextual Considerations

Contextual Consideration	Description
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	OUD is considered a public health emergency with an epidemic of deaths that decrease the overall life expectancy in the US. Providing access to extended-release medications, can contribute to diminish the consequences of the opioid epidemic.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	OUD is a chronic disease that that carries a stigma affecting self-esteem, social relations, and work. Extended-release formulations could improve long-term care.
This intervention is the first to offer any improvement for patients with this condition.	n/a
Compared to transmucosal formulations of buprenorphine/naloxone, there is significant uncertainty about the long-term risk of serious side effects of this intervention.	n/a
Compared to transmucosal formulations of buprenorphine/naloxone, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	There is significant uncertainty about the magnitude or durability of the long-term benefits of extended-release formulations, given the 6-month duration of nearly all trials of these agents. Probuphine implants cannot be used for longer than 12 months according to the FDA label. For the other formulations, their duration of appropriate use is unknown and will only be better defined through clinical experience and long-term observational study.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	For antagonist therapy with Vivitrol, its action cannot be reversed, so it becomes impossible to use opioids for emergency pain management. Regional analgesia or non-opioid analgesics need to be used.

Value-Based Benchmark Prices

We calculated value-based prices for CAM2038 and Probuphine (Table ES9). Since Vivitrol was less effective relative to its comparator in the base case, and since we did not have adequate data to model Sublocade versus SL buprenorphine/naloxone in the base case analysis, we did not estimate their value-based prices.

Table ES9. Value-Based Benchmark Prices for Cam2038 and Probuphine

	Annual WAC	Price to Achieve $100,000 per QALY	Price to Achieve $150,000 per QALY	Discount from WAC Required to Achieve Threshold Prices
CAM2038*	-	$4,082†	$5,301†	-
Probuphine	$4,950‡	$1,741‡	$2,318‡	53% to 65%

QALY: Quality-Adjusted Life Year

*No list or net prices for CAM2038 were available as of the date of this report.

†Annual price

‡Price per implant lasting six months. Probuphine implant cannot be used more than twice in the treatment for OUD for each patient

Potential Budget Impact

We used results from the cost-effectiveness model to estimate the potential total budgetary impact of CAM2038 in the patients aged 18 years and above with OUD. Given the presence of other MATs in the US marketplace for over a year, we excluded them from the budget impact analysis. In the absence of a list or net price or any published price estimate for CAM2038, we calculated its budget impact using only the prices to reach WTP thresholds between $50,000 to $150,000 per QALY.

We applied the 2015 OUD prevalence estimate to the projected 2018 to 2022 US population to calculate the candidate population for treatment with CAM2038. This resulted in approximately 312,000 treatment eligible patients each year.

The per-patient budget impact using CAM2038's prices to reach $150,000, $100,000, and $50,000 per QALY gained WTP thresholds for CAM2038 ($5,301, $4,082, and $2,863 per year, respectively) compared to generic buprenorphine/naloxone are presented below in Table ES10.

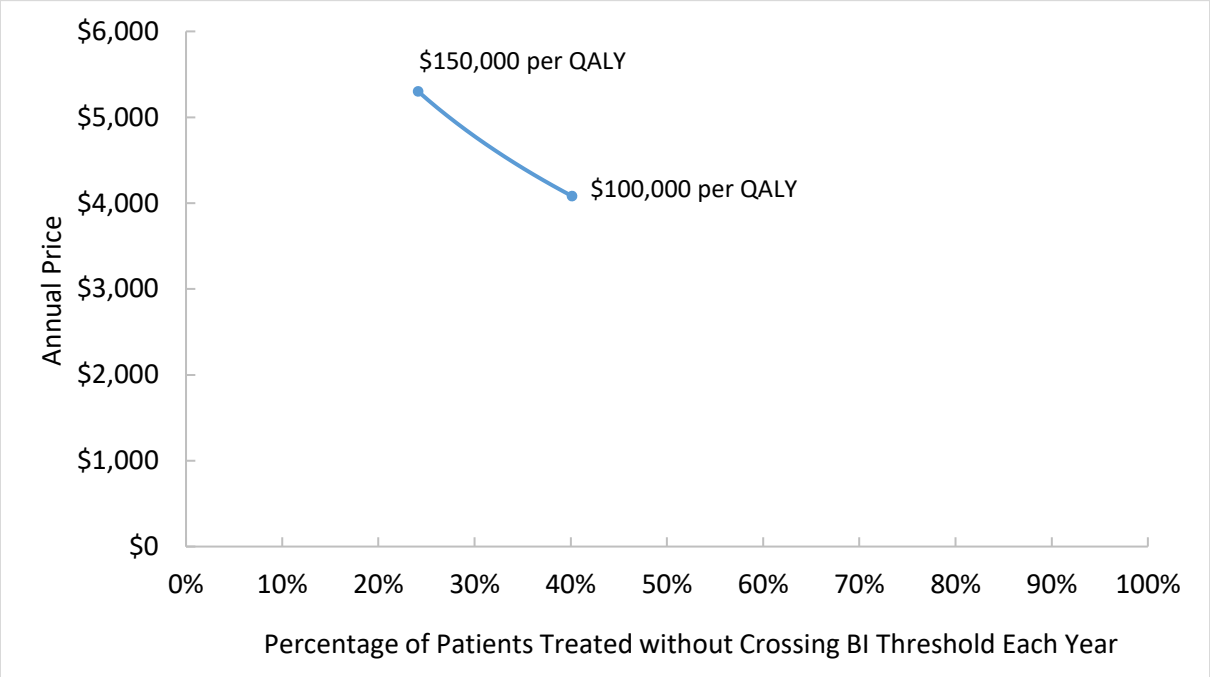
Table ES10. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon

	Average Annual Per Patient Budget Impact		
	$150,000/QALY	$100,000/QALY	$50,000/QALY
CAM2038	$35,420	$33,883	$32,346
Generic Buprenorphine/Naloxone	$31,653		
Difference	$3,768	$2,231	$694

QALY: Quality-Adjusted Life Year

As shown in Figure ES11, only 24% and 40% of the entire population could be treated each year at the prices that would reach the $150,000 to $100,000 per QALY thresholds respectively, before the total budget exceeded the ICER annual budget impact threshold. The entire eligible population could be treated each year at the price that would reach $50,000 per QALY.

Figure ES11. Potential Budget Impact Scenarios at Different Prices of CAM2038 to Treat Adults with OUD



1. Introduction

1.1 Background

Opioid use disorder (OUD) is an increasingly common public health concern that is central to the public health crisis in the US known as the opioid epidemic. In 2016, it was estimated that 2.1 million people suffered from an OUD in the US and 116 Americans died daily from opioid-related drug overdoses.[1] Overall life expectancy in the US began to decrease in 2015 due to the opioid epidemic,[2] and this trend continued through 2016, the first such decrease since the 1960s.[3] On October 27, 2017, the Acting Secretary of Health and Human Services declared a nationwide public health emergency regarding the opioid crisis[4]. The Council of Economic Advisers estimates the overall economic cost of the opioid crisis to society to be $504 billion, or 2.8% of US gross domestic product.[5]

Treatment of OUD that is grounded in the use of medication, collectively known as medication for addiction treatment (MAT), has received increasing attention in recent years as one of the essential elements for countering the opioid epidemic. (Note: this term is used interchangeably with "medication-assisted treatment;" we refer to both in this report through the MAT acronym.) The 2010 Affordable Care Act increased access to substance abuse treatment at the federal level, both for commercial plans and Medicaid. In 2015, the Department of Health and Human Services created a specific grant program for MAT that extended to 11 states and expanded to others in subsequent years. The 21st Century Cures Act of 2016 allocated $1 billion over two years to enhance states' response to the epidemic[28] and recent state legislation has been enacted to increase access to MAT, either by expanding OUD treatment programs or enhancing health insurance coverage.[29] Initiatives in New England states are often considered models for other programs: Vermont's "Hub and Spoke" is referred to as a success for integrating treatment facilities and programs into its health care system,[29-32] and Rhode Island is a leading example for providing access to MAT in correctional facilities[29,33].

In 2014, ICER conducted an assessment on clinical, delivery system, and policy options for the management of patients with opioid dependence.[34] The report found that "long-term maintenance treatment approaches using methadone or Suboxone® (Indivior) to reduce the craving for opioids have been found to be more effective than short-term managed withdrawal methods that seek to discontinue all opioid use and detoxify patients" and concluded that coordinated efforts are needed to improve access to opioid dependence treatment. Since that initial review, newer, extended-release medications for addiction treatment have been approved or are currently undergoing regulatory review. The present report does not seek to revisit the policy challenges and options highlighted in 2014, but to specifically assess the effectiveness and value of these newer medication options in patients with OUD.

Opioid Use Disorder

Opioids are substances that act on specific receptors in the brain and produce various effects such as pain relief, euphoria, respiratory depression, and constipation.[35] They are either extracted from opium, obtained from the pods of poppy varieties, or produced semi-synthetically or synthetically. Opioids reduce pain by affecting the mu receptor in the brain and spinal cord.[36] The mu receptor in the brain is also central to the feelings of reward or pleasure, leading to abuse.[37] The analgesic effects are mediated mainly through the spinal mu receptor's release of substance P,[36,38] the central neurotransmitter for pain. The rewarding effect involves the dopaminergic system, which is implicated in all addictive behaviors including those of alcohol and nicotine.[39]

The concepts and terminology around illicit drug use are constantly evolving. In the 1980s, a committee of experts convened by the American Psychiatric Association defined by consensus a set of diagnostic criteria for compulsive, uncontrolled, drug-seeking behavior. However, some members of the committee felt that using the term "addiction" to define this behavior constitutes a moral judgment that stigmatizes patients. The term "dependence" was chosen instead, even though this term was not directly related to the physical dependence that leads to withdrawal symptoms by abrupt cessation, rapid dose reduction, or administration of an opioid antagonist. The term was used in versions III and IV of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM) as a term for the compulsive, uncontrolled, drug-seeking behavior that is known to others as addiction. An intermediate state between drug use and dependence called "abuse" was also created in DSM-III.[40]

In 2013, DSM-5 replaced the categories of substance abuse and dependence with a single classification of OUD, based on criteria related to the following dimensions: impaired control, social impairment, risky use, increased tolerance, and withdrawal.[6] The language of OUD is now generally accepted and has led to a general change in "terminology that will not reinforce prejudice, negative attitudes, or discrimination."[12] OUD is generally considered to be a chronic, treatable illness that requires long-term treatment and is marked by periods of "remission" (reduction in or elimination of signs and symptoms) and relapse.

Considering the chronic nature and behavioral impacts of OUD, the primary aim of treatment is recovery rather than cure. Recovery is defined as a process of change through which individuals improve their wellness and health, live self-directed lives, and strive to reach their full potential. A person in recovery refers to an individual who abstains from further use, reduces their substance use to a safer level, or takes steps to mitigate the potential physical and emotional harm resulting from continued use.[8] Though some individuals enter and sustain recovery on their own, recovery is mostly achieved via access to evidence-based clinical treatment and recovery support services.[9]

Misuse of opioids occurs in many different patient subpopulations comprising patients who have followed many different paths to the disorder. For example, recreational users obtain and use

opioids to get high, but as they do not use the drugs in a compulsive and uncontrolled manner they are not considered to have OUD.[41] This does not mean that they do not need support and treatment, however, as recreational use is considered one of the precursors to OUD. In all age groups, medical use of prescription opioids can lead to OUD, but younger adults are more likely to abuse heroin and synthetic opioids, while older individuals are more likely to move from therapeutically-appropriate use of opioids for acute or chronic pain to misuse of those same opioids.[10] Overall, OUD patients do present with important psychiatric comorbidities, especially depression, post-traumatic stress disorder, and personality disorders.[11]

Medications for Addiction Treatment

The 2014 assessment by ICER stressed the importance of medication-based long-term maintenance treatments, and their superiority over medication-free "detoxification" protocols.[34] The central role of medications in the treatment of OUD has been confirmed by more recent assessments.[42] The Treatment Improvement Protocol (TIP) for Medications for OUD published in 2018 by the Substance Abuse and Mental Health Services Administration (SAMHSA) states as one if its key messages that "the science demonstrating the effectiveness of medication for OUD is strong."[12].

The FDA has approved three medications (in various forms) for the treatment of OUD: methadone, buprenorphine, and naltrexone.[13] All three drugs are to be used in combination with counseling and psychosocial support[14], described as a "multipronged approach that can include counseling, vocational training, psychosocial therapy, family support, and building connections to community resources,"[14] also including safe/supportive housing as an essential dimension for many patients. The FDA also questions the term "MAT," "Because OUD is a chronic illness, we should consider treating it much like we would any other chronic condition. We do not think of the medications used to treat diabetes or hypertension as 'medication assisted treatment.' We simply call it 'treatment.' OUD should be viewed similarly."[14] Table 1.1 provides an overview of the three FDA-approved drugs for the treatment of OUD.

Table 1.1. Comparison of Medications for OUD[15,16-18]

	Methadone	Buprenorphine	Naltrexone
Mechanism of Action at mu-Opioid Receptor	Agonist	Partial agonist	Antagonist
Phase of Treatment	Medically supervised withdrawal, maintenance	Medically supervised withdrawal, maintenance	Maintenance, following medically supervised withdrawal
Route of Administration	Oral	Sublingual buccal, subdermal implant, subcutaneous extended-release	Oral, intramuscular extended-release
Effective Dosage by Mouth	Usually 60mg–120mg daily	Usual sublingual/buccal stabilizing dose between 12 mg–16 mg daily	Limited effectiveness of oral naltrexone due to limited treatment retention
Regulation through Controlled Substances Act	Schedule II	Schedule III	Not regulated through Controlled Substances Act
Availability	Only available in opioid treatment programs with SAMHSA certification and DEA registration	Prescribed by physicians, nurse practitioners and physician assistants with a SAMHSA prescribing waiver	Available by prescription

Methadone is a complete synthetic mu opioid receptor agonist that does not produce a euphoric effect as opioids do.[12] However, access to methadone treatment is very limited in the US, as it cannot be legally dispensed through community pharmacies or physician offices, but only as part of highly structured treatment programs [43,44]

Buprenorphine is a semi-synthetic mu opioid partial agonist, meaning that it binds and activates the receptor, but the activation is partial with a ceiling effect on its different actions, including the "high" that is achieved. Buprenorphine has historically been administered sublingually or in the form of buccal tablets to improve bioavailability. Prescription of buprenorphine in settings outside of methadone treatment programs requires a waiver that can be obtained by physicians, nurse practitioners and physician assistants, and the number of active OUD patients that any one practitioner can have is capped at 30 patients in the first year, 100 patients thereafter, and 275 by special designation.[12] The combination of buprenorphine with the opioid antagonist naloxone, marketed as Suboxone, is frequently employed in order to avoid intravenous abuse.

Naltrexone is a semi-synthetic mu receptor antagonist, meaning that it binds to the receptor but does not produce a response. Through its high affinity for the receptor it blocks the activation of the receptor by other opioids and displaces other opioids if they are already bound to the receptor. For the treatment of OUD, the patient must first undergo opioid withdrawal therapy for seven days,

which involves abstaining also from buprenorphine and methadone, but taking only symptomatic medication. Attaining the period of opioid abstinence represents a challenge for many patients with OUD, and therefore MAT with oral naltrexone is not recommended due to low retention of patients, except under very specific circumstances.[12]

As stated by Nora Volkow, director of the National Institute on Drug Abuse, "these medications reduce withdrawal symptoms, improve mood, and help restore physiological balance—allowing the patient's brain to heal while he or she works towards recovery."[45] This applies specifically to treatments with agonists. Naltrexone, at least with oral administration, has not been shown to normalize dopaminergic and stress responsive pathways.[18] While this essential role of MAT has been established, it is not yet known definitively if or when to taper these medications. Some patients with OUD may achieve recovery without MAT, many need the medications for years, and others require lifelong treatment.[12]

In a recently published draft guidance document, the FDA recommends using a decrease in opioid use as a primary efficacy endpoint for demonstrating the effectiveness of drugs for OUD. The FDA further states that "sponsors and other stakeholders often mistakenly believe that using a change in drug use patterns as the endpoint always requires complete abstinence." Long-term studies should demonstrate that observed reductions in drug use predict clinical benefit, even if opioid use has not completely stopped.[19] By accepting and recommending a primary endpoint of a clinically relevant decrease in the use of opioids, rather than abstinence, the FDA endorses certain dimensions of "harm reduction strategies" that aim to minimize death, disease, and injury from continuing drug use, with a focus on improving daily social function and productivity.

Despite the essential role of MAT in treating OUD and in preventing harm, including death, an important gap persists between the need for and the availability of MAT. More than 30 million people live in US counties without a single prescriber for addiction treatment[20] and currently only about 20% of patients with OUD are receiving treatment[21] Expanding access to OUD medications is considered an important public health strategy for countering the opioid epidemic.[12]

Populations in prisons and jails present a unique challenge for MAT, as regular use of heroin or other opioids is common prior to incarceration. For example, nearly 50% of people on arrival at the Middlesex Sheriff's office in Massachusetts require medically supervised withdrawal from opioids[46]. However, currently few correctional settings in the US offer MAT for inmates.[20] The lack of access drives diversion for self-medication to control withdrawal and cravings. This diversion reinforces negative beliefs about opioid agonist therapy in correctional settings.[20] During imprisonment, tolerance of opioids is diminished and the risk for death from overdose is greatly increased upon release.

Extended-Release Medications

Extended-release formulations have generated clinical interest because of their potential to improve retention in treatment and circumvent some of the access challenges seen with current forms of MAT. These formulations are currently available only for buprenorphine and naltrexone. Table 1.2 provides an overview of extended-release medications for OUD that are currently available or under consideration by the FDA.

Table 1.2. Extended-Release Formulations for OUD Medications

Substance	Name and Company	FDA Approval	FDA Recommended Dosing
Buprenorphine	Sublocade™, Indivior (Subcutaneous injection)	Nov 30, 2017	After at least seven days of treatment with a transmucosal buprenorphine-containing product delivering the equivalent of 8 to 24 mg of buprenorphine daily, Sublocade abdominal subcutaneous injections are initiated with 300 mg monthly for the first two months followed by a maintenance dose of 100 mg monthly. Maintenance dose can be increased up to 300mg monthly.
	Probuphine®, Titan Pharmaceuticals, Inc. (Subdermal implant)	May 26, 2016	For patients on maintenance treatment with a transmucosal buprenorphine-containing product delivering the equivalence of buprenorphine 8 mg or less per day. Four Probuphine implants inserted subdermally in the upper arm for six months of treatment, after a new insertion in the other arm, transitioned back to a transmucosal buprenorphine-containing product.
	CAM2038, Braeburn (Subcutaneous injection)	PDUFA date expected for December 26, 2018	N/A
Naltrexone	Vivitrol®, Alkermes (Intramuscular injection)	December 10, 2010 for OUD	After an opioid-free duration of a minimum of seven to 10 days. Administered 380 mg intramuscularly every four weeks or once a month.

Of the four extended-release formulations, only Vivitrol was available at the time of the ICER report in 2014[34]. As discussed in the previous section, naltrexone is an opioid receptor antagonist and it is essential that the patient undergoes opioid withdrawal before Vivitrol can be started. An intravenous or subcutaneous naloxone challenge is recommended to ensure complete withdrawal before starting Vivitrol.[12] Patients transitioning from buprenorphine or methadone to Vivitrol can experience withdrawal symptoms for as long as two weeks after having stopped the agonist

treatment. After completed withdrawal, Vivitrol is administered by a healthcare provider as an intramuscular (IM) gluteal injection, alternating buttocks for each subsequent injection. The injection should be made with one of the customized needles provided with the product. As with all medications for OUD, treatment with Vivitrol should be accompanied by psychosocial support.[22] As naltrexone is not regulated by the Controlled Substances Act, Vivitrol can be prescribed without any particular requirements.

Treatment with Sublocade replaces a daily dose of buprenorphine with a transmucosal product with extended-release formulation of buprenorphine. For treatment to be initiated, patients need to be on a stable transmucosal dose of 8 to 24 mg buprenorphine for at least seven days. Sublocade is administered through abdominal subcutaneous injection using the syringe and safety needle included with the product. Sublocade forms a solid mass upon contact with body fluids and if administered intravenously, can cause life-threatening pulmonary emboli, as mentioned in a black box warning in the FDA label. To minimize the risk that would arise from intravenous self-administration, the Risk Evaluation and Mitigation Strategy (REMS) program does not allow the drug to be dispensed directly to the patient. Sublocade must be administered by a healthcare provider.[47] Buprenorphine is a Schedule III substance regulated by the Controlled Substances Act. It can only be prescribed by physicians, nurse practitioners, and physician assistants holding a SAMHSA waiver.

Treatment with Probuphine implants involves surgical subdermal insertion on the inside of the upper arm of a set of four rods, each 2.5 mm in diameter and 26 mm in length, each rod containing the equivalent of 80 mg of buprenorphine. The implants must be removed after six months and a second set of rods can be placed in the other arm. After this second insertion, patients must transition back to a transmucosal buprenorphine-containing product.[23] Peak buprenorphine plasma concentrations occur 12 hours after implant insertion, then slowly decrease, and after about four weeks reach steady-state concentrations comparable to daily transmucosal buprenorphine doses of 8 mg or less.[12]

The CAM2038 buprenorphine injection is currently under regulatory review with an expected approval date in December 2018. In clinical studies, this subcutaneous injection has been administered weekly or monthly with multiple dose strengths, in any subcutaneous tissue. The manufacturer proposes to include treatment initiation in the indication for CAM2038.[24] If the FDA retains this proposal in the label to be approved, this would eliminate the need for prior treatment with transmucosal buprenorphine.

During an FDA advisory committee meeting in November 2017[48], the committee members expressed some concerns about the trial design and the resulting clinical data on effectiveness and safety.[49] In January 2018, the FDA requested additional clinical information from the manufacturer, although the nature of the additional data requested is currently unknown.

1.2 Scope of the Assessment

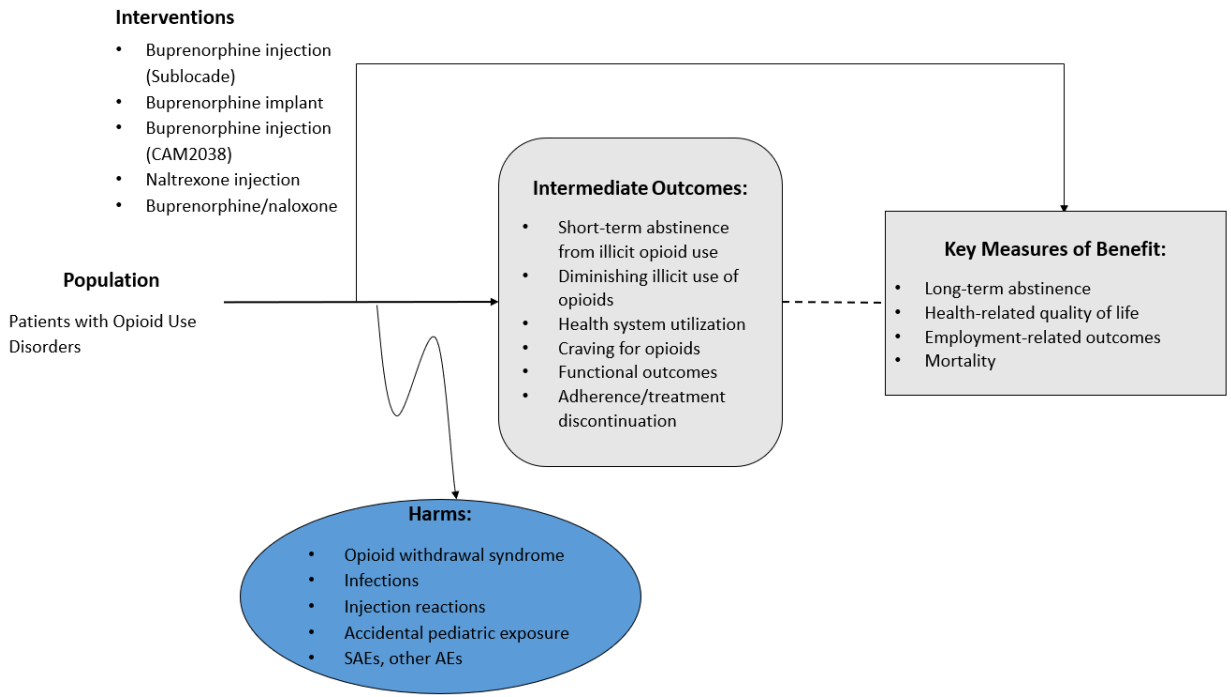
The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was collected from available randomized controlled trials and observational studies.

Our evidence review included input from individuals and advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/)

Analytic Framework

The analytic framework for this assessment is depicted in Figure 1.1.

Figure 1.1. Analytic Framework



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific clinical or health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., short-term abstinence from non-medical opioid use), and those within the squared-off boxes are key measures of benefit (e.g., health-related quality of life). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the potential harms of an action (typically treatment), which are listed within the blue ellipsis.[50]

Populations

The key population of interest for the review included patients aged 16 years and above with OUD in various treatment settings. Given different patient incentives for seeking treatment and differing mechanisms of action for the treatments themselves, we focused on a range of patients with OUD who are being considered for MAT. For the subpopulations we focused on adolescents and young adults (up to 25 years), people who inject drugs, and pregnant women.

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include. The full list of interventions is as follows:

- Buprenorphine subcutaneous extended-release injection (Sublocade)
- Buprenorphine implant (Probuphine)
- Buprenorphine subcutaneous extended-release injection (CAM2038)
- Naltrexone intramuscular extended-release injection (Vivitrol)

Comparators

Comparisons were primarily made to other common medications used for OUD (e.g., buprenorphine/naloxone in sublingual and buccal formulation), as well as to placebo. As described further in Section 3, indirect comparisons of the interventions of interest to each other were not feasible due to differences in study populations, timing of randomization, and outcome measures between key trials.

Outcomes

The outcomes of interest are described in the list below.

- Short-term and long-term abstinence from ongoing use of opioids
- Diminishing illicit use of opioids
- Opioid withdrawal syndrome
- Health system utilization (number of emergency department (ED) visits, number of primary care physician (PCP) visits, days of inpatient hospitalizations)
- Infectious (HIV, hepatitis), injection reactions, and other complications through continued use of injectable opioids
- Functional outcomes (cognitive, occupational, social/behavioral)[51]
- Craving/desire for opioids
- Accidental pediatric exposure
- Mortality (overdose deaths, suicide)
- Health-related quality of life

- Employment-related outcomes
- Adherence/treatment discontinuation (number of times treated in detox/rehab, duration of abstinence)
- Diversion
- Other patient-reported outcomes
- Other adverse events

Timing

Evidence on intervention effectiveness and harms was derived from studies of any follow-up duration.

Settings

The settings of interest included outpatient (including office-based), inpatient, and correctional facility settings in the US.

1.3 Definitions

Agonist

An agonist is a chemical that binds to a receptor and activates the receptor to produce a biological response. A partial agonist, such as buprenorphine, binds and activates the receptor, but the activation is partial, even at maximal receptor occupancy.

Antagonist

An antagonist binds to a receptor but does not produce a response, and in the case of naltrexone also blocks the activation of the receptor by other opioids.

Harm Reduction

Harm reduction for OUD includes policies, programs and practices that aim to minimize death, disease, and injury from continuing drug use, without the explicit goal of reducing or stopping use. Syringe exchange programs are an example of a harm reduction strategy to reduce HIV and HCV infections in people who inject drugs. Although there is often misunderstanding and unnecessary controversy surrounding harm reduction, its goals are congruent with the goals of treatment and recovery. MAT with agonists can be viewed as an example of a harm reduction strategy, when diminishing opioid use, rather than complete abstinence, is accepted as a valid outcome.

Maintenance Treatment

Providing medications to achieve and sustain clinical remission of signs and symptoms of OUD and support the individual process of recovery without a specific endpoint (as with the typical standard of care in medical and psychiatric treatment of other chronic illnesses).[12]

MAT

Medication for addiction treatment (MAT) is helping individuals sustain recovery using medications approved by the FDA in combination with individualized psychosocial supports. It is also often called medication-assisted treatment. Different international organizations are using the term Psychosocially Assisted Pharmacological Treatment of Opioid Dependence to refer to the combination of specific pharmacological and psychosocial measures used to reduce both illicit use of opioids and harms related to opioid use, and improve quality of life.[16]

OUD

Opioid use disorder (OUD) is defined by DSM-5 by the presence of a certain number of the following signs and symptoms: impaired control, social impairment, risky use, increased tolerance, and withdrawal. OUD replaces what DSM-IV termed "opioid abuse" and "opioid dependence." The diagnostic criteria for moderate to severe OUD roughly correspond to what is considered addiction, which is defined as a "primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations, characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving."[7].

Recovery

Recovery is a process of change through which individuals improve their health and wellness, live self-directed lives, and strive to reach their full potential. Four major dimensions support a life in recovery: health, home, purpose, and community. Though some individuals enter and sustain recovery on their own, recovery is mostly achieved via access to evidence-based clinical treatment and recovery support services.[9] A person in recovery refers to an individual who abstains from further use, reduces their substance use to a safer level, or takes steps to mitigate the potential physical and emotional harm resulting from continued use.[8] A person can be considered in recovery while on MAT.

Relapse

A process in which a person with OUD who is being treated and is in remission experiences a loss of control. A relapse is different from a return to opioid use that is limited in scope and time and that does not involve the return of the signs or symptoms of OUD. The different

operational definitions of relapse in clinical trials of medications for OUD are based on different levels of return to opioid use as measured by toxicology tests and questionnaires.

Remission

Remission refers to the disappearance of signs and symptoms of the disease. DSM-5 defines remission as present in people who were diagnosed with OUD but no longer meet OUD criteria, except for craving. Remission is an essential element of recovery.[12]

Withdrawal

Opioid withdrawal is defined by DSM-5 by the presence of at least three of the following signs or symptoms: dysphoric moods; nausea or vomiting; muscle aches; lacrimation or rhinorrhea; pupillary dilation, piloerection, or sweating; diarrhea; yawning; fever, insomnia. A withdrawal syndrome is a sign of physical dependence and can be produced by abrupt cessation, rapid dose reduction, and/or administration of an antagonist, and is a sign of prior physical dependence. Addiction medicine professionals use the term withdrawal management instead of detoxification[27], which was defined under the Narcotic Addict Treatment Act of 1974 as a treatment to achieve an opioid-free state.

1.4 Insights Gained from Discussions with Patients and Patient Groups

As part of our review, we spoke with organizations working with individuals and families affected by OUD. There was a consensus that MAT is often difficult to access, in part because of the stigma attached to OUD. This stigma is rooted in a widespread belief that drug addiction is a moral failing rather than a medical condition that is best addressed through treatment.

OUD needs to be considered a chronic disease that can affect widely varying populations in terms of age, background, and other factors. The expression, "treatment is not one-size-fits-all," was used by several organizations to stress the importance of patients having access to different treatment options on their road to recovery; some patients enter recovery without the assistance of MAT, while others require MAT for long periods of time or even their entire lives.

Equal access to all types of medications is considered important. For example, we received comments that Vivitrol is currently more easily available than other medications. Buprenorphine extended-release medications are considered important new treatment options that could improve recovery and should be widely available for consideration by patients and physicians.

It was also mentioned that peer support is particularly important for young people entering the recovery process, as they usually lack a strong existing social network compared to older adults.

Several organizations stressed that better daily functioning and well-being, and eventually recovery, are the most important outcomes of treatment. For some this may involve complete abstinence from non-medical opioid use, for others a reduced and controlled level of use. It was mentioned that this corresponds specifically to the discussions at the public meeting on Patient-Focused Drug Development for Opioid Use Disorder convened in April 2018 by the FDA.[25].

1.5. Potential Cost-Saving Measures in Extended-Release Opioid Agonists and Antagonist MAT in Patients with OUD

As described in its Final Value Assessment Framework for 2017-2019, ICER now includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) currently used for people with MAT that could be reduced, eliminated, or made more efficient.

ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for people with OUD that could be reduced, eliminated, or made more efficient. We have not received any suggestions for potential cost-saving measures but continue to seek such input.

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

To understand the insurance landscape for MAT, we reviewed publicly available representative coverage policies for Sublocade, Probuphine, and Vivitrol. We reviewed policies from the Centers for Medicare and Medicaid Services (CMS), MassHealth, and from regional and national commercial insurers (Aetna, Anthem, Blue Cross Blue Shield of Massachusetts [BCBS of MA], Cigna, Harvard Pilgrim, and United Healthcare [UHC]). At the time the Evidence Report was published, we were unable to survey policies pertaining to CAM2038, as the FDA had yet to issue a decision on the medication.

Limited information is available regarding Medicare coverage of treatment for OUD. National Coverage Determinations (NCD) describe policies regarding physician-provided, hospital outpatient, and freestanding clinic services for drug abuse treatment. Coverage is subject to general limitations applicable to these settings of care.[52,53] We were unable to locate Local Coverage Determinations (LCD) for any treatment for OUD.

Details of the utilization management policies (UMPs) for Sublocade, Probuphine, and Vivitrol are broadly summarized below. We were unable to locate specific UMPs for Harvard Pilgrim or Cigna, but we located a general Cigna policy for the treatment of substance abuse, which defines established standards of effective care.[54]

Sublocade

We located UMPs for Aetna, Anthem, and UHC. All payers require a diagnosis of moderate-to-severe opioid dependence. Additionally, the three payers require patients to have initiated treatment first with a transmucosal or sublingual buprenorphine-containing product before beginning treatment with Sublocade. Anthem and UHC specify that patients undergoing treatment with Sublocade may not receive supplemental oral, sublingual, or transmucosal buprenorphine. Aetna and Anthem state that psychosocial counseling must accompany treatment with Sublocade. UHC specifies a further requirement that the initial authorization for Sublocade may not exceed six months.[55-57]

Sublocade is not listed on the 2018 formularies for Aetna's 3-Tier Value Plan, Anthem's National 3-Tier Drug Plan, Harvard Pilgrim's Value 3-Tier Plan, or UHC's Traditional Three-Tier Plan. However, all plans offer alternative branded and generic forms of buprenorphine and buprenorphine/naloxone for the treatment of OUD. Cigna covers Sublocade under a patient's

medical benefit. BCBS of MA was the only payer to include Sublocade on its 3-Tier Plan formulary. Sublocade is placed on the mid-range tier and does not require prior authorization.[58]

Probuphine

We located UMPs for Aetna, Anthem, BCBS of MA, and UHC. All payers require a diagnosis of moderate-to-severe opioid dependence. Further, all payers state that the patient must have achieved prolonged stability on transmucosal buprenorphine before initiating treatment with Probuphine. Anthem, BCBA of MA, and UHC also specify that patients must be currently maintained on an appropriate dose of sublingual or transmucosal buprenorphine. Aetna, Anthem, and BCBS of MA specify that psychosocial counseling must accompany treatment with Probuphine. UHC specifies two further requirements: one, the patient may not receive supplemental oral, sublingual, or transmucosal buprenorphine, and two, the patient cannot have had an opioid positive urine drug screen in the past 90 days prior to the insertion of Probuphine.[55,57,59,60]

Probuphine is not listed on the 2018 formularies for Aetna's 3-Tier Value Plan, BCBA of MA's 3-Tier Plan, Harvard Pilgrim's Value 3-Tier Plan, or UHC's Traditional Three-Tier Plan.[58,61-64] Cigna covers Sublocade under a patient's medical benefit. Anthem covers Probuphine on its three-tier plan on the highest formulary tier and requires prior authorization.[65]

Vivitrol

Since Vivitrol has fewer prescribing restrictions and criteria than both Sublocade and Probuphine, we were unable to locate UMPs from commercial and regional payers indicated for the treatment of OUD.

Vivitrol is not listed on the 2018 formulary UHC's Traditional Three-Tier Plan.[62,64] Aetna, Anthem, BCBS of MA, and Harvard Pilgrim cover Vivitrol on the highest formulary tier.[58,61,64,65] Anthem is the only payer that requires prior authorization.

Medicaid Policies

To begin treatment with Sublocade, MassHealth requires a diagnosis of opioid dependency, documentation that the patient is stabilized on buprenorphine for at least seven days, and evidence that the patient needs the extended-release injection formulation. Prior authorization is required. Similarly, Probuphine may be prescribed if the patient is diagnosed with opioid dependence, is currently stabilized on buprenorphine or equivalent for at least six months and requires the implant formulation due to an adverse reaction, contraindication, or diversion with other therapeutic alternatives. Prior authorization is required. Vivitrol may be prescribed without prior authorization and is not subject to a utilization management policy.[66]

The Department of Vermont Health Access (DVHA) covers Sublocade and Probuphine as non-preferred brands for the treatment of OUD. All covered forms of buprenorphine require prior authorization, and patients undergoing treatment with Sublocade and Probuphine must receive psychosocial counseling and therapy. Patients may be prescribed Vivitrol if they pass the naloxone challenge and partake in a comprehensive treatment plan that includes psychosocial counseling and therapy.[67]

2.2 Clinical Guidelines

We reviewed guidelines on MAT issued by major US clinical societies, working groups, and health technology assessment organizations. A majority of these guidelines do not include recommendations concerning Probuphine and Sublocade because they were only recently approved. The third long-acting buprenorphine formulation, CAM2038, is currently under review by the FDA and, as such, was not listed in any clinical practice guidelines. The 2010 guideline from the American Psychiatric Association, which was summarized in ICER's 2014 report on opioid dependence, has not been updated since and may be found in Appendix F.

American Association for the Treatment of Opioid Dependence (AATOD)

AATOD Guidelines for Using Naltrexone (Vivitrol) in OTPs (2012)[68]

The 2012 AATOD guidelines state that Vivitrol may be an effective treatment for patients who struggle with a daily dosing routine. Before a patient begins treatment with Vivitrol, they must be opioid-free for at least seven to 10 days. Additionally, the AATOD recommends that a patient passes the naloxone challenge before initiating treatment with Vivitrol. The guidelines also state that Vivitrol treatment should be combined with drug rehabilitation programs, psychological counseling, and/or Narcotics Anonymous meetings.

Academy of Managed Care Pharmacy (AMCP)

Findings and Considerations for the Evidence-Based Use of Medications Used in the Treatment of Substance Abuse Disorder (2016)[69]

In their 2016 recommendations, the AMCP recommends that all patients with substance abuse disorder, including opioid addiction, should be offered medication. However, the decision to begin medication for opioid addiction should be an individualized decision between the doctor and patient. In conjunction with pharmacologic treatment, the AMCP recommendations also emphasize that psychosocial treatment should be utilized as an important aspect of recovery.

American Society of Addiction Medicine (ASAM)

The ASAM National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use (2015)[70]

Buprenorphine (Sublingual)

In their 2015 guidelines, the ASAM recommends that sublingual buprenorphine should be initiated in opioid-dependent patients once they begin to experience mild-to-moderate opioid withdrawal. Psychosocial treatment should be employed in conjunction with buprenorphine in order to maximize the benefit of treatment. In order to prevent diversion, the ASAM recommends that patients undergoing treatment should have frequent doctor visits (especially early in treatment when weekly visits are recommended), urine drug tests, and visits for pill counts. In addition, the ASAM states that patients should be tested for buprenorphine, additional substances, and prescription medications. Lastly, the ASAM states that if a patient switches from buprenorphine to naltrexone, there should be a seven to 14 day waiting period before treatment with naltrexone is initiated.

Naltrexone (Vivitrol)

The ASAM guidelines state that Vivitrol is also an effective treatment for OUD, and may be especially effective in patients with contraindications to buprenorphine or for patients for whom treatment with buprenorphine failed. The ASAM notes that Vivitrol may also be effective for patients confined to prison or inpatient habilitation, patients with co-occurring opioid disorders, and patients living in locations where methadone or buprenorphine treatment is unavailable. The ASAM strongly recommends psychosocial treatment in conjunction with Vivitrol. Lastly, the ASAM notes that treatment with Vivitrol does not have a specified timeframe and that the duration of treatment is based on clinical determinations and a patient's situation.

National Institute on Drug Abuse (NIDA)

Principles of Drug Addiction Treatment: A Research-Based Guide (2018)[71]

The 2018 NIDA guidelines offer recommendations for both drug addiction broadly and addiction to opioids. Overall, the NIDA emphasizes that the treatment program must take into consideration not only the individual's psychological, social, professional, and legal situation, but also their age, gender, and ethnicity. The NIDA recommends that the treatment plan be continually reviewed and modified if indicated.

Behavioral therapy and psychosocial counseling are also essential to treating drug addiction, and may include individual, family, or group therapy.

The NIDA states that pharmacologic therapy is also an important aspect of drug addiction treatment, and that methadone, buprenorphine (sublingual, injectable, and an implantable form), and naltrexone may be effective for individuals with opioid addiction. Individuals undergoing pharmacologic therapy for addiction must be continually monitored to ensure the efficacy of the treatment.

Substance Abuse and Mental Health Services Administration (SAMHSA)

Medications for Opioid Use Disorder for Healthcare and Addiction Professionals, Policymakers, Patients, and Families: Treatment Improvement Protocol (TIP) 63 (2018)[12]

In the 2018 TIP 63, SAMHSA states that opioid use disorder should be approached as a chronic illness, and to be effective, treatment for the disorder may need to be ongoing and continuous. Patients seeking treatment should be fully informed about opioid use disorder and the various pharmacologic treatment options available, including methadone, injectable naltrexone, and extended-release buprenorphine formulations. SAMHSA emphasizes that treatment should be individualized to the patient's needs, considering patient preference, occupation, use of other substances, and past treatment.

SAMHSA stresses that the length of treatment with injectable naltrexone and buprenorphine may vary, and some patients may require lifelong treatment. Patients who begin treatment should be monitored closely within the first few days and weeks of induction to encourage retention and to assess the effectiveness of treatment. To improve the efficacy of pharmacologic treatment, SAMHSA recommends that patients have access to counseling, recovery, and addiction services. Additionally, pharmacologic treatments should be integrated with outpatient and home treatment, and some patients may require different levels and sites of care that range from inpatient treatment to outpatient counseling.

SAMHSA and the US Department of Health and Human Services (HHS)

Federal Guidelines for Opioid Treatment Programs (2015)[44]

The 2015 SAMHSA/HHS guidelines refer specifically to treatment with methadone and all products containing buprenorphine (the guidelines also note that extended-release injectable naltrexone may be appropriate for some patients, but is not subject to these SAMHSA/HHS regulations). The guidelines state that the pharmacologic selection should be determined by a clinician and should take into consideration the patient's medical history, psychological state, complicating conditions, age, gender, and past and present substance use. Dosages should be adjusted when clinically indicated, and the SAMHSA/HHS guidelines note that dosage caps and ceilings should be eliminated. The guidelines state that medication-assisted treatment may be continued indefinitely and recommends against fixed treatment lengths. Patients undergoing pharmacologic treatment should also undergo psychosocial treatment.

3. Comparative Clinical Effectiveness

3.1 Overview

In this review of the comparative clinical effectiveness of newer, extended-release treatments for MAT (two buprenorphine injections, one buprenorphine implant, and a naltrexone injection), we systematically identified and synthesized the existing evidence from clinical studies. Full PICOTS criteria are described in Section 1.2. In brief, we evaluated studies of patients 16 years or older with OUD. Our review focused on the efficacy, safety, and effectiveness of Sublocade, Probuphine, CAM2038, and Vivitrol versus each other and versus transmucosal formulations of buprenorphine/naloxone. We extracted any relevant data, whether in published or unpublished form (e.g., conference abstracts or presentations, FDA review documents). Due to important differences in study characteristics and outcomes assessed, we did not compare the interventions of interest through direct or indirect quantitative assessments.

Essential to our review was the evidence on the clinical benefits common to trials on MAT and reported tolerability/harms. We sought evidence on all outcomes listed below:

- Relapse and abstinence outcomes based on urinalysis or self-report
- All-cause discontinuation/study retention
- Craving/desire for opioids
- Opioid withdrawal syndrome (Clinical Opiate Withdrawal Scale [COWS], Subjective Opiate Withdrawal Scale [SOWS])
- Diminishing illicit use of opioids
- Health-related quality of life (EuroQol-5 dimensions questionnaire, 36-item short form health survey [SF-36])
- Health system utilization (number of emergency department [ED] visits, number of primary care physician [PCP] visits, days of inpatient hospitalizations)
- Functional outcomes (cognitive, occupational, social/behavioral)
- Mortality (overdose deaths, suicide)
- Employment-related outcomes
- Other patient-reported outcomes
- Infections (HIV, hepatitis), injection reactions, and other complications through continued use of injectable opioids
- Accidental pediatric exposure
- Diversion
- Adverse Event (AE): serious adverse events (SAEs), discontinuation due to AEs, any AE reported by ≥ 5% of a trial arm

3.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on MAT for OUD followed established best research methods.[72] The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[73] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix Table A1.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search and submitted by manufacturers. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described in Section 1. The search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Appendix Tables A2-A4. The date of the most recent search was September 25, 2018.

To supplement the database searches, we performed a manual check of the reference lists of included trials and reviews and invited key stakeholders to share references germane to the scope of this project. We further supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Study Selection

Two reviewers independently screened the abstracts and full-texts of studies using DistillerSR (Evidence Partners, Ottawa, Canada), with any incongruencies resolved through consensus. We included relevant published and unpublished randomized clinical trials (RCTs) of any sample size as well as non-randomized comparative studies where available. To support the comparative evidence and to gain insights into the duration of treatment benefits and harms, we included non-comparative single arm observational studies with a minimum of 50 participants, and open-label extensions (OLEs) of RCTs of any size and duration. Studies assessing transmucosal buprenorphine formulations not containing naloxone and any routes of administration outside of scope (e.g., naltrexone implant) were excluded. We excluded conference abstracts reporting data that were also available in a full-text peer-reviewed publication. A detailed protocol of the methods was registered on Prospero (CRD42018103836).

Data Extraction and Quality Assessment

Data were extracted into Microsoft Excel by one researcher and independently verified by another researcher. Data elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features (e.g., open-label), interventions (drug, dosage, frequency, schedules), outcome assessments (e.g., timing, definitions, and methods of assessment), results, and quality assessment for each study. Quality assessment was based on US Preventive Services Task Force (USPSTF)[74] criteria that included presence of comparable groups, non-differential loss to follow-up, use of blinding, clear definition of interventions and outcomes, and appropriate handling of missing data. For more information on data extraction and quality assessment, refer to Appendix D.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[75]

Assessment of Bias

We assessed the presence of publication bias by utilizing the ClinicalTrials.gov database of trials. Search terms included "buprenorphine injection," "Sublocade," "CAM2038," "buprenorphine implant," "Probuphine," "naltrexone," "Vivitrol," and prior terms for these therapeutics. Publication bias was evident if any registered trials meeting our inclusion criteria remained unpublished after more than two years since their completion. We did not identify any completed, but unpublished trials of our interventions. Therefore, we did not find any evidence of publication bias. We did identify three registered and ongoing trials of the injectable naltrexone of focus. These trials are described in the Ongoing Trials sections in Appendix C and not included in any qualitative analyses.

Data Synthesis and Statistical Analyses

Data on relevant outcomes are summarized in evidence tables in Appendix D and are synthesized qualitatively in the text of the report. Relevant data include those listed in the data extraction section. Where possible, data on key outcomes of interest were evaluated on an intent-to-treat (ITT) basis. Due to differences between the studies in terms of the study design, patient characteristics, (including dosing and frequency), and outcomes (including definitions and methods of assessments), we were unable to directly or indirectly compare the interventions of interest by quantitative assessments. Hence, we focused on narratively describing the comparisons made within the clinical trials of each intervention.

3.3 Results

Study Selection

Our literature search identified a total of 557 potentially relevant references (see Appendix Figure A1). We included 23 references, of which 18 focused on comparative clinical trials, three were on OLEs, and two on observational studies. These references consisted of 15 publications, five conference abstracts, and three web-based references. Primary reasons for study exclusion included use of interventions outside of our scope, different study population (e.g., recreational opioid users), small sample size (sample size <50 for observational studies), and conference abstracts with duplicate data to the full-text publications.

The 18 references of comparative trials correspond to 11 trials, of which five of the trials were identified as key trials evaluating the four drugs of interest (Table 3.1). In four of the key trials, three of the interventions of interest (CAM2038, Probuphine and Vivitrol) were compared to buprenorphine/naloxone, while the remaining one key trial (Sublocade) was placebo-controlled with no active comparator. We identified no head-to-head trials of the interventions of interest. Below, we describe these trials and efficacy results, followed by a discussion of the tolerability and harms.

Trial Characteristics

CAM2038 (Buprenorphine Subcutaneous Extended-Release Injection)

Data to inform our assessment of CAM2038 in patients with OUD were obtained from one published Phase III RCT (Lofwall 2018).[76] This 24-week multicentered non-inferiority trial compared CAM2038 on a weekly and monthly basis to sublingual buprenorphine/naloxone in patients with moderate-to-severe OUD aged 18 to 65 years. There was no detoxification period. Eligible participants were already in opioid withdrawal and able to tolerate an initial sublingual dose of 4 mg of buprenorphine/1 mg of naloxone administered at the start of the study. Participants were randomized on the first day to receive weekly or monthly subcutaneous injections of CAM2038 and daily sublingual placebo tablets, or subcutaneous placebo injections and sublingual buprenorphine/naloxone tablets. Doses were given on a flexible schedule of 16, 24, or 32 mg of weekly CAM2038 for the first 11 weeks (phase 1), and 64, 96, 128, or 160 mg of monthly CAM2038 from weeks 12 to 24 (phase 2).[76] Reinductions were not allowed if participants missed a visit.

The primary outcome was the mean percentage of urine samples testing negative for illicit opioids over 24 weeks.[76] Additionally, responder rate, which is defined as percentage of patients with no evidence of illicit opioid use (as measured by negative urine test results and self-report of drug use) in phase one (for at least two of the three assessments at weeks nine to 11), and in phase two (for five of the six assessments from week 12 to 24) was a co-primary endpoint. Secondary outcomes

included mean percentage of opioid-negative samples from weeks four through week 24, and study retention.

Sublocade (Buprenorphine Subcutaneous Extended-Release Injection)

Data used to inform our assessment of Sublocade was mainly taken from a six-month Phase III randomized placebo-controlled trial.[77] Participants and investigators where blinded to treatment in the trial. Eligible participants ages 18 to 65 first underwent an open-label run-in induction phase with sublingual buprenorphine/naloxone film followed by an open-label run-in dose adjustment period for four to 11 days to achieve a buprenorphine /naloxone dose of eight to 24 mg.[77] Approximately three-fourths completed the run-in phase and were randomized to either the 300 mg dose of Sublocade injection, 100 mg dose of Sublocade injection, or placebo. After randomization, the dose of sublingual buprenorphine/ naloxone was tapered and then discontinued. Those randomized to the 100 mg dose group received an initial monthly dose of 300mg Sublocade for two months before receiving a monthly 100 mg dose for four months, while the 300 mg group received a monthly dose of 300 mg for the six months. In addition, participants received individual counseling at least once a week.[77]

The primary outcome was the percentage of urine samples combined with self-reports negative for illicit opioid use from weeks five to 24. Secondary outcomes included percentage of participants with treatment success defined as having ≥80% of urine samples and self-report negative for illicit opioids from weeks five to 24, percentage of urine samples negative for opioids from weeks five to 24, percentage of self-reports negative for illicit opioid use from weeks five to 24, opioid craving, opioid withdrawal, participants who completed the last visit (completers), participants who were abstinent, and clinician-reported ratings.[77]

In addition, we identified one OLE, an extension of the Sublocade trial.[78] The study population included a combination of participants who were rolled over after completing the RCT and those newly enrolled into the OLE. All participants underwent an induction period of sublingual buprenorphine/naloxone film for up to two weeks to achieve a dose ranging from eight mg to 24 mg/day. All participants received manual-guided individual counseling sessions varying in frequency.[78]

Probuphine (Buprenorphine Implant)

Data used to inform our assessment of Probuphine was obtained from one Phase III RCT (Rosenthal 2016).[79] Rosenthal 2016 was a placebo-controlled, multicentered, six-month trial conducted in the US on participants 18 to 65 years of age with OUD. In this non-inferiority trial, participants were required to be clinically stable and must have received a stable dose of sublingual buprenorphine (8 mg/day or less) for at least 24 weeks with no opioid withdrawal or illicit opioid-positive urine samples for at least 90 days before the study began. Patients were then randomized to receive

either four daily sublingual buprenorphine tablets with four placebo subdermal implants or four buprenorphine implants with daily sublingual placebo tablets.[79] Both the participants and investigators in the trials were blinded to treatments.[79] All participants received manual-guided counseling sessions during each visit and 2 mg/day of supplemental sublingual buprenorphine as needed during the study duration.[79]

The primary outcome in the Rosenthal 2016 trial was the difference in proportion of responders, defined as participants with no illicit opioid use based on monthly urine drug tests and self-reporting in four of the six months screening.[79] Secondary outcomes assessed in Rosenthal 2016 included treatment retention, percentage of illicit opioid use per month, cumulative percentage of negative illicit opioid urine results during six months, opioid craving, and opioid withdrawal.

In addition, we identified two six-month placebo-controlled randomized trials and one six-month OLE all conducted in the US on participants of same age range as Rosenthal 2016.[80-82] In Rosenthal 2013 and Ling 2010, participants were required to complete an open-label induction phase with buprenorphine/naloxone (12 to 16 mg/day sublingual tablets for three consecutive days) within 10 days of screening before randomization.[80,81] Participants who experienced severe withdrawal symptoms (>12 on the Clinical Opiate Withdrawal Scale) or severe cravings for opioids (>20 on the 0-100 Visual Analog Scale) during the induction phase were excluded.[80,81] Participants in both trials were randomized to receive either 320 mg Probuphine implants (four 80 mg subdermal implants) or four placebo implants, with an additional open-label non-inferiority comparison to buprenorphine/naloxone administered in a third arm of participants in Rosenthal 2013. Participants and investigators were blinded to Probuphine and the placebo implant in both trials.[80,81] Participants also received manual-guided counseling sessions biweekly to weekly and 2 mg/day of supplemental sublingual buprenorphine as needed during the study duration.[80,81] The OLE found was a continuation of Rosenthal 2013. Participants who completed the Rosenthal 2013 trial underwent a brief induction phase with sublingual buprenorphine/naloxone (12-16 mg/day) then received four buprenorphine implants in the opposite arm.[82] The primary outcome in Ling 2010 was the percentage of the total urine samples that were negative for illicit opioids during first 16 weeks.[80] In Rosenthal 2013, the primary outcome was the percentage of total urine samples that were negative for illicit opioids during the 24 weeks trial period. In addition, the combination of percentage of urine samples with negative self-report of illicit use was identified as a coprimary endpoint in Rosenthal 2013.[81] Secondary outcomes assessed in these trials included retention, percentage of illicit opioid use per month, opioid craving, and patient-reported and clinician-reported withdrawal scale. The OLE assessed the percent of opioid-negative urine samples, study retention, and reductions in opioid use.

Vivitrol (Naltrexone Intramuscular Extended-Release Injection)

Data used to inform our assessment of Vivitrol were taken from two key trials: one Phase IV trial (Lee 2018, X-BOT) and one Phase III trial (Tanum 2017).[83,84] X-BOT was a 24-week multicentered,

open-label, randomized controlled trial that compared Vivitrol to buprenorphine/naloxone. Participants were 18 years or older, diagnosed with OUD, and had used non-prescribed opioids within 30 days of the trial.[83] Detoxification protocols and length of time varied by site: two sites used clonidine or comfort medications (no opioids); four sites used three to five days of methadone tapers, while the remaining two sites used three to 14 days of buprenorphine tapers.[83] Timing of randomization also varied (during detoxification or after completion of detoxification), but this was designed a priori to assess the difficulty of completing detoxification. Participants were randomized to receive either 380 mg/month of Vivitrol or 8 to 24 mg/day of sublingual buprenorphine/naloxone film and stratified by treatment site and opioid use severity. Before induction with Vivitrol, participants had to complete detoxification, have opioid-negative urine, and a negative naloxone challenge (minimal or no withdrawal symptoms after administration of ≥0.4mg naloxone).[83] Missed Vivitrol injections required participants to be reinducted with a repeat naloxone challenge.[83] The primary outcome in X-BOT trial was the time to relapse event. Relapse was defined as the use of non-study opioids beyond 20 days after randomization.[83] Other secondary outcomes were the proportion of participants who were successfully inducted on an initial dose, frequency of non-study opioid use, and opioid craving.[83]

The second key trial of Vivitrol (Tanum 2017) was a 12-week, multicenter, non-inferiority, open-label, randomized controlled trial that was conducted in outpatient settings in Norway comparing Vivitrol to sublingual buprenorphine/naloxone in participants 18 to 60 years of age diagnosed with OUD.[84] Participants with other drug or alcohol use disorders were excluded from the trial. Following screening, participants were referred to a detoxification unit.[84] After detoxification, participants were randomly assigned to 4 to 24 mg/day of oral buprenorphine/naloxone or 380 mg/month of Vivitrol.[84] The primary outcome in Tanum 2017 measured study retention, proportion of total number of urine drug tests without illicit opioids, and number of days of heroin and other illicit opioids.[84] Secondary outcomes included number of days of injecting intravenous drugs, and heroin craving.[84]

In addition to the two key trials described above, we identified nine other trials of Vivitrol (four RCTs and two OLEs).[85-90] All were government funded in the US and Russia, and ranged in duration from eight to 78 weeks. Comparisons to Vivitrol included placebo or usual treatment, which varied in definition across the trials. The detoxification period also ranged from a week to a month with up to a week of Vivitrol induction. Participants were ages 18-60 years and met either DSM-IV for substance dependence and abuse or DSM-5 criteria for OUD with the majority of the trials assessing treatment in those who were or had been incarcerated. In contrast to these trials, the study population in the key trials was not restricted to incarcerated individuals. Appendix Tables D1-D3 contain data on the study design and baseline characteristics for all studies included.

Table 3.1. Trial Characteristics of Key Trials

Trial	Treatment Arms	Patient Characteristics	Intervention Period	Primary Outcomes
CAM2038				
Lofwall 2018	CAM2038* SL bup/nal*	N=428; Mean age: 38.4; Male: 61.4%; Heroin as primary opioid: 70.8%; Prescription drugs as primary opioid: 29.2%; Intravenous drug use: 52.3%; Mean years since OUD diagnosis: 4.5	24 weeks	• Mean percentage of urine samples with test results negative for illicit opioids during trial period • Responder rate
Sublocade				
Trial 13-0001 (Unpublished)	Sublocade 300mg/100mg Sublocade 300mg/300mg Placebo	N=504; Mean age: 45.2% between 30 and 45; Male: 66.7%; Heroin as primary opioid: NR; Prescription drugs as primary opioid: NR; Intravenous drug use: NR; Mean years since OUD diagnosis: NR	24 weeks	• Percentage of urine samples negative for illicit opioid combined with self-reports negative for illicit opioid use
Probuphine				
Rosenthal 2016	Probuphine 320 mg SL bup/nal ≤8 mg	N=177; Mean age: 39.0; Male: 59.1%; Heroin as primary opioid: 21.0**%;** Prescription drugs as primary opioid: 74.4%; Intravenous drug use: NR; Mean years since OUD diagnosis: 6.2	24 weeks	• Proportion of responders
Vivitrol				
Tanum 2017	Vivitrol 380 mg SL bup/nal 4-24 mg	N=159; Mean age: 36.1; Male: 72.3%; Heroin as primary opioid: NR; Prescription drugs as primary opioid: NR; Intravenous drug use: 85.5%; Mean years of heavy opioid use: 9.3	12 weeks	• Percentage of urine samples that were negative for illicit opioids • Study retention • Number of days of heroin and other illicit opioids
Lee 2018 X:BOT	Vivitrol 380 mg SL bup/nal 8-24 mg	N=570; Mean age: 34.0; Male: 70.4%; Heroin as primary opioid: 81.0**%;** Prescription drugs as primary opioid: 15.8%; Intravenous drug use: 63.2%; Mean years of opioid use: 12.5	24 weeks	• Time to a relapse event

*Flexible dosing

Bup/nal: buprenorphine/naloxone, d: day, mg: milligram, OUD: opioid use disorder, SL: sublingual

Quality of Individual Studies

We rated the one trial of the buprenorphine implant, one trial of CAM2038, one trial of Sublocade, and three trials of Vivitrol to be of good quality. These trials had comparable arms at baseline, did not have differential attrition, were patient and physician/investigator blinded, had clear definitions of intervention and outcomes, and used an intent-to-treat analysis or a modified version. Most of the good quality rated trials did not impute missing data in their primary outcomes, but a few used various imputation techniques across some of the outcomes reported. Three trials of Vivitrol and two trials of Probuphine were rated fair, as they had incomparable groups at baseline, differential attrition during follow-up, or were missing up to two of the USPSTF criteria. No trials were rated poor. Further details on the ratings of all included trials are in Appendix Table D3.

Comparability of Evidence Across interventions of interest

As noted above, we identified seven key trials for this review. Although these trials were similar in eligibility criteria, patient characteristics, and study duration, we were unable to compare the interventions of interest to each other through quantitative indirect assessment primarily due to variations in study characteristics. For example, five of the studies (all three Probuphine trials, the CAM2038 trial, and Sublocade trial) randomized participants following induction, while randomization was conducted before induction in the two Vivitrol trials. In addition, as seen in Table 3.1 above, there are variations in the outcomes assessed in these trials that are further complicated by the use of non-standard clinical measures. For example, time to relapse was an outcome assessed in only one key trial of Vivitrol, while number of days of heroin and other illicit opioid use was only assessed in the other Vivitrol trial. Furthermore, although the majority of the studies were 24 weeks in length, the timing of outcome assessment differed across trials. The percentage of urine samples negative for opioid use was assessed in the Sublocade trial (combined with negative self-reporting) and CAM2038 trial with durations ranging from five to 24 weeks and four to 24 weeks respectively. These differences are summarized in Table 3.2. below.

Table 3.2. Comparability of Evidence: Key Trials Across Interventions of interest

	Trial	Study Design	Treatment Duration (Weeks)	Detoxification/Induction Period	Time of Randomization	Outcomes
CAM2038	Lofwall 2018	Phase III RCT Non-inferiority	24	**Detoxification**: none **Induction**: one day of 4 mg bup/1 mg nal	At start of induction	• Urine samples used to assess abstinence • Outcome measured over 24 weeks
Sublocade	Trial 13-0001	Phase III RCT	24	**Detoxification**: none **Induction**: run-in induction phase with SL bup/nal film followed by open-label phase with 8 to 24 mg doses of buprenorphine/naloxone for four to 11 days	After induction	• Combination of urine samples and self-report used to assess abstinence • Outcome measured over 24 weeks
Probuphine	Rosenthal 2016	Phase III Non-inferiority	24	**Detoxification**: none **Induction**: stable dose of 8 mg/day or less of sublingual buprenorphine received for at least 24 weeks	After induction	• Urine samples and self-report used to assess abstinence • Outcome assessed over 24 weeks
Vivitrol	X-BOT	Phase IV		**Detoxification**: yes, protocols and length of time varied by site	Before induction	• Abstinence not reported • Time to relapse event reported
	Tanum 2017	Phase III RCT Non-inferiority	12	**Detoxification**: yes	After detoxification	• Urine samples used to assess abstinence • Outcome measured over 12 weeks

Bup/nal: buprenorphine/naloxone, d: day, mg: milligram, OUD: opioid use disorder, SL: sublingual

Clinical Benefits

Mortality

We sought evidence on the effect of the interventions of interest on reducing mortality. However, we found no relevant data on this outcome.

All-Cause Discontinuation

Discontinuation rates appeared similar with CAM2038, Probuphine, and Vivitrol compared with sublingual buprenorphine/naloxone. However, tests of statistical significance were not reported. Of note, significantly more patients discontinued before induction with Vivitrol compared to buprenorphine/naloxone. Results from the placebo-controlled trials of Sublocade and Probuphine showed substantially greater attrition in the placebo group than in the active treatment arms. The most common reasons for discontinuation were lack of efficacy, adverse events, withdrawing consent, being unable to complete induction, loss to follow-up, and withdrawal symptoms.

CAM2038

At 28 weeks, a similar proportion of people discontinued in the CAM2038 arm compared to the sublingual buprenorphine/naloxone arm (41% vs 43%; *p*-value: not reported).[76] More than 80% of the total participants who discontinued withdrew consent or were lost to follow-up. Other reasons cited for discontinuation included clinical (physician's) decision and adverse events.

Sublocade

During the initial open label two-week run-in period at the start of the Sublocade trial, about a quarter of the total study population (24.2%) did not complete the trial and were not randomized to receive treatment.[77] Following the run-in period and after randomization, the number of participants who discontinued were similar for both the 300-mg arm and the 100-mg arm of Sublocade (36% vs. 38%, respectively; p-value: not reported), but substantially lower than for the placebo arm (66%), although no statistical significance was reported.[77] Participants mostly withdrew consent or were lost to follow-up (>20% in both active arms). Other reasons included lack of efficacy, adverse events, protocol violations, withdrawal symptoms, non-compliance with study drug, withdrawal by physician's decision, or site closure by sponsor.[77] Additionally, in the OLE, 50% of participants who were newly enrolled dropped out of the trial.[78]

Probuphine

Of the three trials of Probuphine, the Rosenthal 2016 reported very low discontinuation rates, with a total of 7% in the Probuphine arm and 6% in the buprenorphine/naloxone arm with most participants withdrawing or lost to follow-up.[79] Importantly, however, those participants who entered the Rosenthal 2016 trial were already stable on buprenorphine/naloxone. In contrast,

higher rates of discontinuation were generally observed in Rosenthal 2013 and Ling 2010. In Rosenthal 2013, discontinuation in the Probuphine arm and sublingual buprenorphine/naloxone arm was 36% versus 37%, respectively (*p*-value: not reported) with a greater proportion of patients discontinuing in the placebo implant arm (80%).[81] Nearly half of the participants in this trial discontinued for reasons unspecified. A similar finding was observed in Ling 2010 (refer to Appendix Table D6). Major reasons cited for discontinuation in these trials included loss to follow-up, consent withdrawal, lack of treatment efficacy, non-compliance/non-adherence, issues from adverse events, or incarceration.

Vivitrol

In the X-BOT trial, a higher percentage of participants discontinued in the Vivitrol arm than in the buprenorphine/naloxone arm (28% vs. 22%); however statistical significance was not reported. Of note, significantly more participants discontinued before induction in the Vivitrol group compared to the buprenorphine/naloxone group (28% vs. 6%, *p*-value<0.0001).[83] In Tanum 2017 trial, 30% of patients discontinued from the Vivitrol arm compared to 38% in the buprenorphine/naloxone arm, (statistical significance was not reported). However, the study reported similar retention time between the two arms (mean days: 69.3 vs. 63.7; p-value: not significant). In longer-term OLEs of Vivitrol trials lasting 48 to 52 weeks, results showed up to 52% attrition.[89,90] Over 80% of the participants who discontinued withdraw consent or were lost to follow-up in both the X-BOT and Tanum 2017 trials. Other reasons cited for discontinuation in these trials include induction, detoxification failure, adverse effects, and incarceration.

Abstinence and Relapse Outcomes

Abstinence from opioid use was variably defined in available trials. For most interventions, the number of opioid-negative urines did not statistically differ in comparison to sublingual buprenorphine/naloxone. Results from the Probuphine trials showed statistically significantly greater abstinence than buprenorphine/naloxone on various measurements. Participants on Sublocade treatment were also more likely to be abstinent, but in comparison to placebo. Relapse to opioid use was a measure specific to trials of Vivitrol; a statistically significantly higher rate of relapse was seen with Vivitrol versus buprenorphine/naloxone in the intent-to-treat group.

CAM2038

In the Lofwall 2018 trial, abstinence was primarily measured by the proportion of opioid-negative urine samples over 24 weeks. The proportion of urine samples that were opioid negative was 35.1% with CAM2038 and 28.4% with buprenorphine/naloxone. This difference of 6.7% (95% CI -0.1% to 13.6%) excluded the investigator-chosen non-inferiority margin of -11%.[76] As a secondary outcome, the mean percentage of opioid-negative samples along with self-report of abstinence

from weeks four to 24 was assessed, and it was found to be significantly higher in the CAM2038 group compared to the buprenorphine/naloxone group (Mean: 35.1% vs. 26.7%, *p*=0.004). The proportion of responders to treatment was also reported, defined as having no illicit opioid use assessed by urine tests and self-report both negative during phase one (at least two of three assessments at weeks nine to 11, and week 12) and phase two (at least five of six assessments from weeks 12 to 24, and the last month of treatment). The proportion of treatment responders with CAM2038 and sublingual buprenorphine/naloxone was 17.4% and 14.4% respectively (difference = 3.0, 95% CI -4.0 to 9.9).[76]

Sublocade

In the Sublocade trial, abstinence was measured by the percentage of opioid-negative urine samples combined with self-reports negative for illicit opioid use during weeks five to 24. Results of the primary analysis showed that the proportion of participants with 90% or more negative samples was similar between the 300-mg arm and 100-mg arm (24% and 21%), but significantly higher than the placebo arm (2%, *p*<0.0001 for both comparisons to placebo).[77] In a secondary analysis, the numbers of weeks abstinent during weeks five to 24 was the same for the two active arms and also significantly higher than placebo (8.5 for both vs. 1.0, *p*<0.0001).[77] Additionally, results at the 24th week of the treatment period showed a statistically significant higher proportion of abstinent participants in the 300-mg arm than in the 100-mg arm of Sublocade or placebo (44% vs. 37%, vs. 2%, *p*<0.0001).[77]

Probuphine

In the Rosenthal 2016 trial, abstinence was measured by the combination of urine drug tests and self-report both negative to illicit use of opioids. The primary analysis of the proportion of responders was defined as participants with at least four to six months with no illicit use of opioids based on urine samples and self-report. A higher proportion of participants were abstinent with Probuphine than buprenorphine/naloxone in all participants who received treatment (96.4 vs. 87.6; *p*=0.03).[79] Furthermore, in a separate sensitivity analysis in the intent to treat population, a higher proportion of participants were abstinent with Probuphine than buprenorphine/naloxone over the six-month period (80.5% vs. 66.7%, *p*= 0.04).[79] At six months, a greater proportion of participants were abstinent with Probuphine than buprenorphine/naloxone (85.7% vs. 71.9%; *p*=0.03).[79]

The two similar Probuphine trials (Ling 2010 and Rosenthal 2013) differed in the measurement of abstinence. Ling 2010 measured abstinence as the percentage of a total of 48 urine samples negative for illicit opioid use during the first 16 weeks, and showed a greater percentage of reported opioid-negative samples with the buprenorphine implant than placebo (40.4% vs. 28.3% *p*=0.04).[80] Rosenthal 2013 defined abstinence as the percent of opioid-negative urines during the entire study duration. Rosenthal 2013 found a greater proportion of reported opioid-negative urine

samples in the buprenorphine implant arm than with the placebo implant (31.2% vs. 13.4%, p<0.0001); the proportion with open label sublingual buprenorphine/naloxone was 33.5%.

Vivitrol

We found data on abstinence and relapse outcomes in three Vivitrol trials. The abstinence-based outcome presented in Tanum 2017 was defined as the proportion of the total number of urine drug tests with no opioid use. The proportion of the total number of opioid-negative urine drug tests with Vivitrol and buprenorphine/naloxone were 0.9 and 0.8, respectively (difference = 0.1, 95% CI -0.04 to 0.2).[84] In addition, Krupitsky 2011 showed a statistically significant median proportion of weeks with confirmed abstinence to be greater for Vivitrol compared to placebo (90.0% vs. 35.0%, respectively) during weeks five to 24. Confirmed abstinence was defined as a negative urine drug test and negative self-report for opioid use.[86] Also, a significantly higher proportion of participants with confirmed abstinence occurred with Vivitrol than placebo (35.7% vs. 22.6%, Relative Risk (RR) =1.58, 95% CI 1.06 to 2.36, *p*=0.0224).[86] During weeks three to 24, the X-BOT trial found a higher proportion of participants in the intent-to-treat group relapsed after 20 days on Vivitrol compared to those on sublingual buprenorphine/naloxone film (65% vs. 57%, *p*=0.036). In the per-protocol group, more than half the participants relapsed in both groups, and the proportions were not statistically significantly different from each other.[83] Due to its antagonistic action, patients on Vivitrol would not experience any effect from taking opioids, but the relapse rates in the per protocol group may be indicative of continued craving while on Vivitrol.

Diminishing Illicit Use of Opioids

Vivitrol was the only intervention with data on diminishing illicit use of opioids which was assessed in one key trial. That trial found that Vivitrol decreased use of heroin and other illicit opioids when compared to buprenorphine/naloxone over the duration of the trial.

CAM2038

No data on diminishing opioid use were reported in the CAM2038 trial.

Sublocade

No data on diminishing opioid use were reported in the Sublocade trial.

Probuphine

No data on diminishing opioid use were reported in the Probuphine trial.

Vivitrol

Tanum 2017 was the only key trial reporting on diminishing illicit use of opioids. On average during the 12-week trial, patients treated with Vivitrol had fewer days of heroin use and illicit drug use than patients treated with buprenorphine/naloxone (heroin use: -3.2 days, 95% CI -4.9 to -1.5); illicit drug use: -2.7, 95% CI -4.6 to -0.9). At 12 weeks, results also showed that participants receiving Vivitrol had fewer mean days of heroin use than those receiving buprenorphine/naloxone (1.1 vs. 4.1, respectively; mean difference = -3.6 days, 95% CI -6.0 to -1.2), although differences were not statistically significant for other illicit opioid use.[84] Its associated 48-week OLE showed a continued decrease in heroin use days and illicit drug use days.[89] Evidence on intravenous drug use was mixed; the eight-week trial (Lee 2015) showed a higher percent of participants with heroin use after release from prison with Vivitrol than treatment as usual in the first month.[91] In contrast, at 24 weeks in Lee 2016, the proportion of criminal justice offenders using any intravenous drugs was numerically higher in the treatment as usual group versus Vivitrol, although this was not statistically significant.[92]

Opioid craving – Visual Analog Scale

Opioid craving scores on CAM2038 and Probuphine were not statistically significantly different from those on buprenorphine/naloxone. Sublocade decreased opioid craving compared with placebo. One trial found numerically lower opioid craving scores with Vivitrol than buprenorphine/naloxone, but statistical significance was not reported.

Opioid craving is generally defined as a desire to use opioids. It is commonly measured with self-reported questionnaires using the Visual Analogue Scale (VAS). A total of eight studies in our included study set assessed for opioid craving using the VAS, and they are summarized in Table 3.3. below.

Table 3.3. Opioid Craving – VAS Scores* in Key Trials

Study Study Design	Duration of Follow-Up	Treatment Arm Dosage	N	Mean VAS Over Duration of Follow-Up	Mean VAS Change from Baseline	p-Value
CAM2038						
Lofwall 2018[76], RCT	24 weeks	CAM2038	213	17.3 (SD: 25.5)†	NR	NR
		Bup/nal, SL	215	17.3 (SD: 25.5)†	NR	
Sublocade						
Trial 13-0001, RCT	24 weeks	Sublocade 300mg/100mg	192¤	NR	2.1 (SE: 1.63)	vs. placebo: p=0.0003
		Sublocade 300mg/300mg	193¤	NR	-0.9 (SE:1.63)	vs. placebo: p<0.0001
		Placebo	96¤	NR	11.5 (SE: 2.48)	--
Probuphine						
Rosenthal 2016[79], RCT	24 weeks	Probuphine	84	NR	-2.3 (SD: 11.15)‡; -2.7 (SD: 12.58)†	NS for both
		Bup/nal, SL	89	NR	-2.8 (SD: 19.57)‡; -1.9 (SD: 18.97)†	
Vivitrol						
Tanum 2017[84], RCT	12 weeks	Vivitrol	56	0.83 (95% CI: -0.81 to 2.43)§	NR	NR
		Bup/nal, SL	49	2.69 (95% CI: 1.77 to 3.60)§	NR	

Bup: buprenorphine, mg/d: milligrams per day, nal: naloxone, RCT: randomized controlled trial, SL: sublingual, VAS: visual analog scale

*Opioid craving measured on 100 mm scale, where 0=no craving and 100=strongest craving, unless otherwise noted;

†Mean VAS need-to-use score, where 0=no need and 100=strongest need;

‡Mean VAS desire-to-use score, where 0=no desire and 100=strongest desire;

§Craving for heroin, rated on a scale of 0=no craving to 10=very strong;

#Data reported are percentage of patients reporting opioid craving increases, decreases, or no changes compared to baseline, where 0=no craving and 10=strongest craving;

¤Number of participants analyzed for outcome.

CAM2038

Lofwall 2018 showed no differences in opioid cravings between CAM2038 injections and sublingual buprenorphine/naloxone over 24 weeks. Groups were not compared statistically; however, data presented in a graph indicates that CAM2038 and buprenorphine/naloxone resulted in identical Mean VAS scores for opioid craving after 24 weeks of treatment (17.3, SD: 25.5).[76] Likewise, both groups showed a similar pattern in VAS scores over the trial duration.

Sublocade

Compared to placebo, the two Sublocade arms each showed a decrease in opioid cravings (300-mg arm: mean difference = -12.4, 95%CI -17.5 to -7.3, $p<0.0001$; 100-mg arm: mean difference = -9.4, 95% CI -14.6 to -4.3). Refer to Table 3.3 above.[77]

Probuphine

In the Rosenthal 2016 trial, there were no significant differences between Probuphine and buprenorphine/naloxone in the mean change from baseline of desire-to-use and need-to-use scores by six months.[79] In the two trials (Ling 2010 and Rosenthal 2013) comparing Probuphine to placebo implants, a statistically significant benefit favoring Probuphine over placebo was seen when comparing mean VAS scores over 24 weeks (see Appendix Table D7).[80,81] Ling 2010 reported a mean VAS score of 9.9 (95% CI: 7.8 to 12.0) versus 15.8 (95% CI: 12.7 to 18.9) in the buprenorphine and placebo groups, respectively. Similarly, Rosenthal 2013 reported a mean VAS score of 10.2 versus 21.8 in Probuphine and placebo implant groups, respectively. Rosenthal 2013 also compared the same active implant to open-label buprenorphine/naloxone and found no statistically significant difference between the two treatments.

Vivitrol

One key study of Vivitrol (Tanum 2017) comparing Vivitrol to buprenorphine/naloxone assessed opioid craving specific to heroin using a 0-10 VAS scale. The study found cravings to be numerically less intense among participants on Vivitrol compared to the buprenorphine/naloxone arm; however, the statistical significance of this difference was not reported (Table 3.3).[84]

In addition, two placebo-controlled trials of Vivitrol also reported on opioid cravings. The NEW HOPE trial compared Vivitrol to placebo and reported the percentages of participants reporting improved, worsened, or stable opioid cravings among a small subset of participants.[88] These results were not statistically compared. Approximately 10% more participants in the Vivitrol group versus placebo reported experiencing decreased opioid cravings (43.8% vs. 33.3%, respectively) through 24 weeks of treatment while similar proportions of the Vivitrol and placebo groups reported increased opioid craving (18.8% vs. 20.0%, respectively) [88]

Krupitsky 2011 reported a statistically significant treatment difference in opioid craving by VAS scale favoring Vivitrol over placebo treatment after 24 weeks of treatment (Vivitrol mean VAS change from baseline: -10.1; placebo: 0.7; difference = -10.7, $p<0.0001$).[86] Additional data averaging results from weeks eight to 24 showed similar results (Vivitrol: -9.4, placebo: 0.8).[93]

Opioid Withdrawal

No significant differences were shown for CAM2038 and Probuphine each in comparison to buprenorphine/naloxone in the Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS). Only the higher dose arm of Sublocade showed any significant difference from placebo. There were no COWS or SOWS data for Vivitrol.

COWS is administered by clinicians and measures 11 common opioid withdrawal symptoms. Higher scores indicate worse clinician-reported withdrawal symptoms. Four common thresholds are used to indicate mild (5-12), moderate (13-24), moderately severe (25-36), and severe (scores >36) opioid withdrawal symptoms.

SOWS is a self-reported measure for grading 16 common opioid withdrawal symptoms. Each symptom is graded on a scale of 0 (not at all) to 4 (extremely) for a total score of 64, where higher scores indicate more severe patient-reported withdrawal symptoms. Both COWS and SOWS evaluate common opioid withdrawal symptoms including pulse rate, sweating, restlessness, pupil size, bone and joint aches, gastrointestinal upset, tremors, yawning, goosebumps, and anxiety or irritability.

Three key trials included in our systematic review measured COWS over 24 weeks. Two studies reported both COWS and SOWS data; no studies reported only SOWS. Reporting of opioid withdrawal symptoms was more homogenous than reporting of opioid craving. Neither the COWS or SOWS scores, however, have an established and/or validated definition of a minimum clinically important difference, so it is unclear whether the changes reported in the trials summarized below represent clinically meaningful improvements for patients with OUD.

<u>CAM2038</u>

Lofwall 2018 showed no differences between CAM2038 injections and sublingual buprenorphine/naloxone over 24 weeks.[76] Groups were not compared statistically, however, graphical data published shows nearly identical weekly (weeks one to 12) or monthly (weeks 12-24) COWS scores over 24 weeks. COWS data estimated from this graph reported mean COWS scores of 3.3 (SD 3.5) and 2.7 (SD 4.0) for the CAM2038 and sublingual buprenorphine/naloxone groups, respectively.

Sublocade

The Sublocade trial showed a significant difference in COWS and SOWS in the 300-mg arm when compared to placebo (COWS -1.1 vs. -0.1, mean difference: -1.0, 95% CI -1.72 to -0.23; SOWS -2.0 vs. 0.7, mean difference: -2.6, 95% CI -4.32 to -0.90), but no significant difference in the 100-mg arm.[77]

Probuphine

Rosenthal 2016 showed no significant differences in COWS and SOWS from baseline between Probuphine and buprenorphine/naloxone.[79] In addition, two studies – Ling 2010 and Rosenthal 2013 – evaluated buprenorphine implants versus placebo.[80,81] Both studies showed buprenorphine implants were statistically superior compared to placebo implants over 24 weeks of treatment in COWS (2.49 vs. 4.52, p<0.001) and SOWS (5.30 vs. 8.42, p<0.0001). As noted above, Rosenthal 2013 also included an open-label buprenorphine/naloxone group.[81] Exploratory analyses showed buprenorphine implants was associated with worse withdrawal symptoms compared to open-label buprenorphine/naloxone (COWS 2.49 vs. 1.71, , p=0.0005; SOWS 5.30 vs. 2.83, , p=0.0006).

Vivitrol

There was no evidence on COWS or SOWS in the key trials of Vivitrol.

Health-Related Quality of Life and Other Outcomes

Evidence on health-related quality of life and patient specific outcomes were reported only in trials of Vivitrol. Results showed an overall increase in quality of life in patients receiving Vivitrol compared with placebo. Patient satisfaction with treatment occurred more with Vivitrol than with buprenorphine/naloxone.

CAM2038

No data on health-related quality of life, incidence of infectious diseases, functional outcomes, employment-related outcomes, diversion, accidental pediatric exposure, or other patient outcomes were reported in the CAM2038 trial.

Sublocade

No data on health-related quality of life, incidence of infectious diseases, functional outcomes, employment outcomes, diversion, accidental pediatric exposure, or other patient outcomes were reported in the Sublocade trial on clinicaltrials.gov.

Probuphine

No data on health-related quality of life, incidence of infectious diseases, functional outcomes, employment-related outcomes, diversion, or other patient outcomes were reported in the Probuphine trial.

Vivitrol

Health-related quality of life was measured only in the Vivitrol placebo-controlled trial. This was assessed using the 36-item short form health survey (SF-36) and the VAS self-rating assessment of patients' general health EuroQol-5 dimensions questionnaire.[86] In the 24-week trial, the difference in mean change from baseline in patients' VAS assessments showed a statistically significant increase in general health with Vivitrol when compared to placebo (14.1 vs. 2.7, difference of 11.4, 95% CI 5.0-17.8, p-value = 0.0005).[86] The mean score for the mental component of SF-36 was also higher in the Vivitrol arm than the placebo arm (50.37 vs. 45.28; difference of 5.09 95%CI 2.09 to 8.09; *p*-value not reported).[86]

In addition, patient satisfaction was assessed in one of the key trials of Vivitrol (Tanum 2017). Tanum 2017 measured satisfaction with treatment by the visual analog scale (VAS) with 0 indicating very low and 10 indicating very high. By 12 weeks, participants' satisfaction with treatment was found to be higher among participants receiving Vivitrol than those receiving buprenorphine/naloxone (estimated values: 8.61 vs 3.66; p-value not reported).[84]

No data on incidence of infectious diseases, functional outcomes, employment-related outcomes, accidental pediatric exposure, or diversion were reported in the Vivitrol trials that met our inclusion criteria.

Health Care Utilization

Limited data were reported on health care utilization, and only for Vivitrol. Evidence from available trials found no differences in health care utilization between Vivitrol and treatment as usual. Results from one observational study showed reduced inpatient admissions with Vivitrol.

Health care utilization was reported in a post-hoc analysis of Lee 2016.[92,94] During the 24-week treatment phase of the study, the percentage of participants with health care utilization, defined as any ED visits or hospital admissions, did not significantly differ between patients randomized to Vivitrol and treatment as usual (31.5% vs. 35.0%, respectively).[94] When stratified by health care utilization type, there also were no significant differences in the percentages of participants randomized to Vivitrol and treatment as usual in terms of drug detox hospitalizations (2.7% vs. 2.1%), psychiatric hospitalizations (1.4% vs. 3.5%), or ED visits (25.3% vs. 28.0%).[94] However, significantly fewer patients randomized to Vivitrol had medical or surgical hospitalizations

compared to patients randomized to treatment as usual (6.9% vs. 14.0%; incidence rate ratio [IRR]=0.37 95% CI: 0.16, 0.88; p=0.02).[94]

We also identified one observational study assessing health care utilization among cohorts of patients with OUD receiving treatment with Vivitrol (n=1,041), non-specific buprenorphine (n=20,566), and nonpharmacological therapy (n=6,883).[95] Comparing the 12-month period before treatment (baseline) to the 12-month period after starting treatment (follow-up), the mean number of inpatient admissions was reduced by 46.6%, 20.8%, and 15.1% in the Vivitrol, buprenorphine, and nonpharmacological therapy cohorts, respectively (p<0.05 baseline vs. follow-up for all); the study did not report the statistical significance of the differences among the cohorts. The mean days in inpatient care was significantly reduced in the Vivitrol (-56.8%) and buprenorphine cohorts (-8.8%) (p<0.05 baseline vs. follow-up for both) but not in the nonpharmacological therapy cohort (-0.6%). In addition, the mean number of ED visits was reduced by 26.1% in the Vivitrol cohort, 13.3% in the buprenorphine cohort, and 15.5% in the nonpharmacological therapy cohort (p<0.05 baseline vs. follow-up for all).

Harms

Serious adverse events were generally low and similar in trials of CAM2038, Probuphine, and Vivitrol in comparison to buprenorphine/naloxone and in the Sublocade trial vs placebo. Discontinuation due to adverse events was not reported in most trials. Results from one Vivitrol trial showed that similarly low numbers of participants discontinued when compared to buprenorphine/naloxone. The most common adverse events reported in the trials were injection/implant site pain, gastrointestinal issues, headaches, and insomnia.

In the CAM2038 trial (Lofwall 2018), the incidence of serious adverse events (SAEs) occurred in 2.3% of participants receiving CAM2038 arm versus 6% of those receiving sublingual buprenorphine/naloxone at 24 weeks (see Table 3.4 below). Seven participants discontinued due to AEs in the CAM2038 arm, while three discontinued in the buprenorphine/naloxone arm.[76] Although no participant died from overdose, there was one unrelated death in the buprenorphine/naloxone arm of the trial. The most commonly occurring AEs in the CAM2038 arm (see Table 3.4 below) were injection-site pain, injection-site pruritus and erythema, headache, constipation, and nausea. Additional AEs of urinary tract infection and insomnia occurred in the buprenorphine/naloxone arm.[76]

During the 24-week Sublocade trial, results showed SAEs occurring in <5% of participants in the 300 mg Sublocade arm versus 2% of participants in the 100 mg arm and 5% in the placebo arm. One death occurred in the 300-mg Sublocade arm unrelated to overdose. Ten participants discontinued due to AEs in the 300-mg arm, seven discontinued due to AEs in the 100-mg arm, and two discontinued in the placebo arm. The most common AE in the Sublocade arms were similar to

CAM2038, and included gastrointestinal disorders, injection site pruritus and pain, upper respiratory tract infections, nasopharyngitis, headache, and insomnia.

In the 24-week Probuphine key trial,[79] similar proportions of participants receiving Probuphine and placebo had an SAE (2.3% vs. 3.4%). Similar results were seen in the other trials with the exception of Ling 2010 which had a higher rate of SAEs occurring in the placebo arm.[80,81] There was one accidental pediatric exposure in the buprenorphine/naloxone arm that led to the notification of child protective services.[79] Deaths were unreported in Rosenthal 2016. However, one death occurred in the Rosenthal 2013 trial and was overdose-related in the buprenorphine/naloxone arm.[81] In the Rosenthal 2016 trial, only one participant discontinued due to an AE in the Probuphine arm.[79] Whereas, no participant discontinued due to AEs in the Rosenthal 2013 trial and four discontinued due to AEs in the Ling 2010 trial both in the Probuphine arms (see Appendix Table D9).[80,81] The most common AEs were related to the implant site (erythema, itching, pain), headaches, gastrointestinal problems, and nasopharyngitis.

In the X-BOT trial, at 24 weeks the incidence of AEs was 14% and 11% in the Vivitrol and sublingual buprenorphine/naloxone arms, respectively.[83] Six participants discontinued due to the occurrence of an AE in the Vivitrol arm, while eight discontinued in the buprenorphine/naloxone arm. Out of the five total fatalities that occurred, two were in the Vivitrol arm with the other three in the buprenorphine/naloxone arm. Overdose was the cause of death in two of the three fatalities in the Vivitrol arm and three of the four in the buprenorphine/naloxone arm.[83] No deaths occurred in the Tanum 2017 trial. At 12 weeks, a similar proportion of participants had that experienced a SAE in the Vivitrol arm was 8.5%, whereas 4.2% experienced a SAE in the buprenorphine/naloxone arm.[84] Four participants discontinued due to AE in the Vivitrol arm, while six discontinued in the buprenorphine/naloxone arm in this trial.[84] The most common AEs (also reported in four other trials of Vivitrol versus usual treatment or placebo) were insomnia, psychiatric disorders (anxiety and depression symptoms), and injection site problems.

The label for Vivitrol warns of an increased risk of opioid overdose fatalities, as participants on Vivitrol have reduced tolerance to opioids given that complete withdrawal is a prerequisite for Vivitrol therapy. The label reports that cases of opioid overdose deaths have been reported in patients who used opioids at the end of a dosing interval, after missing a dose, and after discontinuation.[96] We identified a review of case narratives of overdose fatalities among patients who received Vivitrol that were reported to the FDA Adverse Event Reporting System. Results show that most of the overdose deaths occurred within 28 to 56 days after the last reported Vivitrol dose.[97] However, it is unclear whether this time interval corresponds to a biological rebound risk of overdose.

Table 3.4. % of SAE, Discontinuation due to AE (%), and Deaths

	SAE, n (%)	Discontinued Due to AE, n (%)	Death, n (%)
CAM2038 (Lofwall 2018) [76]			
CAM2038	5 (2.3)	7 (3.3)	1 (0.5)
Bup/Nal	13 (6.0)	3 (1.4)	0
Trial 13-0001[77]			
Sublocade (300mg/300mg)	7 (3.5)	10 (5.0)	1 (0.5)
Sublocade (300mg/100mg)	4 (2.0)	7 (3.4)	0
Placebo	5 (5.0)	2 (2.0)	0
Buprenorphine Implant[79]			
Probuphine	2 (2.3)	1 (1.1)	NR
Bup/Nal	3 (3.4)	0	NR
X-BOT[83]			
Vivitrol	29 (14)	6 (2.1)	3 (1.1)
Bup/Nal	29 (11)	8 (2.8)	4 (1.4)
Tanum 2017[84]			
Vivitrol	8.5	4 (5.6)	0
Bup/Nal	4.2	6 (8.3)	0

Table 3.5. ≥5% AEs

	Headache (%)	Nasopharyngitis (%)	Injection/Implant Site Problems (%)	Injection/Implant Site Pain (%)	Depression (%)	Insomnia (%)	GI Upset (%)
CAM2038 (Lofwall 2018)[76]							
CAM2038	7.5		6.1 (pruritus); 5.6 (erythema)	8.9		5.6	7.5 (constipation); 7.0 (nausea)
Bup/Nal	7.9		6.8 (pruritus); 5.6 (erythema)	7.9		2.8	7.4 (constipation); 7.9 (Nausea)
Trial 13-0001[77]							
Sublocade (300mg/300mg)	8.5	5.0	9.5 (pruritus)	6.0		8.5	8.0 (constipation), 8.0 (nausea), 5.5 (vomiting)
Sublocade (300mg/100mg)	9.4	5.4	6.4 (pruritus)	4.9		6.4	9.4 (constipation); 8.9 (nausea); 9.4 (vomiting)
Placebo	6.0	1.0	4.0 (pruritus)	3.0		11	0 (constipation), 5 (nausea), 4 (vomiting)
Buprenorphine Implants[79]							
Probuphine	6.9	8.0	13.8		6.9		8.0
Bup/Nal	3.4	4.5	7.9		2.2		1.1
X-BOT[83]							
Vivitrol			16.3 (any)				12.0
Bup/Nal			NA				20.6
Tanum 2017[84]							
Vivitrol			5.6		16.9 (anxiety or depression)	11.3	
Bup/Nal			NA		8.3 (anxiety or depression)	4.2	

Comparator Evidence

Methadone and Buprenorphine/Naloxone

We did not conduct a systematic search for methadone or buprenorphine/naloxone; rather, we identified and summarized previous systematic reviews published by Cochrane and CADTH, as listed below:

- Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence[98]
- Buprenorphine/naloxone versus methadone for the treatment of opioid dependence[99]

We were unable to identify a systematic review for buprenorphine/naloxone in comparison to no active treatment. Therefore, we summarized the results from the sole placebo-controlled trial of buprenorphine/naloxone.[100] Fudala et al. was a multicenter, placebo-controlled trial including 326 patients with OUD (DSM-IV). Patients were randomly allocated to daily treatment with sublingual tablets of buprenorphine/naloxone, buprenorphine alone, or placebo for four weeks. The trial was terminated early because buprenorphine/naloxone and buprenorphine alone showed much greater efficacy than placebo. After four weeks, 268 patients from the placebo-controlled phase and 193 newly-enrolled patients entered a 48- and 52-week open-label safety study of buprenorphine/naloxone, respectively. We also highlighted findings from a systematic review of RCTs of buprenorphine-containing formulations to supplement the results from Fudala et al.[101] This systematic review evaluated the efficacy of the buprenorphine-containing formulations at low (2-6 mg), medium (7-15 mg), and high doses (≥16 mg) compared to placebo; of note, the authors of this systematic review considered 1 mg of buprenorphine as placebo in addition to true placebo. We summarized results for the medium and high dose levels as the doses of buprenorphine in Fudala et al. and the key trials in our review are within the medium and high dose range.

Mortality

Four studies included in the 2009 Cochrane systematic review of RCTs comparing methadone maintenance treatment to therapies not involving opioid agonists (i.e., placebo, detoxification, nonpharmacological therapy, wait-list controls) for the treatment of OUD reported the number of deaths among patients. Three out of 287 (1%) patients on methadone maintenance treatment and eight out of 289 (2.8%) patients receiving no opioid agonist therapy had died at one to 36 months of follow-up.[98] Five of the eight deaths associated with no opioid agonist therapy resulted from fatal overdoses, and the causes for the other three deaths were not reported. At three years of follow-up, only one of the three deaths associated with methadone maintenance treatment resulted from an alleged overdose.[102] Results from the meta-analysis found that methadone maintenance treatment was not statistically significantly more effective in preventing deaths compared to no

opioid agonist therapy, although the risk ratio points to a reduced risk of mortality for patients on methadone maintenance treatment (risk ratio [RR]: 0.48; 95% CI: 0.10 to 2.39).[98]

We did not find any information from systematic reviews on buprenorphine/naloxone compared to no active treatment or methadone in the ability to prevent deaths.

All-Cause Discontinuation/Study Retention

The 2009 Cochrane systematic review found methadone maintenance treatment to be more effective in retaining patients in treatment compared to therapy with no opioid agonists. To analyze treatment retention, the authors of this review stratified the included studies by those conducted before and after 2000 since they speculated that differences in results occurred over time; however, it is unclear why the authors chose the year 2000 as a cut point and why they did not conduct similar subgroup analyses for the other outcomes (mortality and abstinence). Nevertheless, treatment retention was found to be significantly higher with methadone maintenance treatment compared to no opioid agonist therapy in the older studies at six to 32 weeks (68.1% vs. 25.1% RR: 3.05; 95% CI: 1.75 to 5.35, three studies, 505 patients) and even higher in the newer studies at four to 24 weeks (73.4% vs. 16.4%; RR: 4.44; 95% CI: 3.26 to 6.04, four studies, 750 patients).[98]

In Fudala et al, 10.1% of patients receiving buprenorphine/naloxone, 3.8% receiving buprenorphine, and 11.0% receiving placebo discontinued from the four-week placebo-controlled trial; reasons for discontinuation were not reported.[100] Of the 472 patients assessed for safety in the 48- and 52-week open-label phase of Fudala et al., 385 (81.6%) patients received at least eight weeks and 261 (55.3%) patients received at least six months of treatment with buprenorphine/naloxone.[100] The 2014 Cochrane systematic review and meta-analysis of RCTs of buprenorphine-containing formulations showed treatment with buprenorphine-containing formulations was associated with significantly higher treatment retention compared to placebo at medium doses at two to 48 weeks (65.3% vs 37.6% RR: 1.74; 95% CI: 1.06 to 2.87, four studies, 887 patients) and high doses at four to 48 weeks (65.5% vs. 39.7% RR: 1.82; 95% CI: 1.15 to 2.90, five studies, 1,001 patients).[101]

Five studies summarized in the 2016 CADTH review comparing buprenorphine/naloxone and methadone reported the percent of patients completing treatment with methadone and buprenorphine/naloxone. Three of these studies measured retention at six months and found methadone retained between 46.4% and 74.1% of patients and buprenorphine/naloxone retained between 30.3% and 50.0% of patients[103-105]; two of these studies reported statistical significance favoring methadone ($p<0.01$).[103,105]

Opioid Abstinence

The 2009 Cochrane systematic review found methadone maintenance treatment to be effective in reducing illicit use of opioids compared to no opioid agonist therapy. A meta-analysis of six trials

including 1,129 patients showed 45.7% of patients on methadone maintenance therapy versus 66.5% of patients on no opioid agonist therapy had positive hair or urine analysis at four to 16 weeks of follow-up (RR: 0.66; 95% CI: 0.56 to 0.78).[98]

In Fudala et al., buprenorphine alone and buprenorphine/naloxone both reduced use of opioids as measured by urine tests. At four weeks, the percent of negative urine samples was 17.8% in the buprenorphine/naloxone arm and 20.7% in the buprenorphine alone arm compared to 5.8% in the placebo arm ($p<0.001$ for both vs. placebo).[100] The overall rate of opioid-negative urine samples increased during the open-label study to 67% at week 52.[100] The 2014 Cochrane meta-analysis showed maintenance treatment with buprenorphine significantly reduced the use of opioids as measured by the percent of positive urine tests compared to placebo at high doses at four to 48 weeks (standardized mean difference [d]: -1.17; 95% CI: -1.85 to -0.49; three studies; 729 patients) but not at medium doses at two to 16 weeks (d: -0.08 95% CI: -0.78 to 0.62; two studies; 463 patients).[101]

Seven of the 10 studies included in the 2016 CADTH review measured the use of opioids with urine tests. These studies presented mixed evidence on the efficacy of buprenorphine/naloxone and methadone in reducing illicit use of opioids. Point estimates in five of these studies showed patients treated with buprenorphine/naloxone were numerically less likely to test positive for opioids compared to patients receiving methadone, with two studies reporting statistical significance. A longitudinal one-year study including 3,812 outpatients with OUD reported 47% of patients receiving buprenorphine/naloxone compared to 70% of patients receiving methadone had opioid- and cocaine-positive urine samples at one year of follow-up ($p<0.001$).[106]. Also, a 12-week RCT reported that the percentage of urine tests positive for opioids was 0.2% for patients treated with buprenorphine/naloxone versus 1.5% for patients treated with methadone ($p=0.03$).[107] Point estimates in the remaining two of the seven studies suggested patients receiving methadone were numerically less likely to test positive for opioids compared to patients treated with buprenorphine/naloxone, with one study reporting statistical significance; this open-label extension of a RCT of methadone versus buprenorphine/naloxone followed 795 patients for an average of 4.5 years and found 42.8% versus 31.7% of patients randomized to buprenorphine/naloxone and methadone, respectively, had positive urine samples at follow up ($p<0.01$).[103,108]

Controversies and Uncertainties

As outlined in the section on comparability of evidence, differences in trial designs, population selection, comparators, and outcome measures precluded formal comparisons between the different extended-release formulations. All four formulations also differ in their labeled or potential treatment indications; for example, the manufacturer proposes that the indications for CAM2038 should include OUD treatment directly after diagnosis.[24] Sublocade and Probuphine must be preceded by daily transmucosal use of buprenorphine and Vivitrol by a period of medically supervised opioid withdrawal. Probuphine implants should be used for patients on maintenance

treatment with a transmucosal buprenorphine-containing product delivering a low to moderate dose, the equivalent of buprenorphine 8 mg or less per day. The effective required buprenorphine dosage for most patients is between 12 and 16 mg daily, therefore only patients who can tolerate such doses may be suitable for Probuphine implants.

Various outcome measures were used in the trials of the interventions of interest. Outcome measures are based on different calculations of negative urine samples (Appendix Table D5) and then defining relapse based on some percentage of positive urine samples. However, the clinical term "relapse" refers to a person with OUD who in remission and then experiences a loss of control. A relapse is different from a return to opioid use that is limited in scope and time and that does not involve the return of the signs or symptoms of OUD. It is not certain to which degree different rates of negative urine samples constitute a meaningful measure of success, even for the short duration of the trials.

The lack of any clear guidance on how to obtain the opioid-free state needed for starting Vivitrol makes comparisons between the evidence for the extended-release agonist formulations and the extended-release antagonist formulation very difficult. Head-to-head trials of agonist formulations should be possible, but have not yet been conducted.

In the real world, OUD patients often present with important psychiatric comorbidities, such as depression, post-traumatic stress disorder, and personality disorders.[11] Patients with psychiatric comorbidities are largely excluded from the trials (refer to Appendix Table D2), thus limiting their generalizability. This is not limited to the evidence on extended-release formulations, but present in the evidence base for all MATs.[26]

As noted by SAMHSA in the 2018 TIP, no evidence clearly predicts which patients are best treated with Vivitrol versus methadone or buprenorphine formulations.[12] The treatment sequences for different subpopulations with OUD cannot be based solely on the available evidence, but rather must be informed by clinical knowledge and the local context.

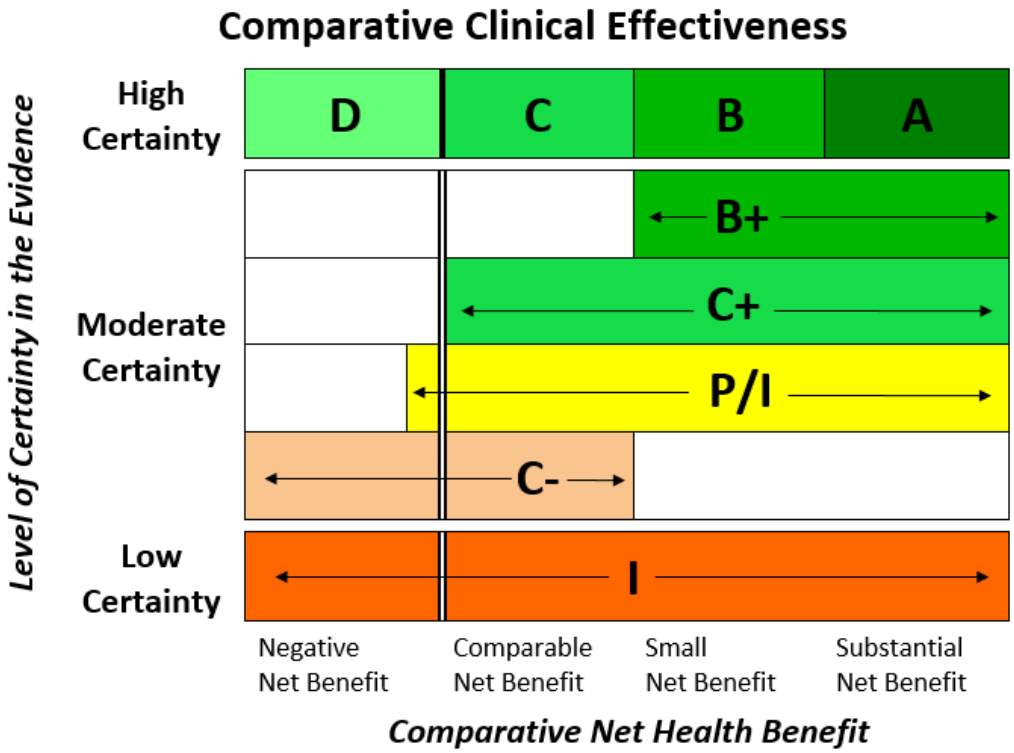
The evidence on the use of the extended-release formulations is subject to the same general limitations as for the other medications for OUD. It is not yet known if or when to best taper these medications, [12] and evidence is lacking on the added value of the different types of counseling and psychosocial support required by the FDA label and the most recent clinical practice guideline.[12]

The available research focuses on short-term outcomes and does not provide any evidence regarding observed reductions or patient control of drug use that are of clinical and social benefit, even if opioid use has not completely stopped.[19,27] In addition, questions around the impact of extended-release formulations on critically important outcomes, such as overdose and other OUD-associated mortality, health-related quality of life, work productivity, educational attainment, and incarceration have largely gone unanswered by the evidence currently available.

3.4 Summary and Comment

Using the ICER Evidence Matrix (Figure 3.1), we assigned evidence ratings independently for each of the interventions of interest compared to transmucosal buprenorphine/naloxone for study participants with OUD being considered for MAT. We recognize that comparisons of Sublocade, Probuphine, and Vivitrol each versus placebo, for which we have relevant data, have shown incremental benefits. However, the most policy relevant comparisons are those involving the interventions of interest with the active treatment of transmucosal buprenorphine/naloxone.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D = "Negative"- High certainty of an inferior net health benefit
B+ = "Incremental or Better" - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

Table 3.6. Evidence Ratings (Versus Transmucosal Buprenorphine/Naloxone)

Comparisons	Evidence Rating
CAM2038	C+
Sublocade	I
Probuphine	P/I
Vivitrol	C

CAM2038

Evidence for CAM2038 is comprised of one 24-week Phase III trial in comparison to buprenorphine/naloxone. Data was limited on clinical outcomes due to the limed number of trials available for synthesis. Results found CAM2038 to be non-inferior to buprenorphine, but not significantly different in abstinence, opioid craving, and opioid withdrawal. Similarly, while discontinuation rates were high, they did not differ between the active arms, and safety profiles were also comparable. For participants with OUD being considered for MAT, we have moderate certainty that CAM2038 provides a small, or substantial net health benefit given the increased convenience and provider interaction associated with subcutaneous injections, but high certainty that it is at least comparable as it is a buprenorphine-containing treatment. Therefore, we consider the evidence on CAM2038 to be comparable or better (C+).

Sublocade

Evidence for Sublocade is limited to one 24-week Phase III trial compared to placebo. Presently, there are no head-to-head trials comparing Sublocade to buprenorphine/naloxone. Therefore, we consider the evidence on Sublocade compared to buprenorphine/naloxone to be insufficient (I).

Probuphine

Evidence for Probuphine compared to buprenorphine/naloxone comprises two 24-week Phase III trials, although only one was considered key. Due to the inclusion criteria and trial design, the populations in the trials may be different from the general population being considered for MAT. The key trial included only participants who were clinically stable and receiving buprenorphine tablets for at least 24 weeks *before* the trial. Additionally, the other trial excluded participants with severe opioid withdrawal symptoms and cravings, which may have inflated the reported benefits of Probuphine on abstinence outcomes in this trial. No significant differences were found for opioid craving and opioid withdrawal. Similar rates of discontinuation occurred between both active arms, along with similar proportions of serious adverse events. For participants with OUD being considered for MAT, we have moderate certainty of a comparable or small net health for the trial populations. However, we have concerns that the study population may not be reflective of the more general population being considered for MAT. Therefore, we consider the evidence on Probuphine in comparison to buprenorphine/naloxone to be promising but inconclusive (P/I).

Vivitrol

Evidence for Vivitrol compared to buprenorphine/naloxone consists of data derived from two trials: one 24-week Phase IV trial, and one shorter 12-week Phase III trial. Results found that Vivitrol was non-inferior to buprenorphine/naloxone on a variety of abstinence outcomes. However, a higher rate of relapse was seen with Vivitrol compared to buprenorphine/naloxone in the intent-to-treat group. Results showed a significant reduction only in heroin use, but not for the use of other illicit opioids. A higher rate of discontinuation was found during induction with Vivitrol than buprenorphine/naloxone, which speaks to the difficulties encountered in attempts to successfully withdraw from all opioid use. In terms of safety, serious adverse events were similar between both active arms. However, while not a phenomenon observed during the clinical trials, the label for Vivitrol warns against the increased risk of opioid overdose deaths based on spontaneous post-marketing adverse event reporting.

Vivitrol has the most mature evidence base of any of the interventions of interest for this review. Differences observed between Vivitrol and buprenorphine/naloxone are due at least in part to differences in treatment intent and goals. Therefore, we considered the evidence on Vivitrol in comparison to buprenorphine/naloxone to have high certainty of a comparable net health benefit (C).

4. Long-Term Cost Effectiveness

4.1 Overview

The primary aim of this analysis was to estimate the lifetime cost-effectiveness of certain drugs used for MAT among a cohort of patients who were considered for OUD treatment, from a US health care sector perspective. A decision-analytic approach was employed. The model compared buprenorphine extended-release subcutaneous injections (CAM2038 [investigational] and Sublocade), extended-release injectable naltrexone (Vivitrol), and buprenorphine subdermal implant (Probuphine), to a transmucosal buprenorphine/naloxone, specifically generic sublingual (SL) buprenorphine/naloxone. We decided against a "no treatment" comparator given the target population of interest, as well as the availability of a common active comparator. We also decided to move our comparison of Sublocade vs. generic SL buprenorphine/naloxone from the base case to a scenario analysis, as further review and public comments we received led us to conclude that the inputs to the NMA were insufficient to support such an indirect treatment comparison. Key model outcomes, namely, quality-adjusted survival and health care costs were summed over a five-year time horizon for each treatment option. We deviated from the ICER Reference Case life-time horizon because of relatively high rates of treatment discontinuation and restart in the MAT environment. While previous models have employed even shorter time horizons,[109,110] we used a five-year horizon to help capture potential downstream effects of MATs. Costs and outcomes were discounted at 3% per year. Incremental outcomes and costs were calculated comparing each intervention to SL buprenorphine/naloxone. The model was developed in hēRo3℠ with some components of the model, such as survival distributions, developed in RStudio (version 1.1.442).

hēRo3 is a Web-based, health economic modeling platform that supports the development of both Markov cohort and partitioned survival models (Policy Analysis Inc., Brookline, MA). Calculations in hēRo3 are performed in the programming language, R, using an open-source health-economics modeling package, called "heRomod" (https://github.com/PolicyAnalysisInc/heRomod), that runs on a cloud-based platform. heRomod is a modified version of the open-source, health-economics modeling package, HEEMOD (http://cran.r-project.org/package=heemod). An extensive set of unit tests is available to validate calculations of the modeling package. Further details on hēRo3 activities and functions are available in Appendix E.

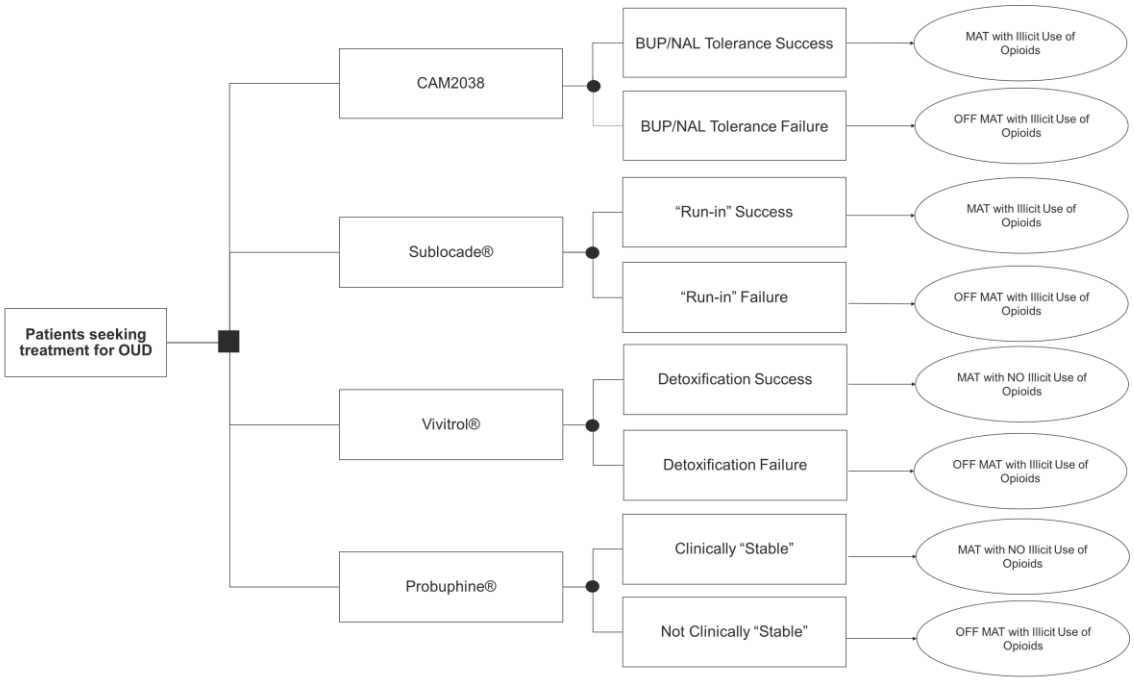
4.2 Methods

Model Structure

We developed a *de novo* decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models. The base case analysis took a health care sector perspective and thus focused on direct medical care costs only. Costs and outcomes were discounted at 3% per year. The analytic framework for this assessment is depicted in Figure 4.1.

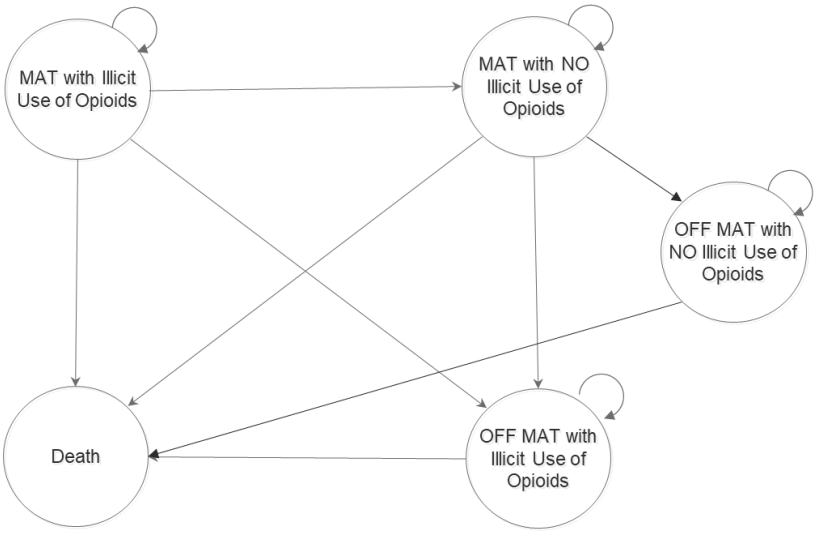
Figure 4.1. Model Schematic

4.1A. Decision Tree



BUP/NAL: buprenorphine/naloxone
Patients in comparator arms of individual treatments enter the model in health states in the same manner as their respective interventions.
Sublocade analysis included only as a scenario

4.1B. Markov Model



The model focused on an intention-to-treat cohort of OUD patients attempting to initiate treatment with MAT at model entry. Model cycle length was set at one month (four weeks)"MAT , reflecting prior economic models evaluating MATs.[109,110] We acknowledge that treatment duration with Vivitrol and Probuphine tend to be shorter compared to those with other MATs that are meant to be maintenance therapies. We hence modeled shorter time-horizons in scenario analyses, while keeping the base-case time horizon at five years.

Initial treatment pathways differed for each intervention based on trial design and FDA label, and patients were assigned initial state probabilities accordingly (Figure 4.1A). For CAM2038, patients who tolerate an initial dose of 4 mg buprenorphine/naloxone initiate therapy on day one of the model with a maximum dose of 8 mg generic SL buprenorphine/naloxone, followed by trial-based doses of CAM2038 injections.[111] Sublocade patients undergo a "run-in" phase during which they are stabilized on 8-24 mg per day of transmucosal buprenorphine product for 11 days, aligning with the mean run-in phase in the Sublocade trial.[112] For Vivitrol, patients undergo a detoxification period (completely opioid-free) for seven days prior to initiating treatment with Vivitrol, aligning with the FDA label and one of the three detoxification regimens in the key trial.[113,114] For Probuphine, patients were required to be "clinically stable" for at least three months on ≤8 mg per day of a buprenorphine-containing product prior to Probuphine implant insertion, as seen in its FDA label and key trial.[115,116] Details on initial state probabilities based on success/failure of the pre-MAT treatment rules are presented below in Table 4.1.

Table 4.1. Intention to Treat Analysis: Intervention-Specific Initial Health State Probabilities, Based on Run-In/Detoxification/Stabilization Protocols from Key Clinical Trials

	MAT with Illicit Use of Opioids	MAT with NO Illicit Use of Opioids	OFF MAT with Illicit Use of Opioids	OFF MAT with NO Illicit Use of Opioids
CAM2038*[111]	0.997*	0	0.003*	0
Generic SL Buprenorphine/Naloxone*[111,117]	0.997*	0	0.003*	0
Vivitrol‡[114]	0	0.721	0.279	0
Generic SL Buprenorphine/Naloxone‡[114]	0	0.941	0.059	0
Probuphine§[116]	0	0.891§	0.109§	0
Generic Buprenorphine/Naloxone§[116]	0	0.891§	0.109§	0

*4 mg buprenorphine/naloxone testing for tolerance to buprenorphine product. Percentage tolerance calculated as per pre-randomization data across both treatment arms.

‡Seven-day opioid detoxification period.

§Three-month period of being 'clinically stable' on ≤8 mg per day of transmucosal buprenorphine-containing product. Dose chosen for the model during "clinically stable" phase was 8 mg per day and 'clinically stable' was assumed as abstinent from illicit use of opioids. Percentage "clinically stable" calculated as per pre-randomization data across both treatment arms.

Note that patients do not need to be in complete opioid withdrawal when initiating treatment with CAM2038. In the CAM2038 arm, patients who tolerated the 4 mg buprenorphine/naloxone test dose started the model in the "MAT with Illicit Use of Opioids" health state while those who did not entered the model in the "OFF MAT with Illicit Use of Opioids" health state. The proportion of patients who successfully completed a "run-in" phase with Sublocade entered the model in the "MAT with Illicit Use of Opioids" health state, while those who fail this "run-in" phase entered the model in the "OFF MAT with Illicit Use of Opioids" health state. Patients transitioned to "MAT with NO Illicit Use of Opioids" from "MAT with Illicit Use of Opioids" health state as they abstained from illicit opioid use, defined as a negative urine sample for opioids plus self-reporting of no illicit use of opioids, or to "OFF MAT with Illicit Use of Opioids" health state due to MAT discontinuation. For CAM2038 and its comparator, the proportion of discontinuation of MATs from the "MAT with NO Illicit Use of Opioids" and "MAT with Illicit Use of Opioids" to the "OFF MAT" health states were assumed the same, and were based on the "illicit use of opioid" status at the time of discontinuation among patients in the Sublocade trial as this was the only data source from which we could parse out discontinuation based on illicit use status.[118] Patients successful at detoxification prior to initiating Vivitrol treatment entered the model in the "MAT with NO Illicit Use of Opioids" health state, while those who did not complete the detoxification period entered the model in the "OFF MAT with Illicit Use of Opioids" health state. Similarly, for Probuphine, patients "clinically stable" at three months on ≤8 mg per day on a buprenorphine-containing product

entered the model in the "MAT with NO Illicit Use of Opioids" health state, while those not "clinically stable" over the same period entered the model in the "OFF MAT with Illicit Use of Opioids" health state. Relapse in the Vivitrol and Probuphine trials is defined by a positive opioid urine sample. Upon relapse, patients enter the "OFF MAT with Illicit use of Opioids" health state. For Probuphine, upon relapse to illicit use, patients are modeled such that they enter the "MAT with Illicit Use of Opioids" health state if relapse occurs within six months of implant insertion, and once implant is removed after the six-month period, all relapsed patients transition to the "OFF MAT with Illicit Use of Opioids" health state. The implant can be removed only at 24 weeks following implant insertion, thus effectively rendering 0% discontinuation for the first six months when using the implant. We found no evidence on immediate removal of implant upon relapse to illicit use of opioids.

As Vivitrol is an opioid antagonist and blocks other opioids from binding to opioid receptors, a relapse (failure of abstinence from illicit opioid use) is considered equivalent to MAT discontinuation, with patients transitioning from "MAT with NO Illicit Use of Opioids" to "OFF MAT with Illicit Use of Opioids." Since patients on Vivitrol have not been taking an opioid or opioid agonist for a period of time (because they are taking an opioid antagonist), there is an increased sensitivity (decreased tolerance) to opioids, resulting in an increased risk of mortality from opioid overdose among patients relapsing to illicit use. However, we found no robust data on this increased risk for mortality, so did not attempt to model this. For those treated with Probuphine, although "clinically stable" could mean illicitly abusing at least low doses of opioids while on ≤8 mg per day of buprenorphine-containing product, our model considered "clinically stable" as abstinent from illicit opioid use. Patients not "clinically stable" were defined as those who did not meet inclusion criteria pre-randomization in the trial.[116] The label also indicates use of Probuphine for no longer than six months in one arm, after which a new implant can be administered subdermally in the contralateral arm, but only if the new implant is administered immediately after the previous implant has been removed.[115] However, treatment efficacy using a second set of implants has not been studied. Thus, for patients abstinent from illicit opioid use on Probuphine at the end of the six-month implant period, the next intervention in the treatment pathway was assumed to be generic SL buprenorphine/naloxone. Beyond the six-month duration of the implant, patients followed the same pathway as those who have been treated with generic SL buprenorphine/naloxone for nine months, depending on which health state they were in at the time of implant removal.

The comparator treatment versus each intervention is SL buprenorphine/naloxone and it follows the same rules associated with initial state probabilities as the interventions when entering the Markov model. The comparator was attributed trial-specific efficacy and discontinuation. Comparator price was based on generic formulations of SL buprenorphine containing product.

In all treatment arms, patients could discontinue MAT when not illicitly using opioids and could move to one of two health states: (1) "OFF MATs with NO illicit use of opioids," occurring in an

assumed 10% of all patients who remained in the "MAT with NO illicit use of opioids" health state for at least 12 months; or (2) "OFF MAT with illicit use of opioids," among all other patients. Once in the "OFF MAT with NO illicit use of opioids" or "OFF MAT with illicit use of opioids" health state, we assumed that patients could not re-enter either the "MAT with illicit opioid use" or "MAT with NO illicit use of opioids" health states in the model (Figure 4.1B). Patients remained in the model until death. All patients could transition to death from all causes from any of the alive health states. In addition, patients could die from opioid overdose in health states where they illicitly use opioids.

Target Population

The populations of focus for this review generally included adults diagnosed with opioid use disorder seeking MAT. Base case population characteristics in the trials were reasonably similar in age and gender ratio. Trial populations varied mostly by type of OUD (prescription or injectables). We therefore used a weighted average from all key trials considered for this analysis to derive the percentage of patients with illicit prescription opioid use and injection drug use (Table 4.2).[111,112,114,116,117]

Table 4.2. Base Case Model Cohort Characteristics

	Mean Age	Percent Female	Percent Illicit Use of Prescription Opioids (vs. Injectable Drug Use)
Baseline Characteristics	36 years	30%	50.7%*

*Weighted average across interventions and comparators in the trials included for this analysis.

Treatment Strategies

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which MATs to include. All listed interventions were compared to generic SL buprenorphine/naloxone. Although SL buprenorphine/naloxone is the common comparator across all interventions, its efficacy and rate of treatment discontinuation varies by intervention due to the varied opioid use status of populations entering the key clinical trials considered for this analysis. The MAT interventions evaluated were:

- Buprenorphine subcutaneous ER injection
  - CAM2038 (Investigational), Braeburn Pharmaceuticals
  - Sublocade, Indivior Pharmaceuticals (scenario analysis)
- Injectable ER naltrexone – Vivitrol, Alkermes Pharmaceuticals
- Buprenorphine ER subdermal implant – Probuphine, Titan Pharmaceuticals

Key Model Choices and Assumptions

Our model was informed by the key choices and assumptions listed in Table 4.3.

Table 4.3. Key Model Choices and Assumptions

Model Assumption	Rationale
Patients continue receiving ancillary counseling services while on MAT, irrespective of whether they maintain abstinence or whether they relapse.	Treatment with MAT is associated with ancillary counseling services, based on stakeholder input.
Patients on MAT, upon relapse to illicit use of opioids, are assumed to return to the same opioid use (prescription or injectable) used pre-MAT.	We found no robust published evidence on the illicit use of specific opioids by category in patients who have relapsed on MAT.
Long-term discontinuation/relapse for all interventions was assumed the same as seen in the trials, if using point estimates, or were extrapolated using the same parametric curve functions used to fit trial-specific data.	There exists no robust data on long-term discontinuation/relapse for all accessed interventions.
We assumed that 10% of all patients who remained in the "MAT with no illicit use of opioids" health state for at least 12 months transitioned to an "OFF MAT with NO illicit use of opioids" health state.	We found no published evidence indicating the percentage of MAT recipients remaining off opioids when they stop MAT. Given the frequency of relapse in this population, we assumed a relatively low rate of permanent abstinence and tested this rate in sensitivity analyses.
The model assumed only a single cost and utility associated with each health state and does not categorize levels of reduction of illicit use of opioids.	We found no published evidence of categories of reduction in illicit use of opioids use while on or after MAT.
Opioid overdose-related mortality was assumed to occur only during periods of illicit use of opioids and was assumed the same whether on concurrent MAT or otherwise.	There exists no robust published evidence on opioid overdose-related mortality by MAT type and concurrent illicit opioid use.
Mortality from opioid overdose was held constant over time.	We found no robust published evidence on time-dependent mortality from opioid-overdose among OUD patients.
Incidence of Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) infections was only attributed to people who inject drugs (PWID).	A significant proportion of HIV and HCV cases among those who illicitly use opioids occur in PWID. We found no published evidence on HIV and HCV incidence among non-PWID illicit opioid users.
The model assumed a constant disutility associated with HIV infection and treatment with anti-retroviral therapy (ART).	We found no robust evidence on time- and disease-status-dependent change in disutility among those infected and diagnosed with HIV and treated with ART.
Among PWID diagnosed with HCV, the model assumed a constant disutility only for those for whom there was no spontaneous clearance of HCV infection and who fail treatment.	Patients with spontaneous HCV infection clearance or those without cirrhosis successfully treated with direct-acting antiviral therapy are assumed to have no HCV-specific disutilities affecting their quality of life.
Additional HCV-specific health care costs, as well as HCV-specific mortality, were attributed only to those patients diagnosed with HCV who are without HCV infection clearance and not cured with treatment.	The proportion of individuals meeting these conditions would be expected to be quite small given the high cure rates associated with current treatments.

Model Assumption	Rationale
HIV drug (anti-retroviral therapy) costs were attributed to all PWID diagnosed with HIV infection, while 75% of these individuals were attributed costs for HIV-specific community care-based programs.	We found evidence that not all HIV-diagnosed individuals enroll in supportive community-care based programs.[119]
Serious adverse event (SAE)-related costs or disutilities were not included in the model.	The trials vary in reporting of SAEs, with most reporting only percentage of SAEs and not specific non-relapse-related SAEs. Individual adverse events when reported were not reported by category of severity. We assume that background health care costs (sourced from a claims analysis) include costs associated with treating SAEs.

Model Inputs

Clinical Inputs

Transition Probabilities

Treatment Efficacy

Transition probabilities related to treatment efficacy were derived from relevant trial data (Table 4.4).[111,114,116,117] All trial efficacy estimates were converted to per-cycle transition probabilities and held constant throughout the modeled time horizon.

Table 4.4. MAT Treatment Efficacy

	Abstinence from Illicit Use of Opioids at 24 Weeks*	
	Intervention	Comparator (SL Buprenorphine/Naloxone)
CAM2038[117]	34.2%	27.4%
Vivitrol[114]	48%‡	44%‡
Probuphine[116]	80.5%‡	67.4%‡

*Abstinence estimates over the 24-week trial duration, were converted to per cycle transition probabilities.
‡KM curves used for modeling relapse over time are based on per protocol observations and not intention-to-treat (ITT) observations since ITT approach has been taken into consideration in the decision tree prior to Markov model entry.

Treatment Discontinuation

Treatment discontinuation to "OFF MAT with illicit use of opioids" could occur from both "MAT with no illicit use of opioids" and "MAT with illicit use of opioids" for CAM2038 and generic SL buprenorphine products. The proportion discontinuing from each of these states was derived from data in the Sublocade trial (calculated from academic-in-confidence data) and applied to the overall discontinuation rate reported for CAM2038 and generic SL buprenorphine products in the trials, since as stated earlier, this trial was the only source from which we could parse out MAT

discontinuation based on illicit use status. Treatment discontinuation was estimated from the trial-reported Kaplan-Meier (KM) curves for discontinuation for CAM2038, Vivitrol, Probuphine, and their respective SL buprenorphine/naloxone comparators.[111,114,116,117] Discontinuation rates for each MAT at the end of trial period is presented in Table 4.5. Note that this comparison was only made for discontinuation; as noted in Section 3, differences in study populations, outcome measures, and run-in protocols prevented a formal and comprehensive NMA.

We fit parametric survival curves to KM data utilizing the approach described by Hoyle and Henley.[120] First, we extracted data points from digitized copies of the trial curves, then used the extracted values, the number of remaining patients at each time interval, and maximum likelihood functions to estimate curve fits to the underlying individual patient data. The fitted model curves included the distributional forms of exponential, Weibull, exponential, log-normal, log-logistic, and gamma. The base-case parametric function was selected based on best model fit using Akaike information criterion (AIC) values and visual comparison (see Appendix Table E2). Beyond trial duration, discontinuation was extrapolated using the best-fitting curve function seen within the trial period.

Table 4.5. MAT Treatment Discontinuation

	Discontinuation	
	Intervention	Comparator (SL Buprenorphine/Naloxone)
CAM2038[117]	31%*	27.4%*
Vivitrol[†114]	52%	54%
Probuphine[†116]	0%[§]	32.6%

*KM curves used for modeling discontinuation over time

[†]KM curves used modeling treatment discontinuation are based on per protocol observations and not intention-to-treat (ITT) observations since ITT approach has been taken into consideration in the decision tree prior to Markov model entry.

[§]0% discontinuation because Probuphine will be implanted for the duration of six months irrespective of abstinence or relapse to illicit use of opioids. Patients who remain abstinent at the time of Probuphine implant removal were assumed to have the same discontinuation rate as those treated with SL buprenorphine product.

Comorbidities Associated with OUD

Key OUD-related comorbidities with significant public health impact include HCV and HIV infections among PWID. A cohort study and a meta-analysis based on four US-specific surveys on PWID reported annual incidence of HIV and HCV among PWID as 0.055% (95% Confidence Interval: 0.042% to 0.080%) and 26.7%, respectively.[121,122] These rates were converted to per-cycle probabilities in the model. While endocarditis is also a potential adverse effect among PWID, it was not included in the model due to relatively low incidence and associated mortality, with available data being non-recent.[123-125]

Mortality

Opioid overdose-related mortality was estimated from observational data, while all-cause gender- and age-specific mortality was sourced from the Human Mortality database's US-specific tables.[126,127] Increased risk of mortality associated with HIV and HCV was attributed to PWID (Table 4.6).[128,129] Among PWID diagnosed with HCV, the increased mortality risk from HCV was applied only to those for whom there was no spontaneous clearance of HCV infection along with treatment failure.[130,131]

Table 4.6. Mortality Inputs

Parameter	Value
Opioid-Related Overdose Death[126]	13.3 per 100,000 people*
HR of Death from HIV[128]	3.15 (95% CI: 2.59 to 3.82)†
MRR of Death from HCV[129]	2.37 (95% CI: 1.28 to 4.38)†
All-Cause Mortality[127]	US Life Tables

All values were converted to per cycle transition probabilities.
HR: hazard ratio, MRR: mortality rate ratio, CI: confidence interval
*Among all illicit users of opioids
†Compared to PWID without infection

Utilities

Health state utilities were derived from a study that used an online US cross-sectional survey.[132] The study comprised hypothetical descriptive vignettes for OUD and associated MAT-related health states that were developed based on inputs from literature, clinical expert opinion, and people diagnosed with OUD. Quality of life assessments were undertaken using the standard gamble technique. For each health state, two sets of vignettes were developed, one including physical/emotional descriptors, and another "expanded" version adding societal to the physical/emotional descriptors (i.e., employment, criminal justice, and family relationship-specific aspects). The study excluded comorbidity-associated vignettes because its primary focus was assessing quality of life associated with OUD alone. Health state utilities when on MAT with concurrent use of illicit opioids were calculated by applying the ratio of utilities when illicitly using opioids with and without MAT (from a UK study[133]) to the base utility when illicitly using opioids when OFF MATs (from the cross-sectional survey) (Table 4.7). Health state utilities in the "OFF MAT with NO Illicit use of opioids" health state was sourced from a nationally representative survey study conducted in the US.[134]

Table 4.7. Health State Utilities

Parameter	Value (Range – 95% CI)
MAT with NO Illicit Use of Opioids[132]	0.766 (0.738 – 0.795)
Relapse – OFF MAT with Illicit Use of Opioids (Prescription)[132]	0.694 (0.660 – 0.727)
Relapse – OFF MAT with Illicit Use of Opioids (IDU)[132]	0.574 (0.538 – 0.611)
MAT with Illicit Use of Opioids (Prescription)[133]	0.700* (0.660[†] - 0.727[‡])[§]
MAT with Illicit Use of Opioids (IDU)[133]	0.618* (0.538[†] – 0.727[‡])[§]
OFF MAT with NO Illicit Use of Opioids[134]	0.852[‡](0.736 – 0.901)[§]
HIV Disutility Multiplier[135]	6.9% (1% - 19.5%)[§]
HCV Disutility Multiplier[136]	7% (1% - 16%)[§]

IDU: injection drug use, CI: confidence interval

*Based on utilities reported by Connock et al., 2007, the ratio of utilities in health states with illicit use of prescription opioids while ON and OFF MATs is approximately 1.01, while the same with illicit use of injectable opioids is approximately 1.07. These ratios were applied to the "relapse" OFF MAT illicit use of opioids health state utilities to derive utilities for prescription and injection-related health states of "MAT with Use of Illicit Opioids."

[†]Same lower bound as when "OFF MAT with Illicit Use of Opioids;" same upper bound as when OFF MAT with illicit use of prescription opioids.

[‡]Calculated as age-range specific population-weighted mean starting in the 30-39 years age range.

[§]Calculated ranges are not 95% CIs

For PWID diagnosed with HIV, we applied a 6.9% disutility to their baseline health state utilities. This estimate was derived from an economic evaluation that assessed the cost-effectiveness of HIV prevention programs among PWID in the U.S.[135] The model sourced baseline quality of life estimates for PWID and HIV stage- and treatment-specific multipliers from published literature. We applied multipliers specific to anti-retroviral therapy (ART) and symptomatic HIV to arrive at a 6.9% reduction from baseline utility among PWID diagnosed with HIV and treated with ART. Detailed calculations are available in Appendix Table E3.

For PWID diagnosed with HCV, we applied a 7% disutility to their baseline health state utilities. This disutility was derived from estimates used in a U.S.-specific cost-effectiveness model assessing anti-HCV treatments in patients diagnosed with HCV.[136] The applied disutility was held constant over time and attributed only to PWID for whom there was no spontaneous clearance of HCV infection or failure of anti-viral treatment.

Adverse Events

The trials vary in reporting of SAEs, with most reporting only percentages of SAEs and not specific non-relapse-related SAEs. Individual adverse events, when reported, were not reported by category of severity. For these reasons, and because separate costing of SAEs was not expected to affect model results in a material fashion, we did not attempt to estimate SAE costs for any treatment of interest. We did, however, use background health care costs from a claims analysis by

Shah et al. that included costs associated with treating SAEs. We found no evidence on disutility associated with serious adverse events in this population, so no impact on utility from SAEs was assumed.

Economic Inputs

The model included all treatment costs associated with each individual regimen, including drug acquisition costs, drug administration costs, and supportive care costs (e.g. clinician visits, counseling, and monitoring).

Drug Acquisition Costs

We found no estimates on net price from SSR Health for the currently approved interventions. In the absence of SSR net price data, we used net price as reported in the Federal Supply Schedule (FSS) for all interventions except Vivitrol.[137] For Vivitrol, we used the net price provided to us by the manufacturer, which was derived from IQVIA estimates.[138] There is no listed price available for CAM2038, as the drug is currently under review, so we calculated only threshold prices (i.e., prices that would achieve certain cost-effectiveness thresholds) for this MAT. For generic SL buprenorphine/naloxone, we used the average of generic Wholesale Acquisition Costs (WAC). Based on the regimen dosage specified earlier in the clinical evidence review section (Table 1.2), the model utilized the lowest-cost combination of vials, tablets, or implants for each regimen. All MAT drug costs are listed in Table 4.8.

Table 4.8. Drug Cost Inputs

Intervention	WAC per Dose*[139]	Net price per Dose[137]	Net Price Discount from WAC	Annual Net Price
CAM2038 24/96 mg	-	-	-	-
Sublocade 300 mg**	$1,580	$1,206.83†	24%	$15,688.79
Vivitrol 380 mg	$1,309	$759.25***	42%	$9,870.25
Probuphine 296.8 mg	$4,950	$3640.32†	26%	$3,640.32‡
Generic SL ER Buprenorphine/Naloxone 16 mg	$8.32	-	-	$3,037.46
Generic ER Oral Buprenorphine 8 mg§	$4.39	-	-	$1,603.02

WAC: wholesale acquisition cost, FSS: Federal Supply Schedule

*WAC as of October 17, 2018

†FSS price as published on October 1, 2018

**Included only in a scenario analysis

***Manufacturer-provided net price

‡One-time cost; does not include MAT cost following implant removal

§For clinical stabilization period for Probuphine

Administration and Monitoring Costs

We included costs of administering CAM2038 and Vivitrol, once per cycle (Table 4.9).[140] We also included administration costs associated with insertion and removal of Probuphine, as Probuphine-associated costs were not available in the background cost publication (Table 4.9).[140,141]

Table 4.9. Administration Costs (National Average Non-Facility Price)

Parameter	Value
Probuphine Implant Insertion (CPT® Code: 11981)[140]	$145.90
Probuphine Implant Removal (CPT® Code: 11982)[140]	$163.08
SC/IM Injection Administration (CPT® Code: 96372)[140]	$20.88

Health Care Utilization Costs

Non-MAT (non-drug) background health care costs have been sourced from a retrospective cohort study using claims data from the Truven Health Analytics MarketScan® database.[141] This analysis reports baseline and follow-up costs specific to treatment with Vivitrol, methadone, buprenorphine, and non-pharmacological therapy in patients diagnosed with OUD. Patients were followed up for one year and costs included those associated with inpatient admissions, emergency department (ED) visits, outpatient visits, and pharmacy costs. We calculated the population-weighted average costs of inpatient, ED, and outpatient visits among the Vivitrol and buprenorphine treated populations at baseline and follow-up, and attributed these costs to the "OFF MAT with Illicit Use of Opioids," "ON MAT with Illicit Use of Opioids," and the "MAT with NO Illicit Use of Opioids." We also excluded pharmacy costs, to avoid double-counting of costs of MAT. When illicitly using opioids while on MATs and when using MAT while not illicitly using opioids, we added MAT drug-specific (except CAM2038) and associated administration costs. While there was a decrease in inpatient and ED costs between follow-up and baseline, there was an increase in outpatient costs, which we believe is attributed to patients making more frequent physician office visits owing to treatment with MATs. We assigned health care costs to the "OFF MAT with NO illicit use of opioids" health state based on health care costs for the general population without OUD. These costs were sourced from the Health Care Cost Institute's 2016 report, which described costs based on claims analyses in the population under 65 years old with employer-sponsored insurance.[142] Components of cost included inpatient, professional, outpatient and prescription drugs. All costs shown in Table 4.10 are per-cycle costs.

Table 4.10. Health Care Costs per Cycle

	ON or OFF MAT with Illicit Use of Opioids[141]	MAT with No Illicit Use of Opioids[141]	OFF MAT with NO Illicit Use of Opioids[142]
Inpatient Admissions	$385.08	$332.94	-
Emergency Department Visits	$81.01	$70.97	
Outpatient Visits	$480.78	$727.98	-
All Health Care Costs	-	-	$427.84

All costs calculated and presented as per-cycle costs, using annual costs reported in source publications.

For PWID diagnosed with HIV or HCV, we attributed drug and other non-drug costs associated with these comorbidities.[119,143] For individuals with PWID and HIV, we attributed only 75% of costs associated with HIV-related community care programs, to reflect the proportion of those diagnosed with HIV who participate in such programs.[119] Spontaneous clearance of HCV infection has been reported in 24.4% (95% Confidence Interval: 19.5% to 29.1%) of HCV-diagnosed PWID, based on a meta-analysis of 28 reports, of which seven were US-specific.[131] Among those for whom no spontaneous HCV infection clearance occurs, treatment with glecaprevir/pibrentasvir (Mavyret™, AbbVie, Inc.), a pan-genotypic eight-week treatment for HCV, was initiated. Ongoing HCV-related health care costs were attributed only to those who failed initial treatment with glecaprevir/pibrentasvir. Costs of glecaprevir/pibrentasvir were estimated from the FSS.[137] Estimates for treatment success with glecaprevir/pibrentasvir were sourced from treatment efficacy trial data presented in the drugs' prescribing label.[130] Appropriate HIV- and HCV-related costs were also attributed to those PWID in the "OFF MAT with NO illicit use of opioids" health state. All HIV and HCV-related costs (per cycle) are presented in Table 4.11.

All costs were inflated to 2018 levels using the health care component of the personal consumption expenditure index,[144] in accordance with the ICER Reference Case.

Table 4.11. HIV and HCV Treatment Costs per Cycle

	HIV[119]	HCV[130,137,143]
Drug Costs	$1,865.04	$19,389.08*
Other Treatment Costs	$396.22†	$849.22‡

HIV: human immunodeficiency virus, HCV: hepatitis C virus
HCV drug cost for patients achieving a cure is assumed to be that of glecaprevir 100mg/pibrentasvir 40mg (Mavyret) for 8 weeks, assuming all new cases of diagnosed HCV patients have no liver cirrhosis.
*FSS net price per four weeks.
†Assuming only 75% of diagnosed individuals attend HIV-specific community care programs.
‡Calculated as additional cost for HCV care relative to cost of non-HCV, non-MAT health care costs in PWID diagnosed with HCV and treatment with Mavyret failed.

Societal Costs

We also included costs associated with lost productivity, criminal justice, and incarceration in a scenario analysis that took a modified societal perspective. For lost productivity, based on trial

population baseline characteristics, we estimated that 34% of the population diagnosed with OUD were employed.[111,114,116-118] Birnbaum et al. reported productivity costs which included lost wages, excess disability, medically-related absenteeism, lost wages from incarceration, and presenteeism associated with opioid abuse, dependence, and misuse in the US.[145] Combining these estimates with SAMHSA data[146], we calculated the productivity loss costs per person (Table 4.11). We then applied these costs to approximately 34% of the modeled cohort while in health states that included illicit use of opioids.

The costs of criminal justice and incarceration were sourced from a retrospective cohort study that included data from the California Outcomes Monitoring System, Automated Criminal History System, Offender Based Information System, and National Death Index.[147] Patients included in the study were those diagnosed with OUD with uniquely identifiable criminal justice records. Criminal justice and incarceration costs comprised costs of policing, court, corrections, and medical expenses, cash losses, property theft, and consequences related to criminal victimization. Approximately 43% of the entire sample was involved in criminal justice and incarceration-related events; we hence applied these costs to the same percentage within our cohort. This study reported daily costs of criminal justice and incarceration when on opioid agonist therapy and "post-treatment," which in our model referred to costs when on MAT (with and without illicit use of opioids) and off MAT (only with illicit use of opioids), respectively (Table 4.12). Details of our calculation are available in Appendix Tables E4 and E5.

Table 4.12. Societal Costs per Cycle

	Value
Productivity Loss[145,146]	$1,334.26*
Criminal Justice and Incarceration[147]	
When ON MAT (With and Without Illicit Use of Opioids)	$1,089.23†
When OFF MAT (Only with Illicit Use of Opioids)	$5,446.13†

*Applied to only 34.42% of cohort.

†Applied to only 43.24% of cohort.

Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Inputs for one-way sensitivity analyses are presented in Appendix Tables E6 to E12. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 1,000 simulations. Details of distributions used for the probabilistic analyses can be found in Appendix Tables E13 to E19. Additionally, we performed a threshold analysis across incremental cost-effectiveness thresholds ranging from $50,000 to $150,000 per QALY gained.

Scenario Analyses

For the final report, we moved the Sublocade vs. SL buprenorphine/naloxone comparison from the base case analysis as presented in our draft report, to scenario analyses. First, we conducted a threshold analysis calculating for Sublocade's per dose price to reach cost-effectiveness thresholds between $50,000 and $150,000 per QALY. Second, we conducted another threshold analysis calculating for efficacy (abstinence from illicit use of opioids), to reach cost-effectiveness thresholds of up to $150,000 per QALY. Finally, we conducted a third scenario analyses that assumed Sublocade to have the same efficacy and discontinuation rate as CAM2038 relative to its comparator, as seen in the CAM2038 key trial. We used Sublocade's FSS price (in the second and third scenario analyses) and induction regimen but favored Sublocade assuming 100% successful induction ("run in") with Sublocade and 99.7% successful induction with its comparator SL buprenorphine/naloxone, again as seen in the CAM2038 key trial. Please refer to the model methods sub-section for Sublocade's "run in" protocol.

For all other interventions, multiple scenario analyses were conducted to evaluate the impact of key model choices and assumptions on the robustness of the results and conclusions.

- We included a modified societal perspective that included the costs associated with productivity loss and criminal justice and incarceration among patients who illicitly use opioids.
- We modeled shorter time-horizons of one and two years. As stated in the model structure sub-section, we acknowledge that treatment with the buprenorphine products (except Probuphine) is meant to be long-term, while treatment with Vivitrol or Probuphine is often intended to be for a shorter time horizon, up to one year, based on feedback received from stakeholders.
- We varied population characteristics such that the entire cohort entering the model were either illicit users of prescription opioids or were PWID.
- We conducted an analysis with a modified model structure that excluded the "OFF MAT with NO Illicit Use of Opioids" health state, to model a scenario in which patients cannot permanently abstain from illicitly using opioids.
- We included an analysis that followed a "per protocol" approach and not an "intention-to-treat" approach wherein all patients entered the model in the "MAT with Illicit Use of Opioids" for CAM2038, Sublocade, and their respective comparators, or in the "MAT with NO Illicit Use of Opioids" for Vivitrol, Probuphine, and their respective comparators.
- We modeled a second implant for Probuphine following the first implant to see its effect on longer-term outcomes.

Model Validation

Model validation followed standard practices in the field. First, we provided preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model. We then tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). Independent modelers also tested the mathematical functions in the model as well as the therapy-specific inputs and corresponding outputs. We also conducted sensitivity analyses with null input values to ensure the model produced findings consistent with expectations. Finally, we compared the ICER model to previously published models. We searched the literature to identify models that were similar to our own, with comparable populations, settings, perspective, and treatments.

4.3 Results

Base Case Results

In the comparison of CAM2038 versus generic SL buprenorphine/naloxone, CAM2038 produced marginally higher QALYs (3.26 vs. 3.20) and similar life years (4.62), as seen in Table 4.13. Note that in all results below life years are different only at the third or subsequent decimal places. CAM2038's higher rate of abstinence was offset by its higher rate of discontinuation relative to its comparator (as seen in the trial data), which led to a marginally higher QALY gain. Since there exists no list or net price for CAM2038, we could not calculate its incremental cost-effectiveness ratio.

Table 4.13. Base Case Results for CAM2038 versus Generic SL Buprenorphine/Naloxone

Treatment	MAT Drug Costs	Other Costs	Total Cost	Life Years	QALYs
CAM2038*	-	$66,100	-	4.62	3.26
Generic SL Buprenorphine/Naloxone	$5,400	$64,700	$70,100	4.62	3.20

QALY: Quality-Adjusted Life Year

*No List or net price available yet for CAM2038

In the comparison of Vivitrol versus generic SL buprenorphine/naloxone, Vivitrol produced marginally fewer QALYs (3.25 vs. 3.28) and similar life years (4.62), as seen in Table 4.15. Drug costs with Vivitrol are higher relative to its comparator, while nondrug costs between the two treatments are similar. Thus, with higher costs and lower effectiveness, Vivitrol is dominated by generic SL buprenorphine/naloxone (Table 4.14).

Table 4.14. Base-Case Results for Vivitrol versus Generic SL Buprenorphine/Naloxone

Treatment	MAT Drug Costs	Other Costs	Total Costs	Life Years	QALYs	Incremental Cost per QALY Gained
Vivitrol	$15,900	$65,500	$81,500	4.62	3.25	More costly, less effective
Generic SL Buprenorphine/Naloxone	$5,900	$65,200	$71,200	4.62	3.28	-

QALY: quality-adjusted life year

In the comparison of Probuphine versus generic SL buprenorphine/naloxone, Probuphine produced QALYs that were essentially identical (3.38 vs. 3.37) and similar life years (4.62), as seen in Table 4.15. Drug costs are higher with Probuphine, by approximately $2,300, while non-drug costs are higher by approximately $400, resulting in higher total cost with Probuphine. Probuphine's cost-effectiveness ratio relative to its comparator is approximately $265,000 per QALY gained; as previously noted, however, only one implant was assumed for base case analyses, consistent with the clinical trial design, even though the FDA label allows for a second implant.

Table 4.15. Base-Case Results for Probuphine versus Generic SL Buprenorphine/Naloxone

Treatment	MAT Drug Costs	Other Costs	Total Costs	Life Years	QALYs	Incremental Cost per QALY Gained
Probuphine	$11,000	$66,900	$77,900	4.62	3.38	$265,000
Generic SL Buprenorphine/Naloxone	$8,600	$66,500	$75,100	4.62	3.37	-

QALY: quality-adjusted life year

Sensitivity Analysis Results

One-way sensitivity analyses showed that results were most sensitive to intervention discontinuation rate (relapse to illicit use of opioids), the incidence of HCV, and intervention costs for Vivitrol and Probuphine. Since CAM2038 currently has no price, we do not present tornado diagrams specific to CAM2038's incremental cost-effectiveness ratios. Intervention-specific tornado diagrams are presented in Appendix Figures E1 and E2.

Results of the probabilistic analyses showed that none of the interventions reached cost-effectiveness thresholds of $50,000 per QALY gained over 1,000 simulations. Zero percent of simulations reached the $100,000 or $150,000 per QALY gained threshold for Vivitrol, while 1% and 12.8% of all simulations for Probuphine achieved the $100,000 and $150,000 per QALY gained threshold (Table 4.16).

Table 4.16. Probabilistic Sensitivity Analyses

	Percentage of 1,000 Simulations at or Below Willingness-To-Pay Thresholds		
	$50,000 per QALY	$100,000 per QALY	$150,000 per QALY
Vivitrol	0%	0%	0%
Probuphine	0%	1%	12.8%

QALY: quality-adjusted life year

We also present the percentage of simulations where MAT interventions are more costly and more effective relative to their respective comparators (Table 4.17). Again, since CAM2038 currently has no published price, we do not present probabilistic results on its incremental cost-effectiveness. Hexbins and cost-effectiveness acceptability curves for each intervention are presented in Appendix Tables E3 to E6.

Table 4.17. Cost-Effectiveness Plane

Quadrant	Vivitrol	Probuphine
Northeast (More Costly and More Effective)	1.2%	76.8%
Northwest (More Costly and Less Effective)	98.8%	23.2%
Southwest (Less Costly and Less Effective)	0%	0%
Southeast (Less Costly and More Effective)	0%	0%

Scenario Analyses Results

Sublocade vs. SL Buprenorphine/Naloxone

As explained in the methods section, in the first scenario we conducted a threshold analysis calculating the price of Sublocade that would reach cost-effectiveness thresholds between $50,000 and $150,000 per QALY. This resulted in Sublocade monthly (four week) prices nearly the same as those of CAM2038 in its threshold analysis (Table 4.20). The second scenario was a threshold analysis to calculate the efficacy (abstinence from illicit use of opioids) required to reach cost-effectiveness thresholds of up to $150,000 per QALY. This analysis showed that even if Sublocade use resulted in 100% adherence (0% discontinuation) and abstinence, its incremental cost-effectiveness ratio relative to SL buprenorphine/naloxone would still be well above the $150,000 per QALY threshold, at approximately $215,000 per QALY. In the third scenario analysis we assumed Sublocade and its comparator would have the same efficacy (abstinence from illicit use of opioids) and treatment adherence as CAM2038 and its comparator. For MAT costs, we use Sublocade's and its comparators' dose costs according to approved regimens. All other aspects of this scenario are similar to the base case model. As with CAM2038, the proportion of patients who successfully completed a "run-in" phase with Sublocade entered the model in the "MAT with Illicit Use of Opioids" health state, while those who fail this "run-in" phase entered the model in the "OFF MAT with Illicit Use of Opioids" health state (Figure 4.1A). This analysis was favorable to Sublocade

since it assumed 100% "run-in" success for the Sublocade arm, and 99.7% "run-in" success for its SL buprenorphine/naloxone comparator as seen in the CAM2038 trial. Under these assumptions, Sublocade's cost-effectiveness relative to generic SL buprenorphine/naloxone was estimated at approximately $577,000 per QALY over five years.

Modified Societal Perspective

In the modified societal perspective, total QALYs did not differ as we did not attribute additional disutilities that may be associated with productivity loss or criminal justice and incarceration; however, total costs in each treatment arm were greater. Intervention-specific costs associated with lost productivity and criminal justice and incarceration are presented in Appendix Tables E20 to E22. Including societal costs increased the total costs across all interventions and their comparators, but did not change the base case findings, specifically for Vivitrol which was more costly and less effective than its comparator. For Probuphine, however, including societal costs led to Probuphine being the dominant strategy, as slightly less costly and slightly more effective than generic SL buprenorphine/naloxone (Tables 4.18 and 4.19). However, the generalizability of the findings for Probuphine are limited, as the population in the trial (i.e., clinically stable on SL buprenorphine products for six months) is quite different from the eligible population in actual practice (i.e., patients diagnosed with OUD seeking MAT).

Table 4.18. Vivitrol versus Generic SL Buprenorphine/Naloxone

Treatment	Total Costs	QALYs	Incremental Cost per QALY gained
Vivitrol	$200,000	3.25	More costly, less effective
Generic SL Buprenorphine/Naloxone	$178,000	3.28	--

QALY: quality-adjusted life year

Table 4.19. Probuphine versus Generic SL Buprenorphine/Naloxone

Treatment	Total Costs	QALYs	Incremental Cost per QALY gained
Probuphine	$155,000	3.38	Less costly, more effective
Generic SL Buprenorphine/Naloxone	$156,000	3.37	--

QALY: quality-adjusted life year

Other Scenario Analyses

Shorter time horizons resulted in results directionally similar to those observed in the base case analyses, with CAM2038 producing higher QALYs relative to its comparator, Vivitrol being dominated by its comparators, and Probuphine producing incremental cost-effectiveness ratios well above willingness-to-pay (WTP) thresholds of $50,000 to $150,000 per QALY gained. Detailed results of this scenario analysis can be found in Appendix Tables E23 and E24.

Conducting analyses in a cohort comprising only PWID diagnosed and seeking MAT for OUD (i.e., no persons illicitly using prescription opioids) resulted in interventions and comparators with fewer QALYs and higher costs for all MATs, compared to those in the base case analyses. Detailed results of this scenario analysis can be found in Appendix Tables E25 to E27.

Varying the model structure to exclude the "permanent abstinence from illicit use of opioids" health state resulted in marginally lower health outcomes (QALYs) and higher costs for all MATs. This is because all patients discontinuing MAT move to the "OFF MAT with Illicit Use of Opioids" health state, which involves lower utilities and higher costs than the "OFF MAT with no illicit use" health state. Detailed results of this scenario analysis can be found in Appendix Tables E28 to E30.

We employed a "per protocol" approach, allowing for all patients in the CAM2038 and its comparator arms to enter the model in the "MAT with Illicit Use of Opioids" health state, and the Vivitrol, Probuphine, and relevant generic SL buprenorphine/naloxone comparator arms to enter the model in the "MAT with NO Illicit Use of Opioids" health state. In this scenario, we found that results were similar to the base case analysis, except in the case of Vivitrol, which resulted in an incremental cost effectiveness ratio of slightly more than $1 million per QALY gained relative to its comparator. Detailed results of this scenario analyses can be found in Appendix Tables E31 to E33.

Aligning with the prescribing label for Probuphine, we modeled a scenario where a second implant is inserted immediately after removal of the first implant. Since there is no trial-related efficacy on the extended use of Probuphine, we assumed that the efficacy during the first six months extended through the subsequent six-month period. Relative to the base case, extended use of Probuphine for an additional six months resulted in increased total costs of approximately $3,200 and QALYs of 0.015 over five years, resulting in a lower incremental cost-effectiveness ratio of approximately $236,000 per QALY gained. Detailed results of this scenario analysis can be found in Appendix Table E34.

Threshold Analyses Results

Prices required to achieve willingness-to-pay thresholds of $50,000, $100,000, and $150,000 per QALY for CAM2038 and Probuphine are presented below in Table 4.20. Vivitrol showed inferior effectiveness but at higher costs relative to its respective comparator (generic SL buprenorphine/naloxone) in the base-case analyses. Therefore, we did not calculate threshold prices for Vivitrol but recommend that its price per unit be no more expensive than generic SL buprenorphine/naloxone.

Table 4.20. Threshold Analysis Results

	WAC per Unit	Net Price per Unit	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY
CAM2038*	-	-	$219†	$313†	$406†
Probuphine	$4,950‡	$3,640‡	$1,165‡	$1,741‡	$2,318‡

QALY: quality-adjusted life year

*No list or net prices for CAM2038 were available as of the date of this report.

†Price per four-week dose

‡Price per implant lasting six months

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Prior Economic Models

We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments. Carter, Dammerman, and Frost recently examined the cost-effectiveness of subdermal implantable buprenorphine (Probuphine) versus sublingual buprenorphine for OUD treatment, using a US societal perspective that included both direct medical costs and non-medical costs such as lost productivity and criminal justice costs.[110] Their analysis used a shorter time horizon (12 months) and allowed for a second implant after the first six months. Their model did not include a health state for off treatment without relapse, but was otherwise similar to those from Jackson et al. and Schackman et al.[109,148] They estimated that Probuphine treatment would lead to a slight increase in QALYs gained (0.031) and higher drug costs but lower overall costs (by approximately -$4,400), largely due to decreases in ED/hospitalization and criminal justice costs. A key difference between this model and the current ICER analysis is that all patients were assumed to start "On treatment, not relapsed," whereas the ICER analysis assumed that 10.9% of patients started in the "Off MAT with Illicit Use of Opioids" health state, to represent those patients who were not "clinically stable" for at least three months on ≤8 mg per day of a buprenorphine-containing product prior to Probuphine implant insertion.

Jackson et al. analyzed the cost-effectiveness of injectable extended-release naltrexone (Vivitrol) compared to methadone maintenance and buprenorphine maintenance treatments for OUD.[148] They estimated the incremental cost per opioid-free day over a six-month time horizon, using a state health program perspective. They found that Vivitrol would cost approximately $72 per opioid-free day (2015 US$) compared to methadone maintenance treatment, while buprenorphine maintenance was dominated (i.e., more costly but less effective) by methadone maintenance. The

analysis by Jackson et al. did not include quality of life estimates or calculate cost per QALY, precluding direct comparison with our model. In addition, the cohort in their model was assumed to be on treatment and did not seem to account for patients who did not complete the detoxification period required for Vivitrol treatment initiation.

Schackman et al. examined cost-effectiveness over a two-year horizon of long-term buprenorphine/naloxone treatment compared to no treatment for OUD, from a health care system perspective.[109] Their base case reported an incremental cost per QALY of $35,100 for buprenorphine/naloxone compared to no treatment, and only a slight change to $35,200 when using a five-year time horizon. They assumed an annual cost for buprenorphine/naloxone of approximately $4,700 (compared to approximately $3,000 per year in our analysis); no generic forms of the treatment were available at the time of their analysis. Estimated cost per QALY in their analysis would decrease to $23,000 if the price of buprenorphine/naloxone were reduced by 50% (2010 US$). Unlike our model, their model assumed a cohort of "clinically stable" OUD patients who had already completed six months of outpatient buprenorphine/naloxone treatment, and who entered the model as "In treatment off drugs." As the authors point out, the inclusion of costs and outcomes for patients in the first six months of treatment (including those who do not become "clinically stable") would likely lead to higher cost-effectiveness ratios. Other analyses have examined comparators outside the scope of the present analysis, such as diacetylmorphine versus methadone treatment (Nosyk 2012)[149], or in different countries, such as the UK (Connock 2007)[133].

4.4 Summary and Comment

Results of our assessment of the long-term cost-effectiveness of MATs for OUD suggest that all therapies generated very similar life years, with only marginal differences in QALYs relative to their respective comparators. Vivitrol was a dominated strategy (being more costly and less effective) relative to generic SL buprenorphine/naloxone. Our analysis indicates that only CAM2038 and Probuphine produce incremental QALYs relative to generic SL buprenorphine/naloxone, and then only marginally. Due to a lack of data, we couldn't calculate the cost-effectiveness of Sublocade in the base case analysis, but even under unreasonably favorable assumptions in a scenario analysis, Sublocade still wasn't cost-effective.

We recognize that the population pursuing Vivitrol for MAT may have different treatment intent and goals, given the need for complete opioid withdrawal. We tested this in a per-protocol analysis that assumed successful withdrawal at model entry. While in this scenario Vivitrol produced greater QALYs than comparator treatment, this gain came at a cost of over $1 million per QALY gained.

We did not calculate an incremental cost-effectiveness ratio for CAM2038, given the lack of an available price. However, threshold analyses suggest that this agent should be priced between $219 and $406 per four-week dose to fall within commonly-cited ranges for cost-effectiveness.

Probuphine's incremental cost-effectiveness ratio was well above the $150,000 per QALY WTP threshold relative to its comparator, a conclusion that did not change across multiple scenario and sensitivity analyses from the healthcare sector perspective. Using a modified societal perspective showed directionally similar results compared to the base case analyses for all interventions except Probuphine, which under a modified societal perspective became the dominant strategy (as slightly less costly and slightly more effective) relative to its comparator. As described above, however, findings for Probuphine are reflective of the population in which this MAT was tested (i.e., clinically stable on SL buprenorphine products for six months), so the generalizability of these results to the broader MAT population is very limited.

Key model drivers included treatment discontinuation rates, intervention costs, and the incidence of HCV infection among PWID. Probabilistic sensitivity analyses confirmed the robustness of our base case findings. Shorter time horizons showed directionally similar results compared with those seen in the base case for all interventions. Changing population characteristics to include only PWIDs resulted in higher costs and lower QALYs for all interventions relative to the base case analyses. Aligning with comments that OUD be considered a chronic disorder, our scenario that excluded permanent abstinence from illicit use of opioids resulted in poorer health outcomes and higher costs.

Limitations

Our model has several limitations. While we acknowledge that OUD is a relapsing condition with patients cycling through the same or different therapies multiple times, we did not model re-use of MATs once patients relapsed, or relapse to illicit use among those considered permanently abstained from illicit use of opioids, as inadequate data exist for these estimates. Additionally, among illicit users of opioids, treatment efficacy and discontinuation may depend on type of illicit use (prescription or injection) which we do not consider as we did not find estimates on these specific to individual MATs. We modeled the pre-Markov decision tree based on trial-reported estimates, which may differ in a real-world setting. Also, quality of life among illicit users may differ based on levels of illicit use, which our model does not consider due to lack of data on these levels. Our estimates of utility came from a study that utilized a direct method of elicitation, wherein participants (with or without OUD) were described hypothetical OUD-related health states and asked to rate them between 0 and 1. However, the health state vignettes were specific to buprenorphine-containing compounds and methadone and not to Vivitrol. We model health care costs based on those for a commercially-insured population, which may not be representative of the real-world OUD demographic. Additionally, we used a weighted average of health care costs across populations using different MATs to arrive at single, state-specific health care costs, as we wanted to model costs for a "typical" patient eligible for MAT. While our objective was to identify MATs with best value relative to current treatment practices, we could not compare all MATs to a comparator with a single efficacy estimate, and instead and had to rely on trial-specific comparator estimates due to differences in population characteristics and trial design. While we acknowledge

that adherence to MATs differ due factors such as the route and frequency of administration, we have no robust and/or long-term data to account for this in our model. Finally, our model does not capture diversion and/or switching to other opioids while on specific MATs, due to a lack of robust data on these estimates. We acknowledge the importance of these issues.

Conclusions

In conclusion, the findings of our analysis suggest that CAM2038, Vivitrol and Probuphine result in only marginal changes in QALYs relative to generic SL buprenorphine/naloxone, but universally higher costs. The incremental cost-effectiveness of these therapies versus generic SL buprenorphine/naloxone therefore falls outside commonly-cited thresholds of $50,000 to $150,000 per QALY gained. Even with assumptions extremely favorable to Sublocade, its incremental cost-effectiveness versus generic SL buprenorphine/naloxone also falls outside these commonly-cited thresholds.

5. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, delivery system, other patients, or public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements are listed in the table below, and the subsequent text provides detail about the elements that are applicable to the comparison of extended-release opioid agonists and antagonist MAT to transmucosal formulations of buprenorphine/naloxone.

Table 5.1. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to buprenorphine/naloxone, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to buprenorphine/naloxone, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

5.1 Potential Other Benefits

As stressed by several organizations representing patients with OUD, "treatment is not one-size-fits-all" and patients need to have access to different treatment options on their road to recovery. Extended-release formulations are important additional treatment options that could improve long term recovery by lowering the constraints of daily adherence to transmucosal buprenorphine formulations.

Extended-release buprenorphine formulations are currently subjected to the limits of number of patients that health care providers can treat annually. These limits intend to control diversion of buprenorphine products that are taken without direct medical observation. As extended-release buprenorphine products are administered by health care professionals, the risk of diversion by the patient is extremely low compared to transmucosal buprenorphine products. Regulators could consider not requiring waivers for extended-release formulations thus increasing overall access to MAT. Additionally, administration by a health professional should also prevent accidental poisonings in children that currently occur with transmucosal products.

For OUD patients who are subjected to a program with external monitoring with important consequences of adherence, such as healthcare professionals, pilots, probationers or parolees, the use of extended-release formulations may also significantly improve rates of retention.[12]

In correctional settings with their high prevalence of OUD, extended-release formulations offer the potential of decreasing diversion. It must be noted, however, that the risk of diversion of transmucosal buprenorphine products is, at least in part, related to the fact that inmates with OUD are entering withdrawal and buprenorphine is diverted for controlling withdrawal.[20] Offering buprenorphine through extended-release formulations may diminish negative beliefs about opioid agonist therapy and improve general access to MAT for inmates.

5.2 Contextual Considerations

OUD is considered a public health emergency[4] with an epidemic of deaths that decrease the overall life expectancy in the US[2,3] and impacts all parts of society: families, the health system, social services, the judiciary system, and the economy. For the affected person, OUD is a chronic disease that is often compared to other chronic diseases, such as diabetes, but that carries a stigma affecting self-esteem, social relations, and work.[12] Providing access to extended-release medications, can contribute to diminish the consequences of the opioid epidemic.

Compared to transmucosal formulations of buprenorphine/naloxone or to methadone, there is significant uncertainty about the magnitude or durability of the long-term benefits of extended-release formulations, given the 6-month duration of nearly all trials of these agents. In addition, Probuphine implants cannot be used for longer than 12 months according to the FDA label. For the

other formulations, their duration of appropriate use is unknown and will only be better defined through clinical experience and long-term observational study.

For antagonist therapy with Vivitrol, its action cannot be reversed, so it becomes impossible to use opioids for emergency pain management. Regional analgesia or non-opioid analgesics need to be used.[22]

6. Value-Based Price Benchmarks

ICER's value-based price benchmarks are meant to showcase drug prices that are required to align with value, defined as a willingness-to-pay (WTP) price range of between $100,000 to $150,000 per QALY. In cases where prices fall outside the upper bound and sometimes within this range, we present value-based prices.

We calculated value-based prices for CAM2038 and Probuphine (Table 6.1). Since Vivitrol was less effective relative to its comparator in the base case, and since we did not have adequate data to model Sublocade versus SL buprenorphine/naloxone in the base case analysis, we did not estimate their value-based prices.

Table 6.1. Value-Based Benchmark Prices for CAM2038 and Probuphine

	Annual WAC	Price to Achieve $100,000 per QALY	Price to Achieve $150,000 per QALY	Discount from WAC Required to Achieve Threshold Prices
CAM2038*	-	$4,082[†]	$5,301[†]	-
Probuphine	$4,950[‡]	$1,741[‡]	$2,318[‡]	53% to 65%

QALY: Quality-Adjusted Life Year

*No list or net prices for CAM2038 were available as of the date of this report.

[†]Annual price

[‡]Price per implant lasting six months. Probuphine implant cannot be used more than twice in the treatment for OUD for each patient

7. Potential Budget Impact

7.1 Overview

We used the cost-effectiveness model to estimate the potential total budgetary impact of CAM2038 in the patients aged 18 years and above with OUD. We calculated budget impact using the prices to achieve willingness-to-pay (WTP) thresholds between $50,000 to $150,000 per QALY gained in our estimates of budget impact. Since CAM2038 hasn't been approved for use yet, no WAC or net price exists for the drug and we hence could not calculate budget impact at these prices. We did not include Probuphine, Sublocade, or Vivitrol in our calculations given their presence in the US marketplace for one year or longer.

7.2 Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

The potential budget impact analysis included the candidate populations eligible for treatment: patients aged 18 years and above with OUD. To estimate the size of the potential candidate populations for treatment, we used the reported prevalence for the year 2015 as those diagnosed with OUD, and applied it to the 2015 adult population to derive a point estimate of prevalence.[150] We then applied the estimated prevalence to the projected 2018 to 2022 adult population in the US to derive the average number of OUD patients each year over the five-year period. This resulted in a population size of approximately 1.5 million patients over five years, or approximately 312,000 patients each year. While not all patients diagnosed with OUD seek treatment with MAT and only providers with adequate addition treatment training can prescribe certain MATs, we do not have data on the former or data on the later-specific to CAM2038. We hence assumed that all patients diagnosed with OUD were eligible for treatment with CAM2038.

ICER's methods for estimating potential budget impact are described in detail elsewhere[151] and have been recently updated. The intent of our revised approach to budgetary impact is to document the percentage of patients who could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy. For 2018-19, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $991 million per year for new drugs. To

estimate potential budget impact, we evaluate a new drug that would take market share from one or more drugs, and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we assumed that all patients diagnosed with OUD would be treated with CAM2038 in place of generic buprenorphine/naloxone.

7.3 Results

Table 7.2 illustrates the per-patient budget impact calculations in more detail, based on the prices to reach $150,000, $100,000, and $50,000 per QALY gained WTP thresholds for CAM2038 ($5,301, $4,082, and $2,863 per year, respectively) compared to generic buprenorphine/naloxone.

Table 7.2. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon

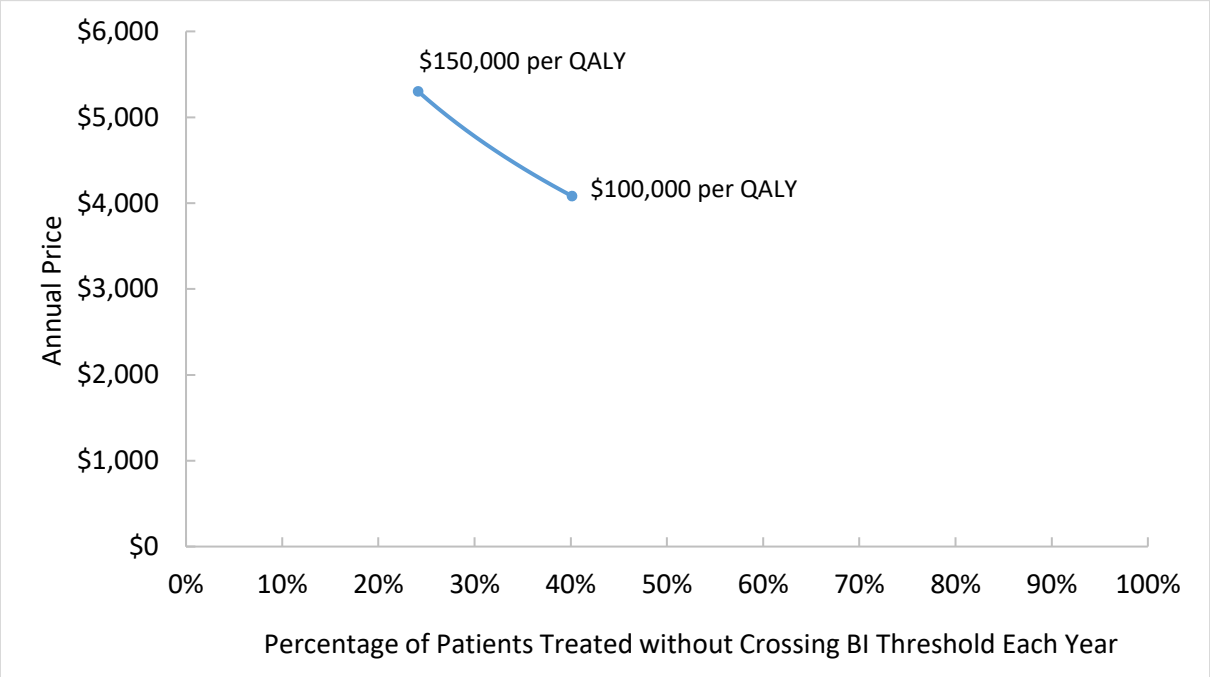
	Average Annual Per Patient Budget Impact		
	$150,000/QALY	$100,000/QALY	$50,000/QALY
CAM2038	$35,420	$33,883	$32,346
Generic Buprenorphine/Naloxone	$31,653		
Difference	$3,768	$2,231	$694

QALY: quality-adjusted life year

The average potential budgetary impact at the three cost-effectiveness threshold prices for the drug ranged from approximately $3,768 per patient using the annual price to achieve $150,000 per QALY to approximately $694 using the annual price to achieve a $50,000 per QALY cost-effectiveness threshold.

The annual potential budgetary impact of treating the entire population over five years did not exceed the $991 million ICER budget impact threshold at the price ($2,863) to achieve $50,000 WTP, approaching approximately 87% of the threshold. However, as shown in Figure 7.1, only 24% and 40% of the entire population could be treated each year at the prices that would reach the $150,000 to $100,000 per QALY thresholds respectively, before the total budget exceeded the ICER annual budget impact threshold.

Figure 7.1. Potential Budget Impact Scenarios at Different Prices of CAM2038 to Treat Adults with OUD



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This is the second ICER review of MAT for OUD. The first ICER review can be found here: https://icer-review.org/topic/opioid-dependence/

References

1. HHS. What is the U.S. Opioid Epidemic? 2018; https://www.hhs.gov/opioids/about-the-epidemic/index.html. Accessed Aug 8, 2018.
2. Dowell D, Arias E, Kochanek K, et al. Contribution of Opioid-Involved Poisoning to the Change in Life Expectancy in the United States, 2000-2015. *Jama.* 2017;318(11):1065-1067.
3. Wakeman SE, Barnett ML. Primary Care and the Opioid-Overdose Crisis - Buprenorphine Myths and Realities. *N Engl J Med.* 2018;379(1):1-4.
4. HHS Press Office. HHS Acting Secretary Declares Public Health Emergency to Address National Opioid Crisis. 2017; https://www.hhs.gov/about/news/2017/10/26/hhs-acting-secretary-declares-public-health-emergency-address-national-opioid-crisis.html.
5. Council of Economic Advisers. The Underestimated Cost of the Opioid Crisis. 2017; https://www.whitehouse.gov/sites/whitehouse.gov/files/images/The%20Underestimated%20Cost%20of%20the%20Opioid%20Crisis.pdf. Accessed April 23, 2018.
6. SAMHSA. EXHIBIT 2.13. DSM-5 Criteria for OUD in TIP 63: Medications for Opioid Use Disorder. 2018; https://store.samhsa.gov/shin/content//SMA18-5063FULLDOC/SMA18-5063FULLDOC.pdf#page=57. Accessed Aug 13, 2018.
7. American Academy of Pain Medicine, American Pain Society, American Society of Addiction Medicine. Definitions Related to the Use of Opioids for the Treatment of Pain: Consensus Statement of the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine. 2001; http://www.asam.org/docs/default-source/public-policy-statements/1opioid-definitions-consensus-2-011.pdf? Accessed 2018-08-03, 2018.
8. White House Office of National Drug Control Policy. Changing the Language of Addiction. In: Washington, DC:: White House Office of National Drug Control Policy; 2017: https://obamawhitehouse.archives.gov/blog/2017/01/13/changing-language-addiction. Accessed 2018-08-09.
9. SAMHSA. Recovery and Recovery Support. 2018; https://www.samhsa.gov/recovery. Accessed 2018-08-03.
10. McBain R, Rose AJ, LaRochelle MR. The U.S. opioid epidemic: One disease, diverging tales. *Prev Med.* 2018;112:176-178.
11. Ross J, Teesson M, Darke S, et al. The characteristics of heroin users entering treatment: findings from the Australian treatment outcome study (ATOS). *Drug Alcohol Rev.* 2005;24(5):411-418.
12. SAMHSA. TIP 63: Medications for Opioid Use Disorder. *Treatment Improvement Protocol (TIP) series* 2018; https://store.samhsa.gov/shin/content//SMA18-5063FULLDOC/SMA18-5063FULLDOC.pdf. Accessed April 18, 2018.
13. FDA. Information about Medication-Assisted Treatment (MAT). 2018; https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm600092.htm. Accessed Aug 12, 2018.
14. FDA. CDER Conversation: Treatment for Opioid Use Disorder. 2018; https://www.fda.gov/Drugs/NewsEvents/ucm611659.htm. Accessed Aug 10, 2018.
15. SAMHSA. EXHIBIT 1.2. Comparison of Medications for OUD in in TIP 63: Medications for Opioid Use Disorder. 2018; https://store.samhsa.gov/shin/content//SMA18-5063FULLDOC/SMA18-5063FULLDOC.pdf#page=28. Accessed Aug 13, 2018.
16. World Health Organization, International Narcotics Control Board, United Nations Office on Drugs and Crime. Guidelines for the psychosocially assisted pharmacological treatment of opioid

dependence. 2009; xviii, 111 p. Available at: http://www.who.int/substance_abuse/publications/opioid_dependence_guidelines.pdf.
17. ASAM. The ASAM National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. 2015; https://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf. Accessed Aug 10, 2018.
18. Bart G. Maintenance medication for opiate addiction: the foundation of recovery. *Journal of addictive diseases.* 2012;31(3):207-225.
19. FDA. Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Medication-Assisted Treatment - Draft Guidance for Industry. In:2018: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM615743.pdf.
20. Wakeman SE, Rich JD. Barriers to Medications for Addiction Treatment: How Stigma Kills. *Subst Use Misuse.* 2018;53(2):330-333.
21. Saloner B, Karthikeyan S. Changes in Substance Abuse Treatment Use Among Individuals With Opioid Use Disorders in the United States, 2004-2013. *Jama.* 2015;314(14):1515-1517.
22. FDA. Vivitrol label. 2015; https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021897s029lbl.pdf. Accessed Aug 10, 2018.
23. FDA. Probuphine label. 2018; https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204442s006lbl.pdf. Accessed Aug 13, 2018.
24. Braeburn Pharmaceuticals. Slides for the November 1, 2017 Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. 2017; https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM586734.pdf#page=4. Accessed Aug 13, 2018.
25. FDA. Public Meeting on Patient-Focused Drug Development for Opioid Use Disorder-April 17, 2018. 2018; https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm591290.htm. Accessed April 23, 2018.
26. Dennis BB, Roshanov PS, Naji L, et al. Opioid substitution and antagonist therapy trials exclude the common addiction patient: a systematic review and analysis of eligibility criteria. *Trials.* 2015;16:475.
27. FDA. FDA Briefing Information for the March 27, 2018 Meeting of the Psychopharmacologic Drugs Advisory Committee. In:2018: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM602417.pdf#page=13.
28. Barlas S. U.S. and States Ramp Up Response to Opioid Crisis: Regulatory, Legislative, and Legal Tools Brought to Bear. *P T.* 2017;42(9):569-592.
29. Takkunen A, Hanson K. States fight the opioid epidemic by expanding access to treatment. *National Conference of State Legislatures Blog* 2018; http://www.ncsl.org/blog/2018/08/08/states-fight-the-opioid-epidemic-by-expanding-access-to-treatment.aspx. Accessed August 17, 2018.
30. Clemans-Cope L, Wishner JB, Allen EH, Lallemand N, Epstein M, Spillman BC. Experiences of three states implementing the Medicaid health home model to address opioid use disorder—Case studies in Maryland, Rhode Island, and Vermont. *Journal of substance abuse treatment.* 2017;83:27-35.

31. Mohlman MK, Tanzman B, Finison K, Pinette M, Jones C. Impact of Medication-Assisted Treatment for Opioid Addiction on Medicaid Expenditures and Health Services Utilization Rates in Vermont. *Journal of substance abuse treatment.* 2016;67:9-14.
32. Simpatico TA. Vermont responds to its opioid crisis. *Prev Med.* 2015;80:10-11.
33. Green TC, Clarke J, Brinkley-Rubinstein L, et al. Postincarceration Fatal Overdoses After Implementing Medications for Addiction Treatment in a Statewide Correctional System. *JAMA psychiatry.* 2018;75(4):405-407.
34. Institute for Clinical and Economic Review. Management of Patients with Opioid Dependence: A Review of Clinical, Delivery System, and Policy Options. In: Institute for Clinical and Economic Review, ed. Boston2014: https://icer-review.org/wp-content/uploads/2016/01/CEPAC-Opioid-Dependence-Final-Report-For-Posting-July-21.pdf. Accessed 2018-04-11.
35. Health NIo. Opioids, opioid antagonists. https://livertox.nih.gov/Opioids.htm
36. Jensen TS. Opioids in the brain: supraspinal mechanisms in pain control. *Acta Anaesthesiol Scand.* 1997;41(1 Pt 2):123-132.
37. Fields HL, Margolis EB. Understanding opioid reward. *Trends Neurosci.* 2015;38(4):217-225.
38. Holden JE, Jeong Y, Forrest JM. The endogenous opioid system and clinical pain management. *AACN Clin Issues.* 2005;16(3):291-301.
39. Hou H, Wang C, Jia S, Hu S, Tian M. Brain dopaminergic system changes in drug addiction: a review of positron emission tomography findings. *Neurosci Bull.* 2014;30(5):765-776.
40. O'Brien C. Addiction and dependence in DSM-V. *Addiction.* 2011;106(5):866-867.
41. Savage SR, Joranson DE, Covington EC, Schnoll SH, Heit HA, Gilson AM. Definitions related to the medical use of opioids: Evolution towards universal agreement. *Journal of Pain and Symptom Management.* 2003;26(1):655–667. https://www.jpsmjournal.com/article/S0885-3924(03)00219-7/pdf. Accessed 2018-08-06.
42. California Health Benefits Review Program. Analysis of California Assembly Bill 2384 Medication-Assisted Treatment. In:2018-05-15: http://analyses.chbrp.com/document/view.php?id=1343. Accessed 2008-04-18.
43. Institute for Clinical and Economic Review. Management of Patients with Opioid Dependence: A Review of Clinical, Delivery System, and Policy Options - Appendices. In: Boston2014: https://icer-review.org/wp-content/uploads/2016/02/Appendices-Final-Opioid-Dependence-Report-CEPAC-10-6.pdf. Accessed 2018-07-11.
44. SAMHSA. Federal Guidelines for Opioid Treatment Programs. *HHS Publication No. (SMA) PEP15-FEDGUIDEOTP* 2015; https://store.samhsa.gov/shin/content/PEP15-FEDGUIDEOTP/PEP15-FEDGUIDEOTP.pdf.
45. Volkow ND. Medications for opioid use disorder: bridging the gap in care. *Lancet.* 2018;391(10118):285-287.
46. Middlesex Sheriff's Office. The MATADOR Program - Utilizing Incarceration to Tackle Addiction and Save Lives: Implementing Medication Assisted Treatment Programs in Jails. In: Middlesex Sheriff's Office, Middlesex County, MA; 2018: https://www.sheriffs.org/sites/default/files/MATADOR%20White%20Paper_April2018.pdf. Accessed 2018-08-10.
47. FDA. Sublocade label. 2018; https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209819s001lbl.pdf. Accessed Aug 14, 2018.
48. FDA. 2017 Meeting Materials, Drug Safety and Risk Management Advisory Committee. 2017; https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm536632.htm. Accessed August 14, 2018.

49. FDA. Minutes for the November 1, 2017 Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. 2017; https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM592675.pdf. Accessed Aug 14, 2018.
50. Woolf S. An organized analytic framework for practice guideline development: using the analytic logic as a guide for reviewing evidence, developing recommendations, and explaining the rationale. *Clinical Practice Guideline Development: Methodology Perspectives. AHCPR Pub* 1994; 105-113. Available at: https://ntrl.ntis.gov/NTRL/ under number PB95195848.
51. Maglione MA, Raaen L, Chen C, et al. Effects of medication assisted treatment (MAT) for opioid use disorder on functional outcomes: A systematic review. *Journal of substance abuse treatment.* 2018;89:28-51.
52. CMS.gov. National Coverage Determination (NCD) for Treatment of Alcoholism and Drug Abuse in a Freestanding Clinic (130.5). In: Services CfMM, ed. cms.gov2018.
53. CMS.gov. National Coverage Determination (NCD) for Treatment of Drug Abuse (Chemical Dependency) (130.6). In: Services CfMM, ed. cms.gov2018.
54. Cigna. Cigna Standards and Guidelines/Medical Necessity Criteria for Treatment of Mental Health and Substance Use Disorders. In: Cigna, ed. Revised Edition ed. cigna.com2018.
55. Aetna. Buprenorphine Implant (Probuphine) and Extended-Release Injectable (Sublocade). 2018; http://www.aetna.com/cpb/medical/data/900_999/0910.html. Accessed 08/15/18.
56. Anthem. Sublocade (buprenorphine extended-release). In:2018.
57. UnitedHealthcare. Medical Benefit Drug Policy: BUPRENORPHINE (PROBUPHINE & SUBLOCADE). In. uhcprovider.com2018.
58. BlueCrossBlueShieldMA. Medication Look Up. 2018; https://www.bluecrossma.com/wps/portal/members/using-my-plan/manage-my-plan/pharmacy-coverage/medication-look-up/. Accessed 08/15/18, 2018.
59. Anthem. Probuphine (buprenorphine implant). 2018.
60. BlueCrossBlueShieldMA. Pharmacy Medical Policy: Medical Utilization Management (MED UM) & Pharmacy Prior Authorization Policy. 2018.
61. Aetna. 2018 Aetna Pharmacy Drug Guide: Aetna Value Plus Plan. 2018.
62. Cigna. Cigna Value 3-Tier Prescription Drug List. 2018.
63. Care HPH. 3-Tier Value Formulary Drug Tier Look-Up (2018). 2018; https://www.harvardpilgrim.org/hphconnect/formulary/drugLookup.htm?&formularyId=VALUE_3_TIER&year=2018. Accessed 08/15/18, 2018.
64. UnitedHealthcare. Your 2018 Prescription Drug List: Traditional Three-Tier. 2018.
65. Anthem. National Drug List - Three (3) Tier Drug Plan. 2018.
66. MassHealth. Table 36: Drug and Alcohol Cessation Agents. 2018; https://masshealthdruglist.ehs.state.ma.us/MHDL/pubtheradetail.do?id=36. Accessed 08/15/18, 2018.
67. DVHA. Department of Vermont Health Access Managed Care Entity Vermont Substance Use Disorder Medication Assisted Treatment Guidelines. 2018.
68. AATOD. AATOD Guidelines for Using Naltrexone (Vivitrol) in OTPs. 2012.
69. AMCP. AMCP Addiction Treatment Advisory Group: Findings and Considerations for the Evidence-Based Use of Medications Used in the Treatment of Substance Use Disorder. 2016.
70. ASAM. 2015.
71. National Institute on Drug Abuse. Principles of Drug Addiction Treatment: A Research-Based Guide (Third Edition). In:2018: https://d14rmgtrwzf5a.cloudfront.net/sites/default/files/675-principles-of-drug-addiction-treatment-a-research-based-guide-third-edition.pdf.

72. Sigmon SC, Dunn KE, Saulsgiver K, et al. A randomized, double-blind evaluation of buprenorphine taper duration in primary prescription opioid abusers. *JAMA psychiatry.* 2013;70(12):1347-1354.
73. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *International journal of surgery (London, England).* 2010;8(5):336-341.
74. *U.S. Preventive Services Task Force Procedure Manual.* Agency for Healthcare Research and Quality; July 2008. Publication No. 08-05118-EF.
75. Review IfCaE. ICER Evidence Rating Matrix: A User's Guide. 2017.
76. 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 internal medicine.* 2018;178(6):764-773.
77. ClinicalTrials.gov. Trial 13-0001 Sublocade vs Placebo. https://clinicaltrials.gov/ct2/show/results/NCT02357901?term=NCT02357901&rank=1&sect=Xfe897d0156#outcome9.
78. ClinicalTrials.gov. Trial 13-0003 Safety and Tolerability Study of Depot Buprenorphine in Treatment Seeking Subjects With Opioid Use Disorder. 2018; https://clinicaltrials.gov/ct2/show/results/NCT02510014?term=NCT02510014&rank=1&sect=X4301256.
79. Rosenthal RN, Lofwall MR, Kim S, Chen M, Beebe KL, Vocci FJ. Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults With Opioid Dependence Treated With Sublingual Buprenorphine: A Randomized Clinical Trial. *Jama.* 2016;316(3):282-290.
80. Ling W, Casadonte P, Bigelow G, et al. Buprenorphine implants for treatment of opioid dependence: A randomized controlled trial. *JAMA: Journal of the American Medical Association.* 2010;304(14):1576-1583.
81. Rosenthal RN, Ling W, Casadonte P, et al. Buprenorphine implants for treatment of opioid dependence: randomized comparison to placebo and sublingual buprenorphine/naloxone. *Addiction.* 2013;108(12):2141-2149.
82. Beebe KL, Chavoustie S, Ling W, Sigmon S, Leiderman D, Bailey G. Buprenorphine implants for the treatment of opioid dependence: Six and 12 month outcomes. *Neuropsychopharmacology.* 2012;38:S266-S267.
83. Lee JD, Nunes EV, Jr., Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *Lancet.* 2018;391(10118):309-318.
84. Tanum L, Solli KK, Latif Z-e-H, et al. Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: A randomized clinical noninferiority trial. *JAMA psychiatry.* 2017;74(12):1197-1205.
85. Lee JD, Friedmann PD, Kinlock TW, et al. Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders. *N Engl J Med.* 2016;374(13):1232-1242.
86. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Lancet.* 2011;377(9776):1506-1513.
87. Lee JD, Friedmann PD, Boney TY, et al. Extended-release naltrexone to prevent relapse among opioid dependent, criminal justice system involved adults: rationale and design of a randomized controlled effectiveness trial. *Contemp Clin Trials.* 2015;41:110-117.
88. ClinicalTrials.gov. NEW HOPE. 2017; https://clinicaltrials.gov/ct2/show/results/NCT01246401?sect=X5643012.

89. Solli KK, Latif ZE, Opheim A, et al. Effectiveness, safety and feasibility of extended-release naltrexone for opioid dependence: a 9-month follow-up to a 3-month randomized trial. *Addiction.* 2018.
90. Krupitsky E, Nunes EV, Ling W, Gastfriend DR, Memisoglu A, Silverman BL. Injectable extended-release naltrexone (XR-NTX) for opioid dependence: Long-term safety and effectiveness. *Addiction.* 2013;108(9):1628-1637.
91. Lee JD, McDonald R, Grossman E, et al. Opioid treatment at release from jail using extended-release naltrexone: A pilot proof-of-concept randomized effectiveness trial. *Addiction.* 2015;110(6):1008-1014.
92. Lee JD, Friedmann PD, Kinlock TW, et al. Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders. *New England Journal of Medicine.* 2016;374(13):1232-1242.
93. Krupitsky E. Naltrexone for opiate dependence: Oral, implantable, and injectable. *European Neuropsychopharmacology.* 2011;21:S104-S105.
94. Soares WE, Iii W, Donna R, et al. Healthcare utilization in adults with opioid dependence receiving extended release naltrexone compared to treatment as usual. *Journal of substance abuse treatment.* 2018;85:66-69.
95. Shah A, Duncan M, Atreja N, Tai KS, Gore M. Healthcare utilization and costs associated with treatment for opioid dependence. *J Med Econ.* 2018;21(4):406-415.
96. Vivitrol pacakage insert.
97. Saucier R, Wolfe D, Dasgupta N. Review of Case Narratives from Fatal Overdoses Associated with Injectable Naltrexone for Opioid Dependence. *Drug Safety.* 2018:1-8.
98. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database of Systematic Reviews.* 2009(3).
99. CADTH. Buprenorphine/naloxone versus methadone for the treatment of opioid dependence: A review of comparative clinical effectiveness, cost-effectiveness and guidelines. 2016.
100. Fudala PJ, Bridge TP, Herbert S, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med.* 2003;349(10):949-958.
101. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Systematic Reviews.* 2014(2).
102. Newman RG, Whitehill WB. Double-blind comparison of methadone and placebo maintenance treatments of narcotic addicts in Hong Kong. *Lancet.* 1979;2(8141):485-488.
103. Saxon AJ, Hser YI, Woody G, Ling W. Medication-assisted treatment for opioid addiction: methadone and buprenorphine. *Journal of food and drug analysis.* 2013;21(4):S69-s72.
104. Neumann AM, Blondell RD, Jaanimagi U, et al. A preliminary study comparing methadone and buprenorphine in patients with chronic pain and coexistent opioid addiction. *Journal of addictive diseases.* 2013;32(1):68-78.
105. Proctor SL, Copeland AL, Kopak AM, Herschman PL, Polukhina N. A naturalistic comparison of the effectiveness of methadone and two sublingual formulations of buprenorphine on maintenance treatment outcomes: findings from a retrospective multisite study. *Experimental and clinical psychopharmacology.* 2014;22(5):424-433.
106. Curcio F, Franco T, Topa M, Baldassarre C. Buprenorphine/naloxone versus methadone in opioid dependence: a longitudinal survey. *European review for medical and pharmacological sciences.* 2011;15(8):871-874.

107. Otiashvili D, Piralishvili G, Sikharulidze Z, Kamkamidze G, Poole S, Woody GE. Methadone and buprenorphine-naloxone are effective in reducing illicit buprenorphine and other opioid use, and reducing HIV risk behavior--outcomes of a randomized trial. *Drug and alcohol dependence.* 2013;133(2):376-382.
108. Hser YI, Evans E, Huang D, et al. Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial. *Addiction.* 2016;111(4):695-705.
109. Schackman BR, Leff JA, Polsky D, Moore BA, Fiellin DA. Cost-effectiveness of long-term outpatient buprenorphine-naloxone treatment for opioid dependence in primary care. *Journal of general internal medicine.* 2012;27(6):669-676.
110. Carter JA, Dammerman R, Frost M. Cost-effectiveness of subdermal implantable buprenorphine versus sublingual buprenorphine to treat opioid use disorder. *J Med Econ.* 2017;20(8):893-901.
111. Alderks CE. Trends in the Use of Methadone and Buprenorphine at Substance Abuse Treatment Facilities: 2003 to 2011. In: *The CBHSQ Report.* Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 2013:1-7.
112. Treatment Seeking Participants With Opioid Use Disorders Assessing Tolerability of Depot Injections of Buprenorphine. National Institute of Health; 2018. https://clinicaltrials.gov/ct2/show/study/NCT02357901. Accessed July 1, 2018.
113. U.S. Food and Drug Administration. VIVITROL® (naltrexone for extended-release injectable suspension) Intramuscular. In:2015.
114. Lee JD, Nunes EV, Jr., Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *The Lancet.* 2018;391(10118):309-318.
115. U.S. Food and Drug Administration. PROBUPHINE (buprenorphine) implant for subdermal administration CIII. In:2002.
116. Rosenthal RN, Lofwall MR, Kim S, et al. Effect of buprenorphine implants on illicit opioid use among abstinent adults with opioid dependence treated with sublingual buprenorphine: A randomized clinical trial. *Jama.* 2016;316(3):282-290.
117. 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 internal medicine.* 2018;178(6):764-773.
118. Indivior. Data on File. 2018.
119. Bernard CL, Owens DK, Goldhaber-Fiebert JD, Brandeau ML. Estimation of the cost-effectiveness of HIV prevention portfolios for people who inject drugs in the United States: A model-based analysis. *PLoS medicine.* 2017;14(5):e1002312.
120. Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. *BMC medical research methodology.* 2011;11:139.
121. Lansky A, Finlayson T, Johnson C, et al. Estimating the number of persons who inject drugs in the united states by meta-analysis to calculate national rates of HIV and hepatitis C virus infections. *PloS one.* 2014;9(5):e97596.
122. Page K, Morris MD, Hahn JA, Maher L, Prins M. Injection drug use and hepatitis C virus infection in young adult injectors: using evidence to inform comprehensive prevention. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2013;57 Suppl 2:S32-38.
123. Berlin JA, Abrutyn E, Strom BL, et al. Incidence of infective endocarditis in the Delaware Valley, 1988-1990. *The American journal of cardiology.* 1995;76(12):933-936.
124. Spijkerman IJ, van Ameijden EJ, Mientjes GH, Coutinho RA, van den Hoek A. Human immunodeficiency virus infection and other risk factors for skin abscesses and endocarditis among injection drug users. *J Clin Epidemiol.* 1996;49(10):1149-1154.

125. Sande MA, Lee BL, Millills J, Chambers HF. *Endocarditis in intravenous drug users.* 2nd ed. New York: Raven Press; 1992.
126. Opioid Overdose Death Rates and All Drug Overdose Death Rates per 100,000 Population (Age-Adjusted). 2016. https://www.kff.org/other/state-indicator/opioid-overdose-death-rates/?currentTimeframe=0&selectedDistributions=opioid-overdose-death-rate-age-adjusted&selectedRows=%7B%22wrapups%22:%7B%22united-states%22:%7B%7D%7D%7D&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D. Accessed 07/11/2018.
127. Human Mortality Database. 2016. www.mortality.org. Accessed 07/15/2018.
128. Lappalainen L, Hayashi K, Dong H, Milloy MJ, Kerr T, Wood E. Ongoing Impact of HIV Infection on Mortality among Persons who Inject Drugs Despite Free Antiretroviral Therapy. *Addiction (Abingdon, England).* 2015;110(1):111-119.
129. El-Kamary SS, Jhaveri R, Shardell MD. All-Cause, Liver-Related, and Non–Liver-Related Mortality Among HCV-Infected Individuals in the General US Population. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America.* 2011;53(2):150-157.
130. U.S. Food and Drug Administration. MAVYRET™ (glecaprevir and pibrentasvir) tablets, for oral use. In:2017.
131. Smith DJ, Jordan AE, Frank M, Hagan H. Spontaneous viral clearance of hepatitis C virus (HCV) infection among people who inject drugs (PWID) and HIV-positive men who have sex with men (HIV+ MSM): a systematic review and meta-analysis. *BMC Infectious Diseases.* 2016;16(1):471.
132. Wittenberg E, Bray JW, Aden B, Gebremariam A, Nosyk B, Schackman BR. Measuring benefits of opioid misuse treatment for economic evaluation: health-related quality of life of opioid-dependent individuals and their spouses as assessed by a sample of the US population. *Addiction.* 2015;111(4):675-684.
133. Connock M, Juarez-Garcia A, Jowett S, et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. *Health technology assessment (Winchester, England).* 2007;11(9):1-171, iii-iv.
134. Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making.* 2006;26(4):410-420.
135. Bernard CL, Brandeau ML, Humphreys K, et al. Cost-Effectiveness of HIV Preexposure Prophylaxis for People Who Inject Drugs in the United States. *Annals of internal medicine.* 2016:10.7326/M7315-2634.
136. Chhatwal J, Kanwal F, Roberts MS, Dunn MA. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. *Ann Intern Med.* 2015;162(6):397-406.
137. Pharmaceutical Prices. U.S. Department of Veterans Affairs; 2018. Accessed July 15, 2018.
138. Alkermes. Data on File. 2018.
139. Redbook. 2018. Accessed July 11, 2018.
140. Physician Fee Schedule Search. 2018. https://www.cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx. Accessed August 14, 2018.
141. Shah A, Duncan M, Atreja N, Tai KS, Gore M. Healthcare utilization and costs associated with treatment for opioid dependence. *Journal of Medical Economics.* 2018;21(4):406-415.
142. Health Care Cost Institute. *2016 Health Care Cost and Utilization Report.* Washington, DC: Health Care Cost Institute;2018.
143. Johnson RL, Blumen HE, Ferro C. *The burden of hepatitis C virus disease in commercial and managed Medicaid populations.* Milliman;2015.
144. National Economic Accounts. United States Department of Labor; 2018. https://www.bea.gov/national/#gdp. Accessed August 10, 2018.

145. Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. *Pain medicine (Malden, Mass).* 2011;12(4):657-667.
146. Substance Abuse & Mental Health Data Archive. *National Survey on Drug Use and Health (NSDUH-2007).* Substance Abuse & Mental Health Data Archive;2007.
147. Krebs E, Urada D, Evans E, Huang D, Hser YI, Nosyk B. The costs of crime during and after publicly funded treatment for opioid use disorders: a population-level study for the state of California. *Addiction.* 2017;112(5):838-851.
148. Jackson H, Mandell K, Johnson K, Chatterjee D, Vanness DJ. Cost-Effectiveness of Injectable Extended-Release Naltrexone Compared With Methadone Maintenance and Buprenorphine Maintenance Treatment for Opioid Dependence. *Substance abuse.* 2015;36(2):226-231.
149. Nosyk B, Guh DP, Bansback NJ, et al. Cost-effectiveness of diacetylmorphine versus methadone for chronic opioid dependence refractory to treatment. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2012;184(6):E317-328.
150. Davenport S, Weaver A, Caverly M. *Opioid prescription drug patterns in diagosed and non-diagnosed opioid use disorder populations.* Milliman;2018.
151. Pearson SD. The ICER Value Framework: Integrating Cost Effectiveness and Affordability in the Assessment of Health Care Value. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2018;21(3):258-265.
152. Lofwall MR, Bailey GL, Frost MP, et al. *An efficacy and safety comparision of CAM2038 vs SL BPN/NX for the treatment of patients with OUD who inject opioids.* 2018.
153. Lofwall MR, Frost M, Bailey GL, et al. *Phase 3 trial comparing depot buprenorphine (CAM2038) to sublingual buprenorphine/naloxone for OUD treatment: Subanalysis among persons with heroin as the primary opioid of abuse.* 2018.
154. Haight B, Andorn A, Laffont C, et al. RBP-6000 buprenorphine monthly depot demonstrates sustained clinical efficacy and safety in phase III opioid use disorder trials. *Neuropsychopharmacology.* 2017;43:S463-S464.
155. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama.* 2016;316(10):1093-1103.
156. Hourly Earnings (MEI). Organisation for Economic Co-operation and Development; 2018. https://stats.oecd.org/Index.aspx?DataSetCode=EAR_MEI#. Accessed August 20, 2018.
157. Databases, Tables & Calculators by Subject. United States Department of Labor; 2018. https://www.bls.gov/data/#prices. Accessed August 20, 2018.

APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist item	Pages
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p. 40
ABSTRACT			
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	p. 1 - 11
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P. 21
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p. 9 - 11
METHODS			
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	p. 23
Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	p. 9 – 11, p. 22-23
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	p. 22 - 23
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix Table A2
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	p. 25 - 31
Data Collection Process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p. 23 - 24
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p. 10 - 14
Risk of Bias in Individual Studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	p. 23

Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	p. 21
Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Risk of Bias Across Studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	p. 23
Additional Analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Appendix Fig. A1
Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	p. 25 - 29
Risk of Bias Within Studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	p. 33 - 45
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	p. 33 - 45
Synthesis of Results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of Bias Across Studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	p. 23
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	p. 33 - 52
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	p. E9 – ES10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	p. 52 - 55
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	p. iv - v

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

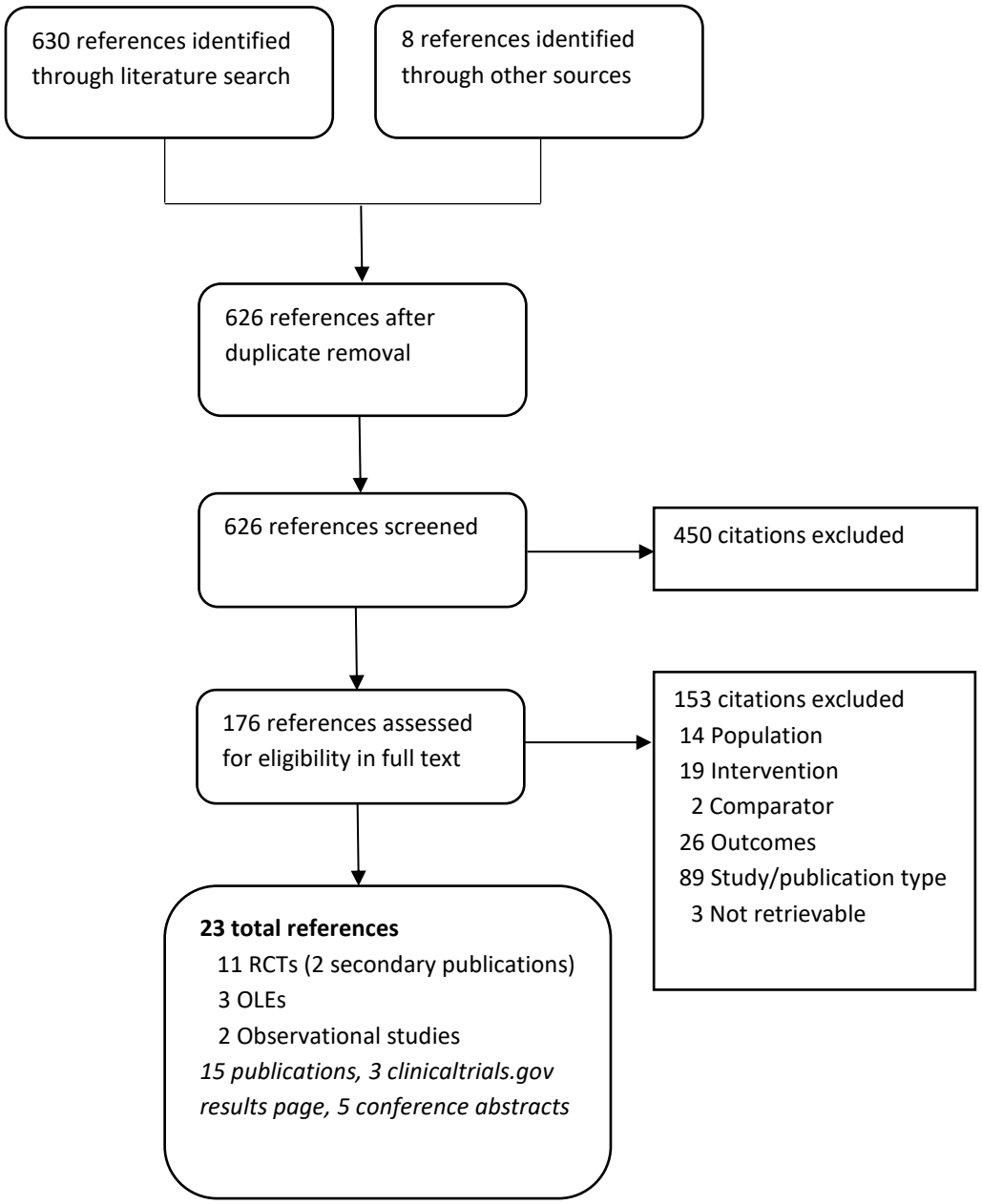
Table A2. Search Strategy of Medline 1996 to Present with Daily Update, PsycINFO, Cochrane Central Register of Controlled Trials via Ovid, September 25, 2018.

#	Search Terms
1	opioid related disorder*.mp.
2	(narcotic* or opiate* or opioid* or heroin) and (misuse or abus* or addict* or habit* or dependenc* or withdraw).ti,ab.
3	1 or 2
4	(buprenorphine or Sublocade).mp.
5	(buprenorphine implant or Probuphine).mp.
6	(buprenorphine or CAM2038).mp.
7	(naltrexone or Vivitrol).mp.
8	(extended release or slow release or controlled release or sustained release).mp.
9	(4 or 6 or 7) and 8
10	(medication assisted treatment or (medication adj3 addiction treatment) or MAT).mp.
11	5 or 9 or 10
12	3 and 11
13	clinical trial.pt. or clinical trial, phase I.pt. or clinical trial, phase ii.pt. or clinical trial, phase iii.pt. or clinical trial, phase iv.pt. or controlled clinical trial.pt. or multicenter study.pt. or randomized controlled trial.pt. or double-blind method/ or clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or early termination of clinical trials as topic/ or multicenter studies as topic/ or ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*))).ti,ab,kw. or (4 arm or four arm).ti,ab,kw.
14	cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab. or case-control studies/ or control groups/ or matched-pair analysis/ or retrospective studies/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab,kw.
15	13 or 14
16	12 and 15
17	(abstract or addresses or autobiography or bibliography or biography or clinical trial, phase I or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt.
18	16 not 17
19	(animals not (humans and animals)).sh.
20	18 not 19
21	limit 20 to english language
22	Remove duplicates from 21

Table A3. Embase Search Strategy, September 25, 2018.

#	Search Terms
#1	'opiate addiction'/exp or 'opiate addiction'
#2	(narcotic* or opiate* or opioid* or heroin) and (misuse or abus* or addict* or habit* or dependenc* or withdraw)
#3	'drug abuse' and 'substance abuse'
#4	#1 or #2 or #3
#5	(buprenorphine or Sublocade)
#6	('buprenorphine implant' or Probuphine)
#7	(buprenorphine or CAM2038)
#8	(naltrexone or Vivitrol)
#9	(extended or slow or controlled or sustained) and release
#10	(#5 or #7 or #8) and #9
#11	(medication assisted treatment or medication NEAR/3 addiction treatment or MAT)
#12	#6 or #10 or #11
#13	#4 and #12
#14	'clinical':ab,ti AND 'trial':ab,ti OR 'clinical trial'/exp OR random* OR 'drug therapy':lnk
#15	'clinical article'/exp OR 'controlled study'/exp OR 'major clinical study'/exp OR 'prospective study'/exp OR 'cohort analysis'/exp OR 'cohort':ab,ti OR 'compared':ab,ti OR 'groups':ab,ti OR 'case control':ab,ti OR 'multivariate':ab,ti
#16	#14 or #15
#17	#13 and #16
#18	#17 AND ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#19	#17 not #18
#20	'animal'/exp or 'nonhuman'/exp or 'animal experiment'/exp
#21	'human'/exp
#22	#20 and #21
#23	#20 not #22
#24	#19 not #23
#25	#24 and [english]/lim
#26	#24 and [medline]/lim
#27	#25 not #26

Figure A1. PRISMA Flow Chart Showing Results of Literature Search



Appendix B. Previous Systematic Reviews and Technology Assessments

We identified two systematic reviews and one technology assessment on the treatment of OUD using naltrexone: (1) the induction and adherence rates of naltrexone (XR-NTX, Vivitrol) in patients with OUD, (2) the effectiveness of sustained-release naltrexone and its adverse events, and (3) a NICE health technology appraisal on naltrexone as a treatment option for the management of OUD. These reviews and technology assessment are summarized below.

Jarvis, B., Et al. (2018). "Extended-Release Injectable Naltrexone for Opioid Use Disorder: A Systematic Review" ***Cochrane Database of Systematic Reviews***

This systematic review evaluated the success of introducing naltrexone, patient's adherence to treatment and its overall efficiency as a treatment option for patients with OUD. Thirty-four studies met the inclusion criteria as peer-reviewed studies with patients who were considered for treatment for opioid use, met the criteria for opioid abuse, or have OUD but were not required to be hospitalized. The pooled results from all studies indicated that the efficiency of naltrexone was lowest when used in patients who did not yet undergo detoxification (62.6% to 85% success rate, respectively). Investigational studies found higher rates of adherence to the treatment (47%), whereas medical records indicated that only 10.5% adhered to treatment outside of a trial setting. The study concluded that extended-release naltrexone is not clinically significant because the need for patient detoxification significantly lowers the pool of patients eligible to complete the treatment successfully. By six months, only 47% of participants were still adhering to the treatment.

Lobmaier, P. Et al. (2008). "Sustained-Release Naltrexone for Opioid Dependence (Review)" ***Cochrane Database of Systematic Reviews***

The purpose of this systematic review was to evaluate the effectiveness of sustained-release naltrexone injection and its adverse effects separately in participants with OUD, participants with alcohol use disorder, and healthy participants. RCTs were included in the review and for the evaluations of the efficacy and safety of naltrexone injection. Researchers concluded that not enough reports exist to evaluate the effectiveness of naltrexone injection. One included trial found that the naltrexone injection's effectiveness was dependent on dose. The high-dose treatment group in the study took a longer amount of time before they dropped out of treatment as compared to the low-dose or placebo group. When evaluating the amount and severity of adverse events (AEs), participants with OUD reported feeling fatigued and having administration-site specific conditions. Six out of ten participants with OUD in one trial, Waal 2003, reported dysphoria but the trial had no control group. In a separate trial (Waal 2006) patients with opioid dependence reported irritability, headache, and nausea, but this decreased as the study continued. Researchers

concluded that there is not enough evidence to evaluate the effectiveness of sustained-release naltrexone as a treatment for OUD.

NICE Health Technology Appraisal

NICE issued a technology appraisal for naltrexone as a treatment for the management of OUD. In the assessment of naltrexone's clinical effectiveness, researchers found 17 studies on the clinical effectiveness of naltrexone: one systematic review, 13 randomized-controlled trials (RCTs) and 3 non-randomized comparative studies. Two RCTs were conducted in a prison setting with follow-ups ranging from 20 days to a full year. All pooled studies mainly focused on reporting retention rates, relapse of opioid use, and re-incarceration in the case of the prison RCTs. Pooled analysis of the relapse rates showed a statistically significant reduction in risk of opioid use with naltrexone as compared to placebo. NICE researchers assessed that the pooled data confirmed naltrexone use showed a significant reduction in relapse. However, there was no difference in retention to treatment with naltrexone as opposed to other treatments, nor was there a significant reduction in mortality of patients being treated with naltrexone.

Appendix C. Ongoing Studies

Appendix Table C. Ongoing Studies of Partial Opioid Agonists and Full Opioid Antagonist

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Vivitrol					
A Strategy to Improve Succes of Treatment Dicontinuation in Buprenorphine Reponders New York State Psychiatric Institute NCT03232346	Phase III, Randomized trial, parallel assignment Enrollement : 60 (currently recruiting)	Experimental: Regimen 1 • Rapid Monday to Friday oral naltrexone-induction procedure • Intervention: Drug: Vivitrol Experimental: Regimen 2 • 5-week buprenorphine taper from maintenance dose of 8, 6, or 4mg • Intervention: Drug: Buprenorphine	Inclusion Criteria: 1. A documented history of treatment with buprenorphine or buprenorphine/naloxone for at least 6 months with sustained abstinence from illicit opioids for at least 3 months. 2. Aged 18 to 60 years 3. In otherwise good health 4. Seeking buprenorphine discontinuation and willing to accept randomization to either taper from buprenorphine or injection naltrexone Exclusion Criteria: 1. Lifetime history of DSM-5 diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder 2. Individuals who meet DSM-5 criteria for any substance use disorders - severe, other than opioid and nicotine use disorder. 3. A recent history of binge-use of alcohol or sedative-hypnotics	• Percent of patients successfully transitioned off buprenorphine • Percent of patients abstinent from any opioids at 25-week trial endpoint	August 1, 2019

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Injectable Pharmacotherapy for Opioid Use Disorders (IPOD) University of California, Berkeley NCT02110264	Phase III, randomized, parallel assignment Enrollement : 151	Experimental: Vivitrol (XR-NTX) • 50 participants will be randomized to the long-acting naltrexone condition (XR-NTX) which will include monthly injections of study drug. Experimental: XR-NTX+PN • 50 participants will be randomized to receive long-acting naltrexone (XR-NTX) and will be assigned to a patient navigator (PN). Active Comparator: ETAU • 50 participants will be randomized to the drug-education/treatment-as-usual group. • Intervention: Behavioral: ETAU	Inclusion Criteria: 1. Be at least 18 years of age or older, 2. Meet criteria for DSM-5 opioid use disorders 3. Be detained for at least 48 hours, 4. Have an expected release date within one year, 1. Plan to reside in area after release. Exclusion Criteria: 1. Have a medical or psychiatric condition that would make participation unsafe in the judgment of the medical staff or the PI, 2. Have current or chronic pain or have plans to undergo pain treatment/therapy, 3. Have known sensitivity to naltrexone or naloxone, 4. Have participated in an investigational drug study within the past 30 days prior to screening, 5. Have a current pattern of alcohol, benzodiazepine, or other depressant or sedative hypnotic use, as determined by the study physician which would preclude safe participation in the study.	• Compare outcomes of the three intervention groups, measured by a combination of self-reports and urine drug screens for opioids at 6-months post-intervention.	February, 2019

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Long-Acting Naltrexone for Pre-release Prisoners Friends Research Institute, Inc. NCT02867124	Phase III, randomized, paralell assignment Enrollment : 240	Experimental: Vivitrol at place of residence • One injection of long-acting naltrexone (XR-NTX) in prison, followed by 6 monthly injections post-release at the participants's place of residence utilizing mobile medical treatment Interventions: Drug: XR-NTX Other: place of residence Active Comparator: Vivitrol at opioid treatment program • One injection of long-acting naltrexone (XR-NTX) in prison, followed by 6 monthly injections post-release at a community opioid treatment program. Interventions: Drug: XR-NTX Other: opioid treatment program	Inclusion Criteria: 1. Adult male or female inmate at MTC, BPRU, JPRU, BCCC, or MCIW and be eligible for release within 30 days 2. History of opiate disorder 3. Suitability for XR-NTX treatment 4. Currently opioid-free by history, with negative urine for all opioids and no signs of opiate withdrawal 5. Willingness to enroll in XR-NTX treatment Exclusion Criteria: 1. Liver function test levels greater than three times normal 2. Active medical illness that may make participation hazardous 3. Untreated psychiatric disorder that may make participation 4. History of allergic reaction to XR-NTX 5. Creatinine above normal limits 6. Suicidal ideation (within the past 6-months) 7. Body Mass Index (BMI) > 40 8. Unadjudicated charges that may result in transfer to another facility and/or additional prison time.	• treatment adherence • XR-NTX+ MMTx vs. XR-NTX-OTx following release from prison • Any illicit opioid used • re-arrest [Time Frame: 12-months following release from prison] • re-incarceration [Time Frame: 12-months following release from prison] • criminal activity [Time Frame: 1,2,3,4,5,6,7 and 12-months following release from prison] • Injection drug use and HIV sexual risk factor [Time Frame: 6 and 12-months following release from prison]	August 2020

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Long Acting Naltrexone for Opioid Addiction: Focus on Sustained Abstinence and Recovery (NaltRec) Lars Tanum, MD NCT03647774	Phase IV, non-randomized, parallel assignment, open-label Enrollment: 300	Experimental: Extended release naltrexone • 380 mg every 4 weeks No Intervention: Treatment As Usual (TAU) • Daily sublingual buprenorphine in flexible dose	Inclusion: 1. 18-65 years old 2. Meets criteria for DSM-5 opioid use disorder 3. Completing a stay in a controlled environment with restricted access to substances of abuse with a minimum duration of seven days Exclusion: 1. Severe psychiatric disorder 2. Alcoholism defined by the criteria in DSM-5	• Perceived change in recovery through week 52 • Perceived change in quality of life through week 52	August 2023

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix D. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. Two reviewers independently screened the abstracts and full-texts of studies identified through electronic searches according to the inclusion and exclusion criteria described earlier using DistillerSR (Evidence Partners, Ottawa, Canada), with any incongruencies resolved through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. Each full-text was independently reviewed by two reviewers and conflicts resolved by a third reviewer. Reasons for exclusion were categorized according to the PICOTS elements during full-text review.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table D3).[74]Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

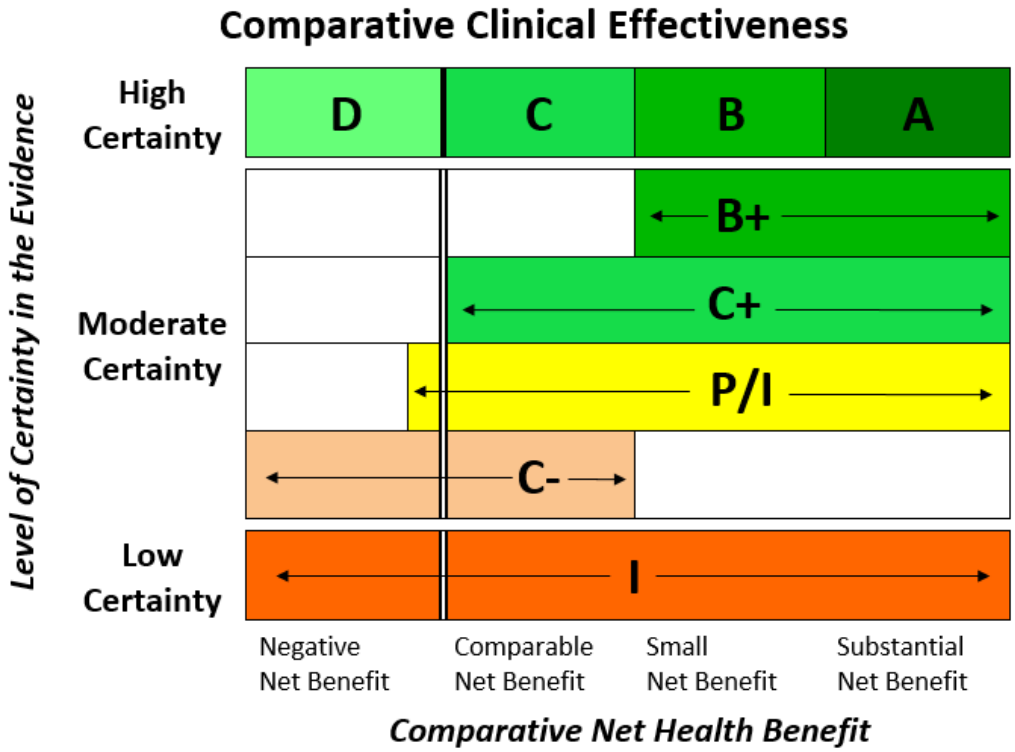
Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[75]

Figure D1. ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D = "Negative"- High certainty of an inferior net health benefit
B+ = "Incremental or Better" - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

Table D1. Key Baseline Characteristics of Included Studies

Study	Arm	N	Mean (SD) Age	Male, %	White, %	Employed, %	Recent Opioid Use, %	Heroin as Primary Opioid, %	Prescription Drugs as Primary Opioid, %	IV Drug Use, %	Mean (SD) Age at First Opioid Use	Mean (SD) Years of Opioid Use/OUD Diagnosis
CAM 2038												
Lofwall 2018[76]	CAM2038	213	38.7 (11.2)	56.8	74.6	35.7	NR	71.4	28.6	53.5	NR	4.3 (7.8) since diagnosis
	SL bup/nal	215	38.0 (10.9)	66.0	76.3	33.5	NR	70.2	29.8	51.2	NR	4.7 (6.0) since diagnosis
CPDD Injection Poster[152]	CAM2038	114	37.3 (11.6)	54.4	78.9	29.8	31.6 tested positive for fentanyl	85.1	NR	100	NR	3.06 (5.29) since diagnosis
	SL bup/nal	110	37.2 (11.5)	66.4	82.7	25.5	21.8 tested positive for fentanyl	86.4	NR	100	NR	2.76 (3.54) since diagnosis
CPDD Heroin Poster[153]	CAM2038	152	38.9 (11.2)	56.6	66.4	27.6	35.5 tested positive for fentanyl	100	0	63.8	NR	4.03 (8.74) since diagnosis
	SL bup/nal	151	38.9 (11.4)	69.5	69.5	27.2	25.8 tested positive for fentanyl	100	0	62.9	NR	3.19 (4.67) since diagnosis
Sublocade												
Trial 13-0001[77]	Sublocade 300mg/100mg	203	21.7% (18-29), 43.3% (30-44), 31.5% (45-59), 3.4% (60+)	67.0	69.0	NR	NR	NR	NR	NR	NR	NR
	Sublocade 300mg/300mg	201	22.4% (18-29), 47.3% (30-44), 26.4% (45-59), 4.0% (60+)	67.2	71.6	NR	NR	NR	NR	NR	NR	NR

Study	Arm	N	Mean (SD) Age	Male, %	White, %	Employed, %	Recent Opioid Use, %	Heroin as Primary Opioid, %	Prescription Drugs as Primary Opioid, %	IV Drug Use, %	Mean (SD) Age at First Opioid Use	Mean (SD) Years of Opioid Use/OUD Diagnosis
	Placebo	100	23.0% (18-29), 45.0% (30-44), 30.0% (45-59), 2.0% (60+)	65.0	78.0	NR	NR	NR	NR	NR	NR	NR
Trial 13-0003[78] (Study following 13-0001)	De Novo	412	38.4 (12.10)	63.8	71.6	NR	NR	NR	NR	NR	NR	NR
	Roll-Over	257	41.6 (11.07)	65.8	64.9	NR	NR	NR	NR	NR	NR	NR
Probuphine												
Rosenthal 2016[79]	Probuphine	87	38 (11.2)	59.8	94.3	78.1	NR	17.2	75.9	NR	NR	6.2 (5.93) since diagnosis
	SL bup/nal	89	39 (10.8)	58.4	95.5	72.0	NR	24.7	73.0	NR	NR	6.2 (6.95) since diagnosis
Rosenthal 2013[81]	Probuphine	114	36.4 (11.0)	63.2	83.3	NR	NR	66.7	33.3	NR	NR	NR
	Placebo implants	54	35.2 (10.3)	57.4	83.3	NR	NR	51.9	48.1	NR	NR	NR
	SL bup/nal	119	35.3 (10.9)	60.5	81.5	NR	NR	63.0	36.1	NR	NR	NR
Ling 2010[80]	Probuphine	108	35.8 (11.0)	66.7	75.9	NR	NR	63.9	36.1	NR	NR	NR
	Placebo implants	55	39.3 (11.7)	72.7	72.7	NR	NR	61.8	38.2	NR	NR	NR
Vivitrol												
	Vivitrol	283	34 (9.5)	69.0	73.0	17.0	NR	81.0	15.0	63.0	21.2 (6.5) opioid use	12.8 (9.0) opioid use

Study	Arm	N	Mean (SD) Age	Male, %	White, %	Employed, %	Recent Opioid Use, %	Heroin as Primary Opioid, %	Prescription Drugs as Primary Opioid, %	IV Drug Use, %	Mean (SD) Age at First Opioid Use	Mean (SD) Years of Opioid Use/OUD Diagnosis
Lee 2018[83] (X-BOT)	SL bup/nal	287	33.7 (9.8)	72.0	75.0	20.0	NR	81.0	16.0	64.0	21.4 (7.6) opioid use	12.2 (9.0) opioid use
Tanum 2017[84]	Vivitrol	80	36.4 (8.8)	76.3	90.0	NR	prior 30 days: 7.6 days using heroin; 8.2 days using other opioids	NR	NR	90.0	NR	8.9 (7.8) heavy opioid use; 6.9 (5.8) heroin use
	SL bup/nal	79	35.7 (8.5)	68.4	88.6	NR	prior 30 days: 12.0 days using heroin; 14.5 days using other opioids	NR	NR	81.0	NR	9.6 (10.5) heavy opioid use; 6.7 (5.2) heroin use
Solli 2018[89] (Tanum 2017 OLE)	Continuing Vivitrol	54	36.2 (95% CI: 33.9, 38.4)	81.5	NR	NR	NR	63.2	NR	NR	22.5 (95%CI 21.1, 24.0) heroin use	6.7 (95%CI 5.5, 7.8) heroin use
	Inducted on Vivitrol	63	35.1 (95% CI 32.9, 37.2)	71.4	NR	NR	NR		NR	NR	21.4 (95%CI 19.5, 23.4) heroin use	6.7 (95%CI 5.2, 8.1) heroin use
Lee 2016[92]	Vivitrol	153	44.4 (9.2)	84.3	20.4	17.0	prior 30 days: 30.9 any opioids	NR	NR	42.1 during lifetime	NR	NR
	Treatment as usual	155	43.2 (9.4)	85.2	19.4	18.7	prior 30 days: 38.1 any opioids	NR	NR	40.0 during lifetime	NR	NR

Study	Arm	N	Mean (SD) Age	Male, %	White, %	Employed, %	Recent Opioid Use, %	Heroin as Primary Opioid, %	Prescription Drugs as Primary Opioid, %	IV Drug Use, %	Mean (SD) Age at First Opioid Use	Mean (SD) Years of Opioid Use/OUD Diagnosis
Lee 2015[91]	Vivitrol	16	40 [range 26-52]	100	NR	31.0	7-days pre-arrest: 13.0 prescription drug; 94.0 heroin	NR	NR	44.0 during lifetime	NR	NR
	Treatment as usual	17	47 [range 39-58]	100	NR	12.0	7-days pre-arrest: 18.0 prescription drug; 100.0 heroin	NR	NR	24.0 during lifetime	NR	NR
Krupitsky 2011[86]	Vivitrol	126	29.4 (4.8)	90.0	98.0	NR	prior 30 days: 88.0 heroin; 12.0 methadone; 13.0 other opioids	NR	NR	NR	NR	9.1 (4.5) since dependence
	Placebo	124	29.7 (3.6)	86.0	100	NR		NR	NR	NR	NR	10.0 (3.9) since dependence
Krupitsky 2013[90] (Krupitsky 2011 OLE)	Continuing Vivitrol	67	29.5 (5.0)	92.5	100	NR	prior 30 days: 89.5 heroin; 8.8 methadone; 9.8 other opioids	NR	NR	NR	NR	9.0 (4.2) since dependence
	Inducted on Vivitrol	47	29.4 (3.8)	85.1	100	NR		NR	NR	NR	NR	9.4 (4.0) since dependence
NEW HOPE[88]	Vivitrol	66	46.6 (8.3)	83.3	NR	NR	NR	NR	NR	NR	NR	20.1 (11.2) heroin use; 2.8 (7.2) other opioid use
	Placebo	27	43.9 (7.8)	77.8	NR	NR	NR	NR	NR	NR	NR	18.4 (10.2) heroin use;

Study	Arm	N	Mean (SD) Age	Male, %	White, %	Employed, %	Recent Opioid Use, %	Heroin as Primary Opioid, %	Prescription Drugs as Primary Opioid, %	IV Drug Use, %	Mean (SD) Age at First Opioid Use	Mean (SD) Years of Opioid Use/OUD Diagnosis
												3.2 (5.4) other opioid use
Observational												
Shah 2018[95]	Naltrexone	1041	29.9 (10.93)	69.0	NR	NR	NR	NR	NR	NR	NR	NR
	Nonpharmaco-logical therapy	6883	33.2 (13.43)	38.9	NR	NR	NR	NR	NR	NR	NR	NR

95% CI: 95% confidence interval; bup/nal: buprenorphine/naloxone; mg: milligram; N: number of participants; NR: not reported; OLE: open-label extension; OUD: opioid use disorder; SD: standard deviation; SL: sublingual

Table D2. Study Designs of Included Studies

Study/ NCT/ Phase	Centers	Location of Sites	Funding	Detox Period (Days)	Induction Period	Intervention Period (Weeks)	Total Follow-Up (Weeks)	Inclusion Criteria	Exclusion Criteria
CAM 2038									
Lofwall 2018[76] NCT02651584 Phase III	Multicenter	US	Industry (Braeburn)	0	1 day of 4 mg bup/1 mg nal	24	28	DSM-5 criteria for moderate or severe OUD	Pharmacotherapy for OUD within 60 days; AIDS; chronic pain requiring opioid therapy
Sublocade									
Trial 13-0001[77] NCT02357901 Phase III Unpublished	Multicenter	US	Industry (Indivior)	0	Open-label run-in induction phase with SL bup/nal for 3 days followed by a 4- to 11-day SL bup/nal open-label run-in dose-adjustment period	24	24	DSM-5 criteria for moderate or severe OUD for 3 months	Condition requiring chronic opioid treatment; substance use disorder (DSM-5) with regard to any substances other than opioids, cocaine, cannabis, tobacco, or alcohol; received MAT for OUD in prior 90 days

Study/ NCT/ Phase	Centers	Location of Sites	Funding	Detox Period (Days)	Induction Period	Intervention Period (Weeks)	Total Follow-Up (Weeks)	Inclusion Criteria	Exclusion Criteria
Trial 13-0003[78] NCT02510014 Phase III Unpublished (Study following 13-0001)	Multicenter	US	Industry (Indivior)	0	Open-label run-in induction phase with SL bup/nal for 3 days followed by a 4- to 11-day SL bup/nal open-label run-in dose-adjustment period	De Novo: 49 weeks Roll-Over: 25 weeks	NR	De novo subjects: DSM-5 criteria for moderate or severe OUD for 3 months Roll-over subjects: Completed trial 13-0001	De novo subjects: Condition requiring chronic opioid treatment; substance use disorder (DSM-5) with regard to any substances other than opioids, cocaine, cannabis, tobacco, or alcohol; received MAT for OUD in prior 90 days Roll over subjects: Major protocol deviations or adverse events in trial 13-0001
Probuphine									
Rosenthal 2016 NCT02180659 Phase III	Multicenter	US	Industry (Braeburn)	0	Stable dose of 8 mg/day or less of SL buprenorphine for at least 24 weeks	24	24	DSM-IV diagnosis of opioid dependence and no evidence of opioid withdrawal or illicit opioid-positive urine	Chronic pain requiring opioids; AIDS; primary diagnosis of substance dependence other than opioids or nicotine
Rosenthal 2013[81] NCT01114308 Phase III	Multicenter	US	Government (NIDA) and Industry (Titan)	0	Open-label induction phase with 12-16 mg/day of SL bup/nal for	24	24	DSM-IV diagnosis of current opioid dependence	AIDS; current dependence on psychoactive substances other than opioids or nicotine (DSM-IV); received

Study/ NCT/ Phase	Centers	Location of Sites	Funding	Detox Period (Days)	Induction Period	Intervention Period (Weeks)	Total Follow-Up (Weeks)	Inclusion Criteria	Exclusion Criteria
					three days within 10 days of screening				MAT for OUD in prior 90 days; current diagnosis of chronic pain that required opioid treatment
Ling 2010[80] NCT 00447564 Phase III	Multicenter	US	Industry (Titan)	0	Open-label induction phase with 12-16 mg/day of SL bup/nal for three days within 10 days of screening	24	24	DSM-IV diagnosis of current opioid dependence	AIDS; current dependence on psychoactive substances other than opioids or nicotine (DSM-IV); received MAT for OUD in prior 90 days; current diagnosis of chronic pain that required opioid treatment
Vivitrol									
Lee 2018[83] (X-BOT) NCT02032433 Phase IV	Multicenter	US	Government (NIDA)	Protocols and length of stay varied by site	Vivitrol arm: ≥3 days since last opioid use and pass naloxone challenge (≥0.4 mg) SL bup/nal arm: Varied	24	36	DSM-5 criteria for OUD; used opioids other than prescribed within 30 days prior to consent	Serious medical, psychiatric disorder, or other substance use disorder; chronic pain requiring opioids
Tanum 2017[84] NCT01717963 Phase III	Multicenter	Norway	Government (Research Council of Norway and the Western Norway Regional	≥7 days	Vivitrol arm: ≥3 days since last opioid use and pass naloxone challenge (2-4 mg) SL bup/nal arm:	12	48	DSM-IV criteria for opioid dependence	Other drug or alcohol dependence; serious somatic or psychiatric illness

Study/ NCT/ Phase	Centers	Location of Sites	Funding	Detox Period (Days)	Induction Period	Intervention Period (Weeks)	Total Follow-Up (Weeks)	Inclusion Criteria	Exclusion Criteria
			Health Authority)		Three to four-day dose titration to reach target dose				
Lee 2016[92] NCT00781898 Phase II/III	Multicenter	US	Government (NIDA)	NA (participants had to be opioid-free)	Vivitrol arm: Pass naloxone challenge (>0.8 mg)	24	78	DSM-IV criteria for opioid dependence; had been incarcerated; opioid-free status at randomization	Other drug or alcohol dependence requiring a high level of care; an untreated psychiatric disorder or medical condition; a current diagnosis of chronic pain requiring opioids; drug overdose in the previous 3 years requiring inpatient hospitalization
Lee 2015[91] NCT01180647 Phase III	Multicenter	US	Academic (NYU) and Industry (Alkermes provided study drug)	NA (partici-pants had to be opioid-free)	Vivitrol arm: Pass naloxone challenge (0.8 mg)	8	8	Opioid-dependent adults incarcerated in NYC DOC meeting DSM-IV criteria for opioid dependence prior to arrest; opioid-free at randomization	Chronic pain requiring opioids; serious, uncontrolled medical or psychiatric illnesses
Krupitsky 2011[86] NCT00678418 Phase III	Multicenter	Russia	Industry (Alkermes)	≤30 days (pre-study detox)	7 days	24	76	DSM-IV criteria for opioid dependence	AIDS-indicator disease; psychosis, bipolar disorder, major depressive disorder with suicidal ideation;

Study/ NCT/ Phase	Centers	Location of Sites	Funding	Detox Period (Days)	Induction Period	Intervention Period (Weeks)	Total Follow-Up (Weeks)	Inclusion Criteria	Exclusion Criteria
									present dependence on substances other than opioids or heroin
NEW HOPE[88] NCT01246401 Phase I/II Unpublished	Multicenter	US	Academic (Yale), Government (NIH), and Industry (Alkermes provided study drug)	If recent opioid use or anticipated withdrawal, five-day buprenor-phine withdrawal protocol was employed	If recent opioid use or anticipated withdrawal, three-five days	24	48	DSM-IV for opioid dependence; confirmed HIV infection; released from prison within ±30 days	Prescription of opioid pain medications or expressing a need for them; already enrolled in an opioid substitution therapy program; in opioid withdrawal (3-5 days since last opioid ingestion)
Observational									
Shah 2018[95] Observational	Multicenter	US	Industry (Alkermes)	NR	NR	12 months	24 months	Diagnosis of opioid dependence (ICD-9 CM) for 6 months	MAT for opioid dependence in one month prior excluded from the buprenorphine and nonpharmacological therapy cohorts

Bup/nal: buprenorphine/naloxone; DSM: Diagnostic and Statistical Manual of Mental Disorders; ICD-9 CM: International Classification of Diseases, Ninth Revision, Clinical Modification MAT: medication for addiction treatment; mg; milligram; NR: not reported; NYC DOC: New York City Department of Corrections; OUD: opioid use disorder; SL: sublingual

Table D3. Quality Ratings of Included Trials

Study	Comparable Groups	Non-Differential Follow-Up	Patient/Physician Blinding	Clear Definition of Interventions (Including Initiation)	Clear Definition of Outcomes	Primary Handling of Missing Urine Tests	USPSTF Rating
CAM 2038							
Lofwall 2018[76]	Yes	Yes	Yes	Yes	Yes	Considered positive	Good
Sublocade							
Trial 13-0001[77]	Yes	Yes	Yes	Yes	Yes	Considered positive	Good
Probuphine							
Rosenthal 2016[79]	Yes	Yes	Yes	Yes	Yes	Data were randomly imputed with 20% relative penalty against Probuphine	Good
Rosenthal 2013[81]	Yes	No	Yes	Yes	Yes	Considered positive	Fair
Ling 2010[80]	Yes	No	Yes	Yes	Yes	Considered positive	Fair
Vivitrol							
Lee 2018[83] (X-BOT)	Yes	Yes	No	Yes	Yes	Considered positive	Good
Tanum 2017[84]	Yes	Yes	No	Yes	Yes	Considered positive	Good
Lee 2016[92]	Yes	Yes	No	No	Yes	Considered positive	Fair
Lee 2015[91]	No	Yes	No	Yes	Yes	Considered positive	Fair
Krupitsky 2011[86]	Yes	No	Yes	Yes	Yes	Considered positive	Fair
NEW HOPE[88]	Yes	Yes	Yes	Yes	Yes	Considered positive	Good

USPSTF: United States Preventive Services Task Force

Table D4. Key Abstinence and Relapse Outcomes in Included Studies I

Study	Arm	N	Week	Relapse and Opioid Use			Opioid-Negative Urine Samples		
				Description	*Data*	*B/W Arm Comparison*	*Description*	*Data*	*B/W Arm Comparison*
CAM2038									
Lofwall 2018[76]	CAM2038	213	1-24	NR			mean (SE) % of negative urine samples	35.1 (2.5)	tx diff (95% CI) 6.7 (-0.1, 13.6) p(NI)<0.001 p(S) is NS
	SL bup/nal	215						28.4 (2.5)	
	CAM2038	213	1-12	NR				35.8 (2.6)	tx diff (95% CI) 5.9 (-1.3, 13.1) p is NS
	SL bup/nal	215						29.9 (2.6)	
	CAM2038	213	13-24	NR				33.9 (2.6)	tx diff (95% CI) 8.5 (1.2, 15.7) p=0.02
	SL bup/nal	215						25.4 (2.6)	
	CAM2038	213	4-24	NR			mean (SE) % of negative urine samples, CDF	35.1 (2.5)*	p=0.004
	SL bup/nal	215						26.7 (2.5)*	
CPDD Injection Poster[152]	CAM2038	114	4-24	NR			mean (SE) % of negative urine samples, CDF	30.9 (3.3)*	p<0.001
	SL bup/nal	110						15.4 (2.7)*	
CPDD Heroin Poster[153]	CAM2038	152	4-24	NR			mean % of negative urine samples, CDF	29.9*	p<0.001
	SL bup/nal	151						12.7*	
Sublocade									
Trial 13-0001[77]	Sublocade 300mg/100 mg	194	5-24	NR			# of participants with ≥90% negative urine samples, CDF	41*	vs. placebo: p<0.0001
	Sublocade 300mg/300 mg	196						48*	vs. placebo: p<0.0001
	Placebo	99						2*	—

Study	Arm	N	Week	Relapse and Opioid Use			Opioid-Negative Urine Samples		
				Description	*Data*	*B/W Arm Comparison*	*Description*	*Data*	*B/W Arm Comparison*
Trial 13-0003[78]	Roll-Over	257	25	NR			% of participants with ≥90% negative urine samples, CDF	28.8*	NR
	De Novo	412	49					15.0*	
Probuphine									
Rosenthal 2013[81]	Probuphine	114	1-24	NR			mean % of negative urine samples, CDF	31.2	vs. placebo: p<0.0001
	Placebo implant	54						13.4	—
	SL bup/nal	119						33.5	—
	Probuphine	114	1-16	NR				39.6	vs. placebo: p<0.0001 vs. SL bup/nal: p is NS
	Placebo implant	54						17.9	—
	SL bup/nal	119						37.8	—
	Probuphine	114	17-24	NR				28.9	vs. placebo: p<0.0001 vs. SL bup/nal p is NS
	Placebo implant	54						7.2	—
	SL bup/nal	119						29.6	—
Ling 2010[80]	Probuphine	108	1-24	NR			mean % of negative urine samples	36.6 (95% CI: 30.5, 42.6)	p=0.01
	Placebo implant	55						22.4 (95% CI: 15.3, 29.5)	

Study	Arm	N	Week	Relapse and Opioid Use			Opioid-Negative Urine Samples		
				Description	*Data*	*B/W Arm Comparison*	*Description*	*Data*	*B/W Arm Comparison*
	Probuphine	108	1-16	NR				40.4 (95% CI: 34.2, 46.7)	p=0.04
	Placebo implant	55						28.3 (95% CI: 20.3, 36.3)	
	Probuphine	108	17-24	NR				NR	p<0.001
	Placebo implant	55						NR	
Vivitrol									
Lee 2018[83] (X-BOT)	Vivitrol	283	3-24	(1): n (%) participants who relapsed† (2): median (IQR) relapse-free survival weeks	(1): 185 (65) (2): 8.4 (3.0, 23.4)	(1): OR (95%CI) 1.44 (1.02, 2.01), p=0.036; (2): HR (95%CI): 1.36 (1.10, 1.68), p=0.004	median (IQR) weekly-negative urine samples	4 (0-19)	p<0.0001
	SL bup/nal	287			(1): 163 (57) (2): 14.4 (5.1, 23.4)			10 (3-20)	
Tanum 2017[84]	Vivitrol	63	4	mean (SD) days using (1): heroin, (2): other illicit opioids, and (3): IV drugs during preceding 4	(1): 0.8 (1.5) (2): 1.2 (2.2) (3): 2.96 (1.32, 4.58)	tx diff (95%CI) (1): -3.0 (-4.9, -1.2), p=0.001 (2): -2.9 (-4.8, -0.9), p=0.004 (3): NR	NR		
	SL bup/nal	65			(1): 3.7 (7.4) (2): 4.2 (7.9)				

Study	Arm	N	Week	Relapse and Opioid Use			Opioid-Negative Urine Samples		
				Description	*Data*	*B/W Arm Comparison*	*Description*	*Data*	*B/W Arm Comparison*
				weeks (95% CI)	(3): 3.97 (1.90, 5.22)				
	Vivitrol	59	8		(1): 0.8 (1.9) (2): 1.8 (4.7) (3): 3.75 (2.13, 5.34)	tx diff (95%CI) (1): -3.3 (-5.1, -1.5), p<0.001 (2): -2.6 (-4.6, -0.7), p=0.007 (3): NR	NR		
	SL bup/nal	55			(1): 4.4 (9.1) (2): 4.0 (8.5) (3): 4.08 (2.38, 5.72)				
	Vivitrol	57	12		(1): 1.1 (2.3) (2): 2.0 (5.0) (3): 4.51 (2.46, 6.61)	tx diff (95%CI) (1): -3.6 (-6, -1.2), p=0.003 (2): -2.4 (-4.9, 0.1), p is NS (3): NR	NR		
	SL bup/nal	50			(1): 4.1 (8.4) (2): 4.4 (8.7) (3): 4.56 (2.33, 6.68)				
	Vivitrol	63	1-12	NR			mean (SD) group proportion of total # of negative samples	0.9 (0.3)	tx diff (95%CI) 0.1 (-0.04, 0.2), p<0.001
	SL bup/nal	65						0.8 (0.4)	

Study	Arm	N	Week	Relapse and Opioid Use			Opioid-Negative Urine Samples		
				Description	*Data*	*B/W Arm Comparison*	*Description*	*Data*	*B/W Arm Comparison*
Solli 2018[89] (Tanum 2017 OLE)	Continuing Vivitrol	28	36	mean (95%CI) days using (1): heroin, (2): other illicit opioids, and (3): IV drugs during preceding 4 weeks	(1): 0.1 (0.0, 0.2) (2): 0.2 (-0.1, 0.4) (3): 2.4 (-0.7, 5.5)	tx diff (95%CI) (1): 0.3 (-0.5, 1.0), p=NS (2): 0.7 (-0.1, 1.6), p=0.088 (3): 1.2 (-2.2, 4.6), p is NS	NR		
	Inducted on Vivitrol	30			(1): 0.8 (-0.3, 1.9) (2): 0.6 (0.0, 1.2) (3): 6.0 (2.2., 9.9)				
Lee 2016[92]	Vivitrol	153	24	(1): median weeks to relapse‡ (2): % of participants who relapsed‡ (3) % of participants reporting IV drug use	(1): 10.5 (2): 43.1 (3): 5.9	(1): HR (95% CI) 0.49 (0.36, 0.68), p<0.001 (2): OR (95% CI) 0.43 (0.28, 0.65), p<0.001 (3): OR (95% CI) 0.67 (0.25, 1.82), p is NS	% of negative samples	74.1	OR (95% CI) 2.30 (1.48, 3.54), p<0.001
	Treatment as usual	155			(1): 5.0 (2): 63.9 (3): 8.6			55.7	
Lee 2015[91]	Vivitrol	16	4	(1): % of participants who relapsed§ (2): % of participants	(1): 38 (2): 25	OR (95%CI) 0.08 (0.01, 0.48), p<0.004 (2): NR	% of negative samples	59	OR (95%CI) 3.5 (1.4, 8.5), p<0.009
	Treatment as usual	17			(1): 88 (2): 6			29	
	Vivitrol	16	8		(1): 50 (2): NR	OR (95%CI)		59	OR (95%CI)

Study	Arm	N	Week	Relapse and Opioid Use			Opioid-Negative Urine Samples		
				Description	*Data*	*B/W Arm Comparison*	*Description*	*Data*	*B/W Arm Comparison*
	Treatment as usual	17		reporting IV drug use	(1): 93 (2): NR	0.13 (0.02, 0.78), p<0.03		24	4.6 (2.1, 10), p<0.0001
Krupitsky 2011[86]	Vivitrol	126	24	% (95%CI) of participants relapsed to physiological dependence (positive naloxone test)	0.8 (0.0, 2.3)	tx diff (95%CI) 17.3 (2.3, 127.8), p<0.0001	NR		
	Placebo	124			13.7 (7.7, 19.8)				
Krupitsky 2013[90] (Krupitsky 2011 OLE)	Continuing Vivitrol	67	52	NR			mean (SD) % of negative monthly samples	73.7 (33.2)*	NR
	Inducted on Vivitrol	47						81.0 (28.6)*	
NEW HOPE[88]	Vivitrol	51	24	median [range] days to first relapse based on self-reported opioid use	137 [0 to 168]	p=0.03	NR		
	Placebo	23			29 [0 to 168]				

Study	Arm	N	Week	Relapse and Opioid Use			Opioid-Negative Urine Samples		
				Description	*Data*	*B/W Arm Comparison*	*Description*	*Data*	*B/W Arm Comparison*

*Urine test results confirmed with self-report;

†Relapse defined as the use of non-study opioids any time after 20-day randomization (at the start of four consecutive opioid use weeks or at the start of seven consecutive days of self-reported opioid use days). A use week was defined as any week where the participant reported at least one day of non-study opioids (buprenorphine, methadone, morphine, heroin, codeine, oxycodone) or did not provide a urine sample;

‡A relapse event was defined as 10 or more days of opioid use in a 28-day (four-week) period as assessed by self-report or by testing of urine samples obtained every two weeks; a positive or missing sample was computed as five days of opioid use;

§Relapse defined as ≥10 of 28 days of self-reported opioid misuse following jail release or two or three positive of the three urine samples during weeks two, three and four. A single positive or missing urine result counted as seven opioid misuse days.

95% CI: 95% confidence interval; bup/nal: buprenorphine/naloxone; b/w: between; CDF: cumulative distribution function; HR: hazard ratio: IQR: interquartile range; IV: intravenous; mg: milligram: mo.: month(s); N: number of participants; NI: noninferiority; NR: not reported; NS: not significant; OR: odds ratio; SE: standard error; SD: standard deviation; tx diff: treatment difference

Table D5. Key Abstinence and Relapse Outcomes in Included Studies II

Study	Arm	N	Week	Responders, n (%)			Other Abstinence Outcomes		
				Description	*Data*	*B/W Arm Comparison*	*Description*	*Data*	*B/W Arm Comparison*
CAM2038									
Lofwall 2018[76]	CAM2038	213	1-24	no evidence of illicit opioid use at prespecified time points† assessed via urine tests	37 (17.4)*	tx diff (95%CI) 3.0 (-4.0, 9.9), p(NI)<0.001	NR		
	SL bup/nal	215			31 (14.4)*				
CPDD Injection Poster[152]	CAM2038	114	1-24	See Lofwall 2018[76] description	18 (15.8)*	tx diff (95%CI) 7.3 (0.2, 16.8) p=0.047	NR		
	SL bup/nal	110			NR				
CPDD Heroin Poster[153]	CAM2038	152	1-24	See Lofwall 2018[76] description	24 (15.8)*	tx diff (95%CI) 11.2 (4.5, 17.9) p<0.001	NR		
	SL bup/nal	151			7 (4.6)*				
Sublocade									
Trial 13-0001[77]	Sublocade 300mg/100mg	194	5-24	≥80% of negative urine samples	55 (28.4)*	vs. placebo: p<0.0001	mean (SE) # of weeks of abstinence assessed via urine tests	8.5 (0.68)*	vs. placebo: p<0.0001
	Sublocade 300mg/300mg	196			57 (29.1)*	vs. placebo: p<0.0001		8.5 (0.68)*	vs. placebo: p<0.0001
	Placebo	99			2 (2.0)*			1.0 (0.84)*	—
	Sublocade 300mg/300mg	194	24	NR			# of participants abstinent assessed via urine tests	71*	vs. placebo: p<0.0001
	Sublocade 300mg/300mg	196						87*	vs. placebo: p<0.0001
	Placebo	99						2*	—
Probuphine									

Study	Arm	N	Week	Responders, n (%)			Other Abstinence Outcomes		
				Description	*Data*	*B/W Arm Comparison*	*Description*	*Data*	*B/W Arm Comparison*
Rosenthal 2016[79]	Probuphine	84	24	≥4 of 6 mo. w/o evidence of illicit opioid use assessed via urine tests	81 (96.4)*	tx diff 8.8%; one-sided 97.5%CI (0.009, ∞); p(NI)<0.001 ; p(S)=0.03	% of participants abstinent over mo. 1-6 assessed via urine tests	85.7*	tx diff (95%CI) 13.8% (0.018, 0.258), p=0.027
	SL bup/nal	89			78 (87.6)*			71.9*	
Vivitrol									
Lee 2018[83] (X-BOT)	Vivitrol	283	3-24	NR			median (IQR) self-reported opioid-abstinent days	39 (1, 144)	p<0.0001
	SL bup/nal	287						81 (16, 144)	
Solli 2018[89] (Tanum 2017 OLE)	Continuing Vivitrol	54	36	NR			% of patients reporting abstinence	53.7	NR
	Inducted on Vivitrol	63						44.4	
Lee 2016[92]	Vivitrol	153	24	NR			% of 2-week intervals with no opioid use as assessed via urine test	71.1*	OR (95%CI) 2.50 (1.66, 3.76), p<0.001
	Treatment as usual	155						49.5*	
Lee 2015[91]	Vivitrol	16	4	NR			% of participants abstinent assessed via urine tests	50*	OR (95%CI) 7.5 (1.3, 44), p<0.03
	Treatment as usual	17						13*	
	Vivitrol	16	8	NR				50*	OR (95%CI) 16 (1.7, 151), p<0.007
	Treatment as usual	17						7*	

Study	Arm	N	Week	Responders, n (%)			Other Abstinence Outcomes		
				Description	*Data*	*B/W Arm Comparison*	*Description*	*Data*	*B/W Arm Comparison*
Krupitsky 2011[86]	Vivitrol	126	24	NR			(1): median % (95% CI) weeks with abstinence (2): % (95%CI) of patients abstinent assessed via urine test	(1): 90.0 (69.9, 92.4)* (2): 35.7 (27.4, 44.1)*	tx diff (95% CI) (1): 55.0 (15.9, 76.1), p=0.0002 (2): 1.58 (1.06, 2.36), p=0.02
	Placebo	124						(1): 35.0 (11.4, 63.8)* (2): 22.6 (15.2, 29.9)	
Krupitsky 2013[90] (Krupitsky 2011 OLE)	Continuing Vivitrol	67	52	NR			(1): % of patients abstinent assessed via urine test (2): mean (SD) % of reported opioid-free days	(1): 49.3* (2): 80.6 (29.7)	NR
	Inducted on Vivitrol	47						(1): 53.2* (2): 87.4 (23.8)	
NEW HOPE[88]	Vivitrol	66	24	NR			% of participants abstinent assessed via urine tests	19.7	NR
	Placebo	27						18.5	

*Urine test results confirmed with self-report;

†Phase 1 at week 12 and for at least 2 of 3 assessments at weeks 9 to 11 and in phase 2 for at least 5 of 6 assessments from weeks 12 to 24, including month 6 (i.e., weeks 21-24)

95% CI: 95% confidence interval; bup/nal: buprenorphine/naloxone; b/w: between; IQR: interquartile range; mg: milligram: mo.: month(s); N: number of participants; NI: non-inferiority; NR: not reported; NS: not significant; OR: odds ratio; S: superiority SE: standard error; SD: standard deviation; tx diff: treatment difference

Table D6. All-Cause Discontinuation and Treatment Retention in Included Studies

Study	Arm	N at Randomization	Discontinued, n (%)*	Number of Days/Weeks Retained
CAM2038				
Lofwall 2018[76]	CAM2038	215	89 (41)	NR
	SL bup/nal	213	92 (43)	NR
Sublocade				
Trial 13-0001[77]	Sublocade 300 mg/ 100 mg	203	78 (38)	NR
	Sublocade 300 mg/ 300 mg	201	72 (36)	NR
	Placebo	100	66 (66)	NR
Trial 13-0003[78]	De Novo	412	206 (50)	NR
	Roll Over	257	57 (22)	NR
Probuphine				
Rosenthal 2016[79]	Probuphine	87	6 (7)	NR
	SL bup/nal	90	5 (6)	NR
Rosenthal 2013[81]	Probuphine	114	41 (36)	NR
	Placebo implant	54	40 (74)	NR
	SL bup/nal	119	43 (36)	NR
Ling 2010[80]	Probuphine	108	37 (34)	NR
	Placebo Implant	55	38 (69)	NR
Vivitrol				
Lee 2018[83] (X-BOT)	Vivitrol	283	78 (28)	NR
	SL bup/nal	287	62 (22)	NR
Tanum 2017[84]	Vivitrol	80	24 (30)	69.3 days†
	SL bup/nal	79	30 (38)	63.7 days†

Study	Arm	N at Randomization	Discontinued, n (%)*	Number of Days/Weeks Retained
Solli 2018[89] (Tanum 2017 OLE)	Continuing XR-NTX	54	26 (48)	25.6 weeks†
	Inducted on XR-NTX	63	33 (52)	25.4 weeks†
Lee 2016[92]	Vivitrol	153	34 (22)	NR
	Treatment as usual	155	29 (19)	NR
Lee 2015[91]	Vivitrol	16	7 (41)	NR
	Treatment as usual	17	10 (59)	NR
Krupitsky 2011[86]	Vivitrol	126	59 (47)	>168 days‡
	Placebo	124	77 (62)	96 days‡
Krupitsky 2013[90] (Krupitsky 2011 OLE)	Continuing XR-NTX	67	28 (42)	NR
	Inducted on XR-NTX	47	15 (32)	NR
NEW HOPE[88]	Vivitrol	66	0	NR
	Placebo	27	0	NR

*Percentage of participants who discontinued was calculated from numbers reported in each trial;
†Mean;
‡Median
bup/nal: buprenorphine/naloxone; mg: milligram; n: number of participants; OLE: open-label extension; SL: sublingual

Table D7. Opioid Craving – VAS Scores*

Study	Duration of Follow-Up	Arm	N	Mean VAS Over Duration of Follow-Up	Mean VAS Change from Baseline	p-Value
CAM2038						
Lofwall 2018[76]	24 weeks	CAM2038	213	17.3 (SD: 25.5)†	NR	NR
		SL bup/nal	215	17.3 (SD: 25.5)†	NR	
Sublocade						
Trial 13-0001[77]	24 weeks	Sublocade 300mg/100mg	192¤	NR	2.1 (SE: 1.63)	vs. placebo: p=0.0003
		Sublocade 300mg/300mg	193¤	NR	-0.9 (SE:1.63)	vs. placebo: p<0.0001
		Placebo	96¤	NR	11.5 (SE: 2.48)	—
Probuphine						
Rosenthal 2016[79]	24 weeks	Probuphine	84	NR	-2.3 (SD: 11.15)‡; -2.7 (SD: 12.58)†	NS for both
		SL bup/nal	89	NR	-2.8 (SD: 19.57)‡; -1.9 (SD: 18.97)†	
Rosenthal 2013[81]	24 weeks	Probuphine	114	10.2	NR	vs. placebo: p<0.0001 vs. SL bup/nal: p=0.054
		Placebo Implant	54	21.8	NR	NR
		SL bup/nal	119	7.1	NR	
Ling 2010[80]	24 weeks	Probuphine	108	9.9 (95% CI: 7.8 to 12.0)	NR	p<0.001
		Placebo Implant	55	15.8 (95% CI: 12.7 to 18.9)	NR	
Vivitrol						
Tanum 2017[84]	12 weeks	Vivitrol	56	0.83 (95% CI: -0.81 to 2.43)§	NR	NR
		SL bup/nal	49	2.69 (95% CI: 1.77 to 3.60)§	NR	
Krupitsky 2011[86]	24 weeks	Vivitrol	126	NR	-10.1 (95% CI: -12.3 to -7.8)†	p<0.0001
		Placebo	124	NR	0.7 (95% CI: -3.1 to 4.4)†	
NEW HOPE[88]	24 weeks	Vivitrol	32¤	NR	VAS increase: 18.8% No change: 37.5% VAS decrease: 43.8%#	NR
		Placebo	15¤	NR	VAS increase: 20.0% No change: 46.7% VAS decrease: 33.3%#	

95% CI: 95% confidence interval; bup/nal: buprenorphine/naloxone, mg: milligram; NR: not reported; NS: not significant; SL: sublingual, VAS: visual analog scale

*Opioid craving measured on 100 mm scale, where 0=no craving and 100=strongest craving, unless otherwise noted;

†Mean VAS need-to-use score, where 0=no need and 100=strongest need;

‡Mean VAS desire-to-use score, where 0=no desire and 100=strongest desire;

§Craving for heroin, rated on a scale of 0=no craving to 10=very strong;

#Data reported are percentage of patients reporting opioid craving increases, decreases, or no changes compared to baseline, where 0=no craving and 10=strongest craving;

¤Number of participants analyzed for outcome.

Table D8. Opioid Withdrawal – Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS)

Study	Duration of Follow-Up	Arm	N	Mean Change in COWS Score	p-Value	Mean Change in SOWS Score	p-Value
CAM2038							
Lofwall 2018[76]	24 weeks	CAM2038	213	3.3 (SD: 3.5)†	NR	NR	NR
		SL bup/nal	215	2.7 (SD: 4.0)†		NR	
Sublocade							
Trial 13-0001[77]	24 weeks	Sublocade 300mg/100mg	191/ 192*	-0.5 (SE: 0.22)	vs. placebo NS	-0.9 (SE: 0.51)	vs. placebo NS
		Sublocade 300mg/300mg	192/ 193*	-1.1 (SE: 0.21)	vs. placebo: p=0.01	-2.0 (SE: 0.51)	vs. placebo: p=0.0028
		Placebo	96/ 96*	-0.1 (SE: 0.35)	—	0.7 (SE: 0.8)	—
Probuphine							
Rosenthal 2016[79]	24 weeks	Probuphine	84	-0.1 (SD: 1.51)	NS	-0.6 (SD: 4.63)	NS
		SL bup/nal	89	-0.1 (SD: 1.69)		0.1 (SD: 5.26)	
Rosenthal 2013[81]	24 weeks	Probuphine	114	2.49 (NR)†	vs. placebo p<0.0001 vs. bup/nal p=0.0005	5.3 (NR)†	vs. placebo p<0.0001 vs. bup/nal p=0.0006
		Placebo implant	54	4.52 (NR)†	NR	8.42 (NR)†	NR
		SL bup/nal	119	1.71 (NR)†		2.83 (NR)†	
Ling 2010[80]	24 weeks	Probuphine	108	2.3 (95% CI: 1.9 to 2.7)†	p<0.001	4.1 (95% CI: 3.1 to 5.1)†	p=0.004
		Placebo implant	55	3.4 (95% CI: 2.8 to 4.0)†		6.5 (95% CI: 5.1 to 7.9)†	

95% CI: 95% confidence interval; bup/nal: buprenorphine/naloxone, COWS: clinical opiate withdrawal scale, mg: milligram, N: number of participants, NR: not reported, NS: not significant SD: standard deviation, SE: standard error; SL: sublingual, SOWS: subjective opioid withdrawal scale

*Number of p analyzed for COWS and SOWS, respectively; †Mean score, not change

Table D9. Serious Adverse Events and Adverse Events Leading to Discontinuation in Included Studies

Study	Arm	Serious Adverse Event, n (%)	Discontinuation Due to Adverse Event, n (%)	At Least One Opioid Overdose Event, n (%)	Fatal Overdoses, n (%)	Death, n (%)
CAM2038						
Lofwall 2018[76]	CAM2038	5 (2.3)	7 (3.3)	0	0	1 (0.5)
	SL bup/nal	13 (6.0)	3 (1.4)	5 (2.3)	0	0
CPDD Injection Poster[152]	CAM2038	2 (1.8)	NR	0	0	NR
	SL bup/nal	16 (14.5)	NR	5 (4.5)	0	0
Sublocade						
Trial 13-0001[77]	Sublocade 300mg/100mg	4 (2.0)	7 (3.4)	0	0	0
	Sublocade 300mg/300mg	7 (3.5)	10 (5.0)	0	NR	1 (0.5)
	Placebo	5 (5.0)	2 (2.0)	1 (1.0)*	0	0
Trial 13-0003[78,154]	Roll-over	9 (3.5)	5 (2.0)	0	0	0
	De Novo	16 (3.9)	12 (3.0)	2 (0.5)*	0	0
Probuphine						
Rosenthal 2016[79]	Probuphine	2 (2.3)	1 (1.1)	NR	NR	NR
	SL bup/nal	3 (3.4)	0	NR	NR	NR
Rosenthal 2013[81]	Probuphine	6 (5.3)	0	NR	0	0
	Placebo implant	3 (5.6)	0	NR	0	0
	SL bup/nal	7 (5.9)	1 (0.8)	at least 1 (0.8)	1 (0.8)	1 (0.8)
Ling 2010[80]	Probuphine	2 (1.9)	4 (3.7)	NR	NR	NR
	Placebo implant	4 (7.3)	0	NR	NR	NR
Vivitrol						
Lee 2018[83] X-BOT	Vivitrol	29 (14.0)	6 (2.1)	15 (5.3)	2 (0.7)	3 (1.1)
	SL bup/nal	29 (11.0)	8 (2.8)	8 (2.8)	3 (1.0)	4 (1.4)
Tanum 2017[84]	Vivitrol	6 (8.5)	4 (5.6)	0	0	0
	SL bup/nal	3 (4.2)	6 (8.3)	1 (1.4)	0	0
Solli 2018[89] (Tanum 2017 OLE)	Continuing Vivitrol	1 (1.9)	4 (7.4)	0	0	0
	Inducted on Vivitrol	4 (6.4)	3 (4.8)	0	0	1 (1.6)

Study	Arm	Serious Adverse Event, n (%)	Discontinuation Due to Adverse Event, n (%)	At Least One Opioid Overdose Event, n (%)	Fatal Overdoses, n (%)	Death, n (%)
Lee 2016[92]	Vivitrol	16 (10.5)	5 (3.3)	0	0	0
	Treatment as usual	45 (29.0)	NA	5 (3.2)	2 (1.3)	2 (1.3)
Lee 2015[91]	Vivitrol	0	NR	0	0	0
	Treatment as usual	0	NR	0	0	0
Krupitsky 2011[86]	Vivitrol	3 (2)	2 (2)	0	0	0
	Placebo	4 (3)	2 (2)	0	0	0
Krupitsky 2013[90] (Krupitsky 2011 OLE)	Continuing Vivitrol	3 (4.5)	0	0	0	0
	Inducted on Vivitrol	0	1 (2.1)	0	0	0
NEW HOPE[88]	Vivitrol	0	0	0	0	0
	Placebo	0	0	0	0	0

*Trial reports accidental overdoses only

bup/nal: buprenorphine/naloxone; mg: milligram; n: number of participants; OLE: open-label extension; SL: sublingual

Table D10. Adverse Events≥5% in Included Studies

Study	Arm	Injection/ Implant Site Reaction, %	Gastrointestinal Upset, %	Headache, %	Psychiatric Issues, %	Nervous System Disorders, %	Fatigue/ Insomnia, %	Infections and Infestations, %
CAM2038								
Lofwall 2018[76]	CAM2038	6.1 (pruritus); 5.6 (erythema); 8.9 (pain)	7.5 (constipation); 7.0 (nausea)	7.5			5.6 (insomnia)	
	SL bup/nal	6.0 (pruritus); 5.6 (erythema); 7.9 (pain)	7.4 (constipation); 7.9 (nausea)	7.9			2.8 (insomnia)	
CPDD Heroin Poster[153]	CAM2038	5.9 (severe reaction); 5.9 (pain)	6.6 (constipation); 5.9 (nausea)	6.6				5.3 (upper respiratory tract)
	SL bup/nal	2.0 (severe reaction); 5.3 (pain)	4.0 (constipation); 2.6 (nausea)	2.0				3.3 (upper respiratory tract)
Sublocade								
Trial 13-0001[77]	Sublocade 300mg/100mg	6.4 (pruritus); 4.9 (pain)	9.4 (constipation); 8.9 (nausea); 9.4 (vomiting)	9.4			3.9 (fatigue); 6.4 (insomnia)	5.4 (nasopharyngitis); 7.4 (upper respiratory tract)
	Sublocade 300mg/300mg	9.5 (pruritus); 6.0 (pain)	8.0 (constipation); 8.0 (nausea); 5.5 (vomiting)	8.5			6.0 (fatigue); 8.5 (insomnia)	5.0 (nasopharyngitis); 6.0 (upper respiratory tract)
	Placebo	4.0 (pruritus); 3.0 (pain)	0 constipation); 5.0 (nausea); 4.0 (vomiting)	6.0			3.0 (fatigue); 11 (insomnia)	1.0 (nasopharyngitis); 1.0 (upper respiratory tract)

Study	Arm	Injection/ Implant Site Reaction, %	Gastrointestinal Upset, %	Headache, %	Psychiatric Issues, %	Nervous System Disorders, %	Fatigue/ Insomnia, %	Infections and Infestations, %
Trial 13-0003[78]	Roll-over	2.7 (pain); 2.0 (erythema)	3.5 (constipation); 3.9 (nausea)	2.0			3.9 (insomnia)	2.3 (nasopharyngitis)
	De Novo	9.5 (pain); 5.3 (erythema)	11.4 (constipation); 9.0 (nausea)	7.5			6.6 (insomnia)	5.8 (nasopharyngitis)
Probuphine								
Rosenthal 2016[79]	Probuphine	13.8 (any)	8.0 (any)	6.9	6.9 (depression)	9.2		8.0 (nasopharyngitis)
	SL bup/nal	7.9 (any)	1.1 (any)	3.4	2.2 (depression)	3.4		4.5 (nasopharyngitis)
Rosenthal 2013[81]	Probuphine	27.2 (any); 7.0 (hematomas); 5.3 (pain)	6.1 (nausea); 6.1 (vomiting)	13.2	8.8 (depression); 1.8 (anxiety)		7.9 (insomnia)	5.3 (nasopharyngitis); 8.8 (upper respiratory tract)
	Placebo implant	25.9 (any); 11.1 (hematomas); 9.3 (pain)	1.9 (nausea); 1.9 (vomiting)	9.3	5.6 (depression); 5.6 (anxiety)		14.8 (insomnia)	5.6 (nasopharyngitis); 7.4 (upper respiratory tract)

Study	Arm	Injection/ Implant Site Reaction, %	Gastrointestinal Upset, %	Headache, %	Psychiatric Issues, %	Nervous System Disorders, %	Fatigue/ Insomnia, %	Infections and Infestations, %
	SL bup/nal	NA	6.7 (nausea); 4.2 (vomiting)	16.0	3.4 (depression); 5.9 (anxiety)		13.4 (insomnia)	10.1 (nasopharyngitis); 9.2 (upper respiratory tract)
Beebe 2012[82] (Study 2 of Rosenthal 2013[81])	Continuing Probuphine	14.0 (any)		11.8				8.2 (upper respiratory tract)
	Placebo implant→ Probuphine	12.5 (any)						
	SL bup/nal→ Probuphine	15.0 (any)						
Ling 2010[80]	Probuphine	56.5 (any); 25.0 (erythema); 13.0 (edema); 25.0 (itching); 22.2 (pain); 12.0 (bleeding)	13.9 (constipation); 5.6 (diarrhea); 13.9 (nausea)	25.0	10.2 (anxiety)		21.3 (insomnia)	13.9 (nasopharyngitis); 13.0 (upper respiratory tract)
	Placebo implant	52.7 (any); 21.8 (erythema); 9.1 (edema); 14.5 (itching); 10.9 (pain); 12.7 (bleeding)	5.5 (constipation); 12.7 (diarrhea); 12.7 (nausea)	18.2	9.1 (anxiety)		21.8 (insomnia)	5.5 (nasopharyngitis); 10.9 (upper respiratory tract)
Vivitrol								
Lee 2018[83] (X-BOT)	Vivitrol	16.3 (any)	12.0 (any)		10.6 (psychiatric disorder)			7.8 (any)

Study	Arm	Injection/ Implant Site Reaction, %	Gastrointestinal Upset, %	Headache, %	Psychiatric Issues, %	Nervous System Disorders, %	Fatigue/ Insomnia, %	Infections and Infestations, %
	SL bup/nal	NA	20.6 (any)		10.1 (psychiatric disorder)			9.4 (any)
Tanum 2017[84]	Vivitrol	5.6 (any)			16.9 (anxiety or depression)		11.3 (insomnia)	
	SL bup/nal	N/A			8.3 (anxiety or depression)		4.2 (insomnia)	
Solli 2018[89] (Tanum 2017 OLE)	Continuing Vivitrol	9.3 (any)		9.3	9.3 (psychological reactions)		3.7 (insomnia)	
	Inducted on Vivitrol	3.2 (any)		11.1	12.7 (psychological reactions)		9.5 (insomnia)	
Lee 2016[92]	Vivitrol	27.5 (mild reaction)	18.3 (any)	19			7.2 (insomnia)	9.8 (nasopharyngitis)
	Treatment as usual	NA	1.9 (any)	8.4			5.2 (insomnia)	11.0 (nasopharyngitis)
Krupitsky 2011[86]	Vivitrol	5.0 (pain)					6.0 (insomnia)	7.0 (nasopharyngitis)
	Placebo	1.0 (pain)					1.0 (insomnia)	2.0 (nasopharyngitis)
NEW HOPE[88]	Vivitrol	15.2 (immediate reaction)		7.6			9.1 (fatigue)	
	Placebo	7.4 (immediate reaction)		0			3.7 (fatigue)	

bup/nal: buprenorphine/naloxone; mg: milligram; n: number of participants; OLE: open-label extension; SL: sublingual

Appendix E. Comparative Value Supplemental Information

Table E1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from… Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	☐	☐	
Medical costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	X	X	
	Future related medical costs	☐	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-related costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	X	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al., 2016.[155]

hēRo3

hēRo3 compiles information and data that users enter into a browser describing the structure and estimated parameters of a model, sends it to the cloud-based platform where necessary calculations are performed in heRomod, and then parses information received from the modeling package to various output displays, including Markov traces, bar charts, area charts, tornado diagrams, waterfall charts, efficiency frontiers, and hexbin and contour plots, as well as tabular displays. hēRo3 effectively allows users to build and run models in the programming language, R, even if they have had limited or no experience programming in R. hēRo3 also generates an Excel workbook with every model that provides a detailed listing of all input variables, intermediate calculations, and final output on a cycle-by-cycle basis to facilitate model checking and auditing.

Table E2. Akaike-Information-Criterion (AIC) for Parametric Curve Functions Fit to Treatment Discontinuation/Relapse

	Parametric Curve Distributions				
	Exponential	Weibull	Log-Normal	Log-Logistic	Gamma
CAM2038[117]	876.7731	876.8574	871.4067*	890.3406	876.1517
Generic SL Buprenorphine/Naloxone[117]	867.3982	867.1221	871.8161	883.9106	866.8735*
Vivitrol[114]	652.9479	633.2282	630.9630*	651.0424	634.6471
Generic SL Buprenorphine/Naloxone[114]	891.1924	874.8861	867.0644*	900.6312	877.4627
Probuphine[116]	115.5127	115.5183	120.7789	131.0022	115.4177*
Generic Buprenorphine/Naloxone[116]	198.8468	198.9383	198.0326*	213.8443	199.2321

*Distribution chosen for the model

Table E3. Disutility Associated with HIV Infection

	Utility	Multiplier	Calculation
PWID [135]	0.90		
Symptomatic HIV[135]		0.81	
ART[135]		1.15	
PWID with Symptomatic HIV treated with ART	0.838		0.90*0.81*1.15
Disutility in PWID with Symptomatic HIV treated with ART	0.069		-(1-(0.838/0.90))

PWID: persons who inject drugs, HIV: human immunodeficiency virus, ART: anti-retroviral therapy

Table E4. Productivity Loss Calculations

Parameter	Original Value	Inflated/Deflated Value	Notes
Total Annual Workplace Productivity Cost[145]	$25,582,000,000	$23,995,751,389	Deflated from 2009 to 2007 to match SAMHSA number of persons abusing prescription opioids in 2007
Annual Number of Persons Abusing Prescription Opioids[146]	1,707,000		SAMHSA number of persons abusing prescription opioids in 2007
Annual Workplace Productivity Cost per Person	$14,058	$17,405	Inflated using OECD Hourly Earnings Index, 2007 Annual to 2018 Q1-Q2 Average[156]

Table E5. Criminal Justice and Incarceration Calculations

Parameter	Original Value	Notes
Per Day Cost when on OAT[147]	$35	Inflated using General CPI 2014 Annual Value to 2018 January -June Average Value.[157]
Per Day Cost Post-Treatment[147]	$175	

Inflated Value multiplied to Calculate Cost per Cycle

One-Way Sensitivity and Probabilistic Analyses Inputs for Treatment Discontinuation

Inputs for One-Way Sensitivity Analyses

When available, varied base case inputs by 95% CIs or published ranges.

- All drug costs were varied by ±25% and non-drug health care costs were varied by ±20% of the base case estimate.
- All utilities were varied by their 95% CIs or assumed/calculated ranges

Only estimates for which ranges were not presented in the main report are presented in the table below.

Table E6. One-Way Sensitivity Analyses Inputs

Estimate	Base Case Estimate	Range	Notes
PWID %	49.34%	39.47% to 59.21%	Assumption (±20%)
Incidence of HCV Infection	26.7%	0.017 to 0.517	Assumption (±25% Points)
Probability of Abstinence over a 24-week period – CAM2038	34.2%	29.3% to 39.1%	95% CI calculated using reported standard error (2.46%)
Probability of Abstinence over a 24-week period – Generic SL Buprenorphine/Naloxone	27.4%	22.5% to 32.3%	95% CI calculated using reported standard error (2.45%)
Proportion Permanently Abstained from Illicit Use of Opioids	10%	0% to 20%	Assumption (±10% Points)
Proportion of Discontinuation from Health States With And Without Illicit Use of Opioids While On MAT	46%	41.1% to 50.3%	Assumption (±10%)
Opioid Overdose-Related Mortality Rate (per 100,000 Illicit Users of Opioids)	13.3	2.4 to 43.4	Range based on lowest and highest US national rates
Physician's Office Visit Cost (CPT: 99211)	$21.96	$19.77 to $27.63	Range based on lowest and highest US national non-facility price
Cost of Probuphine Insertion (CPT:	$145.80	$129.09 to $179.43	Range based on lowest and highest US national non-facility price
Cost of Probuphine Removal (CPT:	$163.08	$144.99 to $202.43	Range based on lowest and highest US national non-facility price
Cost of SC/IM Injection Administration (CPT:	$20.88	$18.78 to $26.26	Range based on lowest and highest US national non-facility price

For all relapse/discontinuation parameters for all MATs and their respective comparators (except Sublocade and its comparator), 95% confidence interval estimates for the parametric curve functions were used in the one-way sensitivity analyses, and are presented in Tables E9 to E14.

Since discontinuation/relapse is a function of two parameters (mean & SD for lognormal distributions OR shape & scale for gamma distributions), we jointly varied the parameters in the "one-way" sensitivity analyses, taking into account their correlation.

Table E7. Time to Discontinuation Parameter Estimates for the Lognormal Model for CAM2038[117]

	Mean Estimate	95% CI Lower Bound	95% CI Upper Bound	Standard Error
Mean Log	3.5041796	3.1923378	3.8160215	0.15910590
SD Log	0.5862179	0.4347833	0.7376525	0.07726397

CI: confidence interval

Table E8. Time to Discontinuation Parameter Estimates for the Gamma Model for Generic SL Buprenorphine/Naloxone (versus CAM2038)[117]

	Mean Estimate	95% CI Lower Bound	95% CI Upper Bound	Standard Error
Shape	-0.1949288	-0.4402407	0.05038306	0.1251614
Scale	-4.1432573	-4.6410451	-3.64546956	0.2539780

CI: confidence interval

Table E9. Time to Discontinuation Parameter Estimates for the Lognormal Model for Vivitrol[114]

	Mean Estimate	95% CI Lower Bound	95% CI Upper Bound	Standard Error
Mean Log	3.0975681	2.7731938	3.4219424	0.16550014
SD Log	0.7018769	0.5193503	0.8844035	0.09312753

CI: confidence interval

Table E10. Time to Discontinuation Parameter Estimates for the Lognormal Model for Generic SL Buprenorphine/Naloxone (versus Vivitrol)[114]

	Mean Estimate	95% CI Lower Bound	95% CI Upper Bound	Standard Error
Mean Log	2.9434162	2.6977650	3.1890673	0.12533454
SD Log	0.5740773	0.4143103	0.7338443	0.08151526

CI: confidence interval

Table E11. Time to Discontinuation Parameter Estimates for the Gamma Model Probuphine[116]

	Mean Estimate	95% CI Lower Bound	95% CI Upper Bound	Standard Error
Shape	-0.4962139	-1.199059	0.2066317	0.3586013
Scale	-6.6180437	-9.290763	-3.9453238	1.3636576

CI: confidence interval

Table E12. Time to Discontinuation Parameter Estimates for the Lognormal Model for Generic SL Buprenorphine/Naloxone (versus Probuphine)[116]

	Mean Estimate	95% CI Lower Bound	95% CI Upper Bound	Standard Error
Mean Log	4.2138822	3.6446007	4.7831637	0.2904551
SD Log	0.6124004	0.3520751	0.8727258	0.1328215

CI: confidence interval

Inputs for Probabilistic Analyses

Triangular distributions were used for all cost parameters with the base case assumed as the "peak," and lower and upper bound of ranges assumed as the "lower" and "upper" bounds of the distribution.

Additional probabilistic analyses inputs are presented below.

Table E13. Probabilistic Analyses Inputs

Parameter	Distribution	Parameters
Utility in "MAT with NO Illicit Use of Opioids" Health State	Beta	α = 648.61 β = 198.14
Utility in "MAT with Illicit Use of Opioids" Health State Among Patients Illicitly Using Prescription Opioids	Beta	α = 502.49 β = 215.36
Utility in "MAT with Illicit Use of Opioids" Health State Among PWID	Beta	α = 420.08 β = 259.66
Utility in "OFF MAT with Illicit Use of Opioids" Health State Among Patients Illicitly Using Prescription Opioids	Beta	α = 503.81 β = 222.14
Utility in "OFF MAT with Illicit Use of Opioids" Health State Among PWID	Beta	α = 404.15 β = 299.94
Utility in "OFF MAT with NO Illicit Use of Opioids" Health State	Triangular	Peak = 0.852 Lower = 0.736 Upper = 0.901
Incidence of HCV Infection	Triangular	Peak = 26.7% Lower = 1.7% Upper = 51.7%
Opioid-Related Overdose Mortality Rate	Beta	α = 32.17 β = 58463.17
Proportion of PWID diagnosed with HCV with Spontaneous Clearance of HCV Infection	Beta	α = 74.80 β = 231.77
Probability of Abstinence over a 24-week period – CAM2038	Beta	α = 182.20 β = 3014.36
Probability of Abstinence over a 24-week period – Generic SL Buprenorphine/Naloxone	Beta	α = 119.32 β = 2493.47
Proportion of Discontinuation from Health States With And Without Illicit Use of Opioids While On MAT	Binomial	Prob = 45.71% Size = 70
Probability of Discontinuation of Sublocade over a 24-week period	Binomial	Prob = 35.8% Size = 196
HIV Disutility Multiplier	Triangular	Peak = 6.9% Lower = 1% Upper = 19.5%
Proportion Permanently Abstained from Illicit Use of Opioids	Triangular	Peak = 10% Lower = 0% Upper = 20%
HCV Disutility Multiplier - Post SVR	Beta	α = 3833.92 β = 3.84
HCV Disutility Multiplier - F0 to F3 Liver Disease	Beta	α = 47.47 β = 3.57
Odds Ratio – Discontinuation of Generic SL Buprenorphine/Naloxone vs. Sublocade	Lognormal	Mean = 0.67 SD Log = 0.45

For all relapse/discontinuation parameters for all MATs and their respective comparators, normal distributions were used for the relevant parametric curve functions in the probabilistic analyses, with distribution parameters being mean, standard deviation, and correlation presented in Tables E16 to E21.

Table E14. Covariance of Discontinuation Parameters for Lognormal Model for CAM2038[117]

	Mean Log	SD Log
Mean Log	0.025314689	0.005866107
SD Log	0.005866107	0.005969721

Correlation coefficient: 0.4771849; SD: standard deviation

Table E15. Covariance of Discontinuation Parameters for Gamma Model for Generic SL Buprenorphine/Naloxone (versus CAM2038)[117]

	Shape	Scale
Shape	0.01566538	0.02794661
Scale	0.02794661	0.06450484

Correlation coefficient: 0.8791488

Table E16. Covariance of Discontinuation Parameters for Lognormal Model for Vivitrol[114]

	Mean Log	SD Log
Mean Log	0.027390297	0.004508215
SD Log	0.004508215	0.008672736

Correlation coefficient: 0.2925016; SD: standard deviation

Table E17. Covariance of Discontinuation Parameters for Lognormal Model for Generic SL Buprenorphine/Naloxone (versus Vivitrol)[114]

	Mean Log	SD Log
Mean Log	0.015708746	0.003050788
SD Log	0.003050788	0.006644737

Correlation coefficient: 0.2986086; SD: standard deviation

Table E18. Covariance of Discontinuation Parameters for Gamma Model for Probuphine[116]

	Shape	Scale
Shape	0.1285949	0.4618465
Scale	0.4618465	1.8595621

Correlation coefficient: 0.9444533

Table E19. Covariance of Discontinuation Parameters for Lognormal Model for Generic SL Buprenorphine/Naloxone (versus Probuphine)[116]

	Mean Log	SD Log
Mean Log	0.08436416	0.02151929
SD Log	0.02151929	0.01764156

Correlation coefficient: 0.5578025; SD: standard deviation

One-Way Sensitivity Analyses

Figure E1. Tornado Diagram – Vivitrol versus Generic SL Buprenorphine/Naloxone

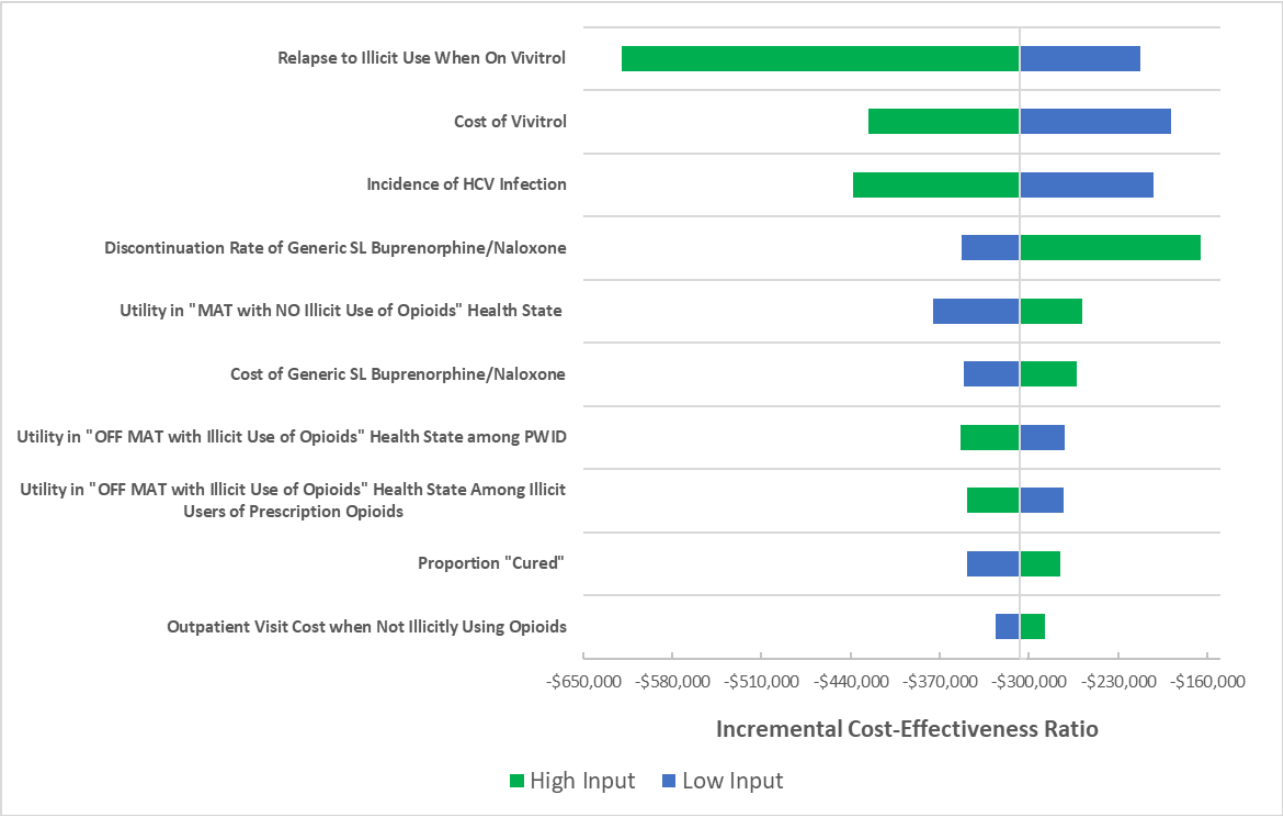
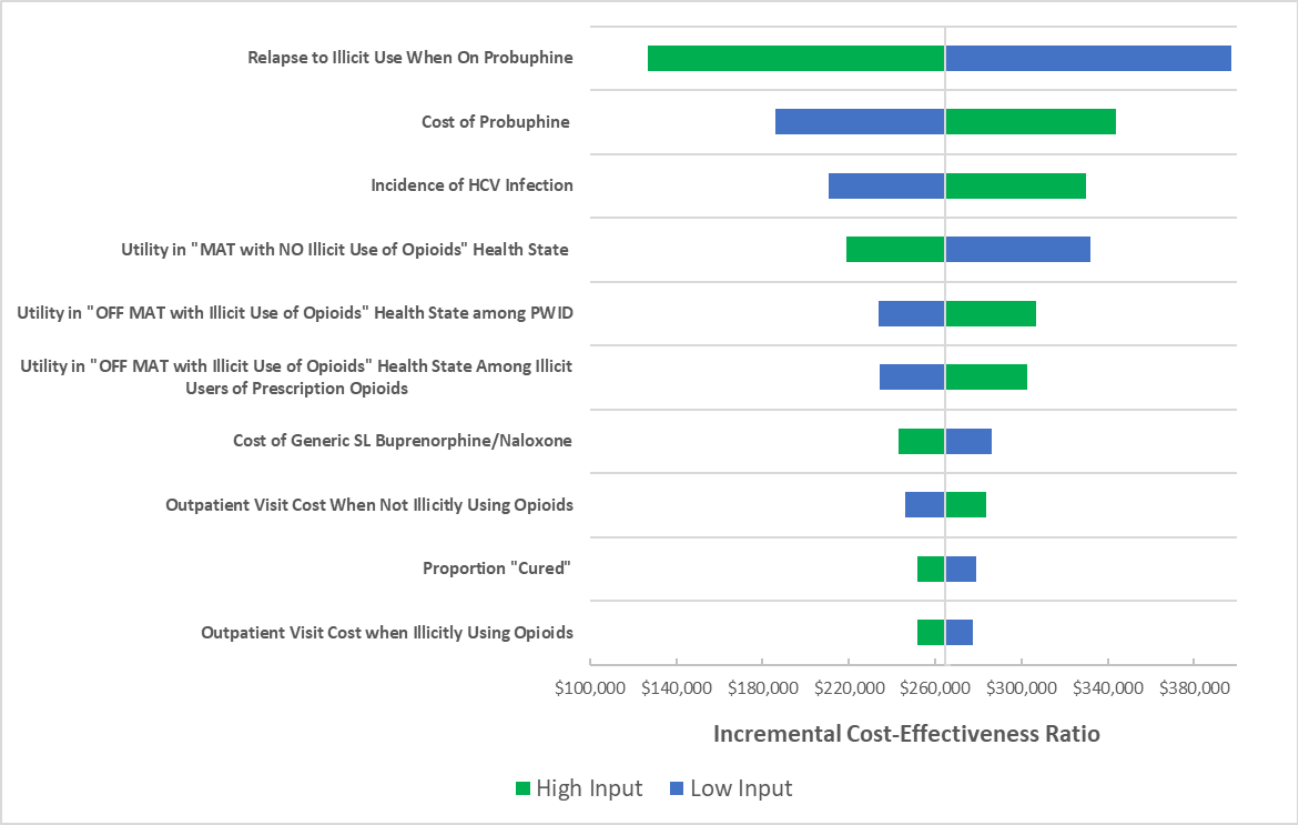


Figure E2. Tornado Diagram – Probuphine versus Generic SL Buprenorphine/Naloxone



Relapse to illicit use of opioids when on generic SL buprenorphine/naloxone was also a key driver of the results. However, that has not been included here since varying this estimate changed not only the costs and QALYs in the comparator arm, but also in the Probuphine arm since the comparator is the treatment choice in those abstinent from illicit use at the time of removal of Probuphine implant.

Probabilistic Analyses

Figure E3. Probabilistic Analyses: Vivitrol versus Generic SL Buprenorphine/Naloxone – Incremental Cost-Effectiveness Ratio HexBin

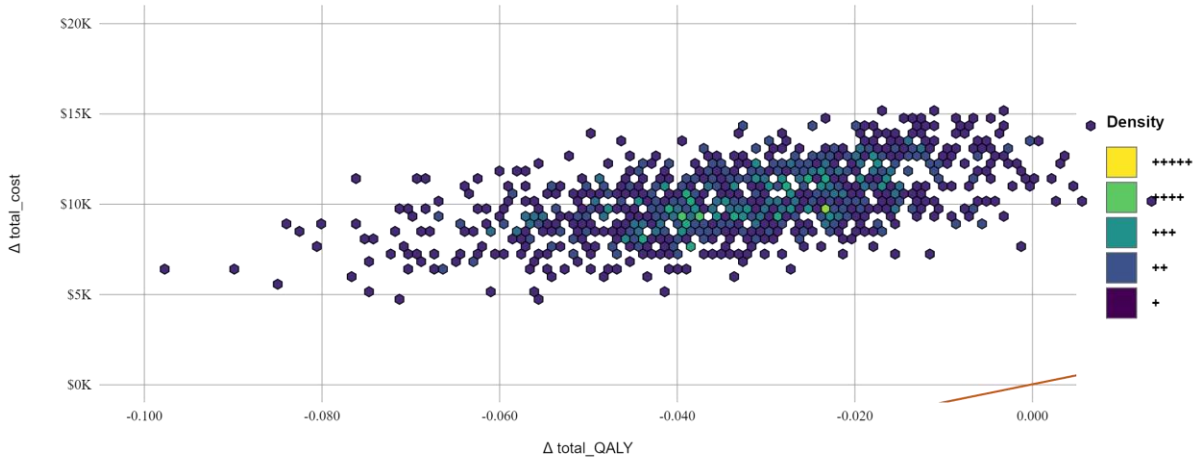


Figure E4. Probabilistic Analyses: Vivitrol versus Generic SL Buprenorphine/Naloxone – Incremental Cost-Effectiveness Ratio Acceptability Curve

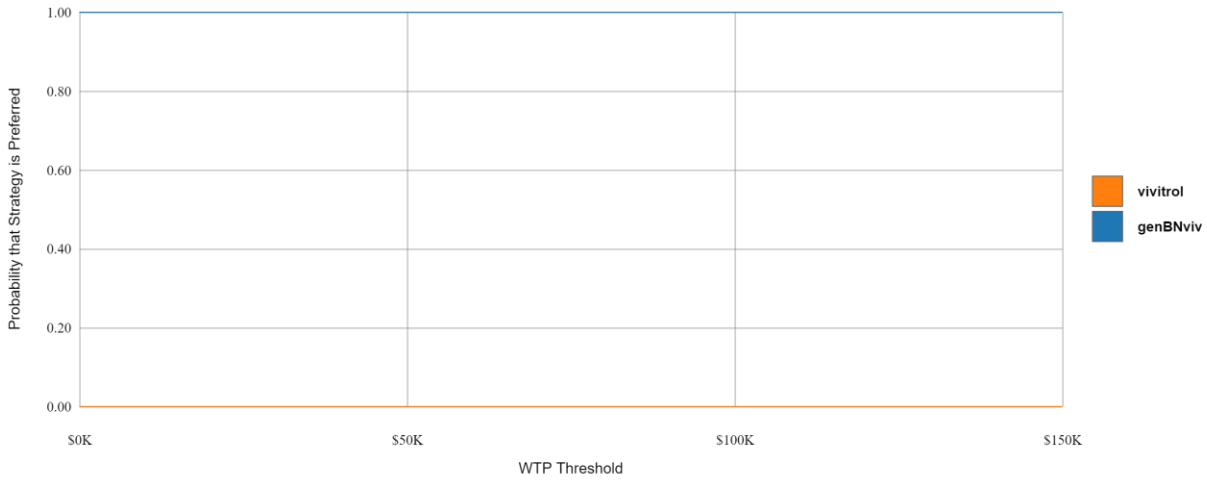


Figure E5. Probabilistic Analyses: Probuphine versus Generic SL Buprenorphine/Naloxone – Incremental Cost-Effectiveness Ratio HexBin

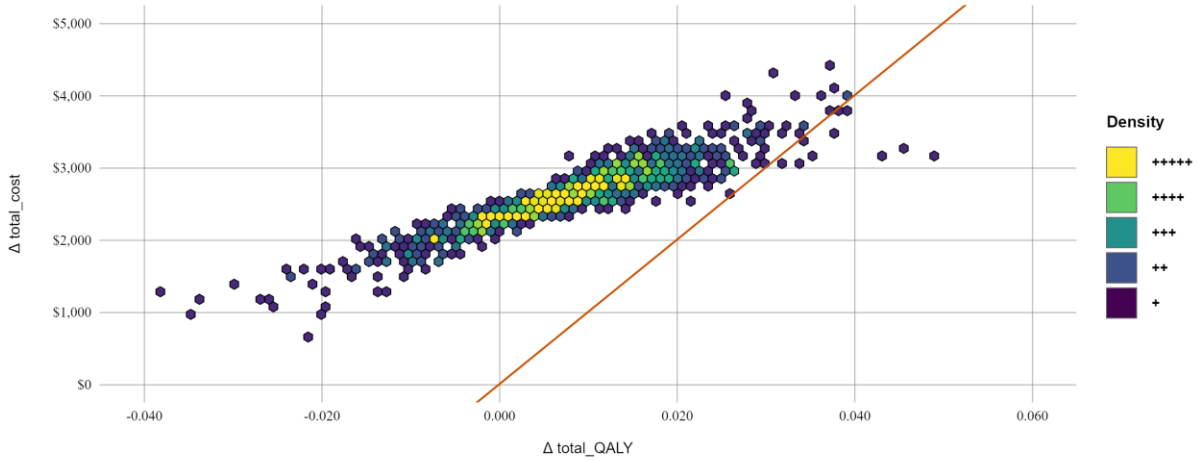
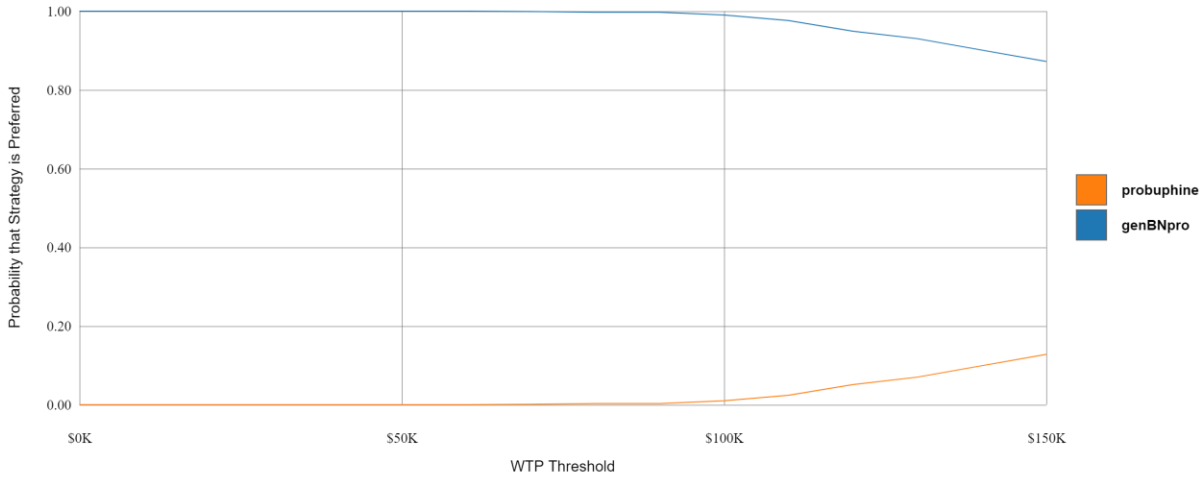


Figure E6. Probabilistic Analyses: Probuphine versus Generic SL Buprenorphine/Naloxone – Incremental Cost-Effectiveness Ratio Acceptability Curve



Modified Societal Perspective

Table E20. CAM2038 versus Generic SL Buprenorphine/Naloxone

Treatment	Lost Productivity Costs	Criminal Justice & Incarceration Costs
CAM2038	$13,600	$81,700
Generic SL Buprenorphine/Naloxone	$17,200	$96,700

Table E21. Vivitrol versus Generic SL Buprenorphine/Naloxone

Treatment	Lost Productivity Costs	Criminal Justice & Incarceration Costs
Vivitrol	$17,700	$101,000
Generic SL Buprenorphine/Naloxone	$15,500	$91,700

Table E22. Probuphine versus Generic SL Buprenorphine/Naloxone

Treatment	Lost Productivity Costs	Criminal Justice & Incarceration Costs
Probuphine	$9,700	$67,700
Generic SL Buprenorphine/Naloxone	$10,300	$70,200

Shorter Time Horizons

Table E23. One-Year Time Horizon

	Incremental QALYs	Incremental Costs	Incremental Cost per QALY
CAM2038*	0.004	-	-
Vivitrol	-0.020	$3,200	More costly, less effective
Probuphine	0.002	$2,400	$963,000

QALY: quality-adjusted life year

Each intervention was compared to its relevant generic buprenorphine/naloxone comparator.

*No incremental costs or cost per QALY is reported since CAM2038 currently does not have a list or net price.

Table E24. Two-Year Time Horizon

	Incremental QALYs	Incremental Costs	Incremental Cost per QALY
CAM2038*	0.014	-	-
Vivitrol	-0.028	$5,500	More costly, less effective
Probuphine	0.005	$2,500	$465,000

QALY: quality-adjusted life year

Each intervention was compared to its relevant generic buprenorphine/naloxone comparator

*No incremental costs or cost per QALY is reported since CAM2038 currently does not have a list or net price

Population Cohort Comprising Only PWID Seeking MAT for OUD

Table E25. CAM2038 versus Generic SL Buprenorphine/Naloxone in an OUD Population Comprising 100% PWID

Treatment	Total Costs	QALYs
CAM2038	-	3.224
Generic SL Buprenorphine/Naloxone	$73,500	3.221

QALY: quality-adjusted life year

Table E26. Vivitrol versus Generic SL Buprenorphine/Naloxone in an OUD Population Comprising 100% PWID

Treatment	Total Costs	QALYs	Incremental Cost per QALY Gained
Vivitrol	$84,100	3.208	More costly, less effective
Generic SL Buprenorphine/Naloxone	$73,600	3.241	

QALY: quality-adjusted life year

Table E27. Probuphine versus Generic SL Buprenorphine/Naloxone in an OUD Population Comprising 100% PWID

Treatment	Total Costs	QALYs	Incremental Cost per QALY Gained
Probuphine	$79,400	3.353	$233,000
Generic SL Buprenorphine/Naloxone	$76,400	3.342	

QALY: quality-adjusted life year

Analyses Excluding the "Permanently Abstained from Illicit Use of Opioids" Health State

Table E28. CAM2038 versus Generic SL Buprenorphine/Naloxone in a Scenario That Excludes Permanent Abstinence from Illicit Use of Opioids

Treatment	Total Costs	QALYs
CAM2038	-	3.255
Generic SL Buprenorphine/Naloxone	$70,500	3.193

QALY: quality-adjusted life year

Table E29. Vivitrol versus Generic SL Buprenorphine/Naloxone in a Scenario That Excludes Permanent Abstinence from Illicit Use of Opioids

Treatment	Total Costs	QALYs	Incremental Cost per QALY Gained
Vivitrol	$81,900	3.239	More costly, less effective
Generic SL Buprenorphine/Naloxone	$71,800	3.268	

QALY: quality-adjusted life year

Table E30. Probuphine versus Generic SL Buprenorphine/Naloxone in a Scenario That Excludes Permanent Abstinence from Illicit Use of Opioids

Treatment	Total Costs	QALYs	Incremental Cost per QALY Gained
Probuphine	$78,300	3.359	$279,000
Generic SL Buprenorphine/Naloxone	$75,600	3.369	

QALY: quality-adjusted life year

"Protocol" Approach to Treatment

Table E31. CAM2038 versus Generic SL Buprenorphine/Naloxone

Treatment	Total Costs	QALYs
CAM2038	-	3.261
Generic SL Buprenorphine/Naloxone	$70,100	3.202

QALY: quality-adjusted life year

Table E32. Vivitrol versus Generic SL Buprenorphine/Naloxone

Treatment	Total Costs	QALYs	Incremental Cost per QALY Gained
Vivitrol	$88,300	3.310	$1,100,000
Generic SL Buprenorphine/Naloxone	$71,600	3.295	

QALY: quality-adjusted life year

Table E33. Probuphine versus Generic SL Buprenorphine/Naloxone

Treatment	Total Costs	QALYs	Incremental Cost per QALY Gained
Probuphine	$79,500	3.416	$64,700
Generic SL Buprenorphine/Naloxone	$76,500	3.404	

QALY: quality-adjusted life year

Consecutive Use of Probuphine per Prescribing Label

Table E34. Probuphine versus Generic SL Buprenorphine/Naloxone when Patients Are Administered Two Probuphine Implants Consecutively

Treatment	Total Costs	QALYs	Incremental Cost per QALY Gained
Probuphine	$81,100	3.395	$236,000
Generic SL Buprenorphine/Naloxone	$75,100	3.370	

QALY: quality-adjusted life year

Appendix F. 2014 APA Clinical Guideline

The following guideline was summarized in ICER's 2014 report on opioid dependence. This guideline has not been updated since the previous report was issued.

American Psychiatric Association

Practice Guideline for the Treatment of Patients with Substance Abuse Disorders (2010)

Buprenorphine or Buprenorphine/Naloxone (Suboxone)

The APA clinical guidelines state that buprenorphine may be effective on a less than daily schedule and as a bridging agent to naltrexone. Therefore, the guidelines recommend that clinicians administer higher, but less frequent doses. Buprenorphine may be best suited for patients with less severe physical dependence. Although the rate of overdose is lower compared to methadone, combining buprenorphine and a benzodiazepine is more likely to be fatal.

Naltrexone and Vivitrol (Injectable Naltrexone)

The APA clinical guidelines recommend naltrexone as a maintenance agent as it is highly effective in blocking short-acting opioids. However, retention is generally poor and treatment with naltrexone poses a high risk of relapse. As such, the APA states that naltrexone should be utilized in particularly motivated patients who are willing to participate in ancillary services, such as psychosocial and behavioral counseling.