The Effectiveness and Value of Extended-Release Opioid Agonists and Antagonists for Addiction Treatment of Opioid Use Disorder

A Summary from the Institute for Clinical and Economic Review's New England Comparative Effectiveness Public Advisory Council

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Opioid use disorder (OUD) is a common and growing public health issue that has become a serious epidemic in the United States. In 2016 alone, an estimated 2.1 million people have suffered from OUD, with 116 Americans dying daily from opioid-related overdose.[1]

OUD is considered a chronic illness that requires long-term treatment and is marked by episodes of remission and relapse. The medication for the treatment of OUD is known as MAT, which stands for either "medication for addiction treatment" or "medication-assisted treatment."[2] The U.S. Food and Drug Administration (FDA) has approved treatments for OUD based on 3 principal underlying medications: methadone, buprenorphine, and naltrexone.[3] The Institute for Clinical and Economic Review (ICER) recently conducted a review of 4 extended-release formulations of these medications: Sublocade (buprenorphine injection, Indivior), Probuphine (buprenorphine implant, Titan Pharmaceuticals), Brixadi (buprenorphine injection, Braeburn)—an agent ineligible for marketing until 2020 due to exclusivity considerations after receiving tentative FDA approval—and Vivitrol (naltrexone injection, Alkermes). Here, we summarize a systematic literature review of the clinical effectiveness, cost-effectiveness analysis, and policy discussion with key stakeholders on the overall value of these therapies from a public meeting held by ICER of the New England Comparative Effectiveness Public Advisory Council (NE CEPAC) on November 8, 2018. The full, detailed report is located on the ICER website.[4]

Summary of Findings

Clinical Effectiveness

Our review compared the safety and effectiveness of the 4 extended-release formulations with transmucosal buprenorphine/naloxone in patients aged 16 years and older. There were no head-to-head studies of the 4 extended-release formulations, and variations in study characteristics, design, and outcomes due to nonstandard clinical measures prevented us from performing quantitative indirect comparisons. Details on ICER's systematic literature search and protocol, including the search strategy and PICOTS criteria, are available on the ICER website. Below, we focus on outcomes related to abstinence and discontinuation in the key trials used in the economic model; see the full report for other reported outcomes and trials.[4]

Sublocade. Evidence for Sublocade came from an investigator-patient–blinded, placebo-controlled 6-month phase 3 trial.[5] Participants underwent an open-label run-in induction period with sublingual buprenorphine/naloxone film followed by an open-label run-in dose adjustment period for 4-11 days to reach a sublingual buprenorphine/naloxone dose of 8 mg to 24 mg. Approximately 75% of the participants completed the run-in phase and were subsequently randomized to a once-monthly injection of either 300 mg of Sublocade, 100 mg of Sublocade, or placebo. The proportion of participants with 90% or more negative urine samples combined with self-reported abstinence of illicit opioids was similar between the Sublocade groups (300 mg: 24% vs. 100 mg: 21%) and significantly higher than placebo (2%, $P > 0.0001$ compared with each active arm) during weeks 5-24. Discontinuation after randomization was similar for both Sublocade groups (300 mg: 36% vs. 100 mg: 38%) and lower than placebo (66%).

Probuphine. For Probuphine, we assessed data from a recent 6-month, placebo-controlled, investigator-patient–blinded, phase 3 trial.[6] Clinically stable patients receiving a stable dose of sublingual buprenorphine for at least 24 weeks with no signs of opioid withdrawal or illicit opioid-positive urine samples before enrollment were randomized to receive either daily sublingual buprenorphine/naloxone tablets or an implant of Probuphine lasting 3 months. As the enrolled patients were clinically stable at the start of the trial, discontinuations were very low (Probuphine: 7%; buprenorphine/naloxone: 6%). A higher proportion of participants were abstinent over 6 months (based on urine drug tests and self-reporting of no illicit opioid use for 4 out of 6 months) with Probuphine than with buprenorphine/naloxone (96.4% vs. 87.6%, $P = 0.03$).

Brixadi. Data on Brixadi was from one 24-week phase 3 trial in adult patients with moderate to severe OUD.[7] Patients were randomized to either a flexible regimen of Brixadi administered as an injection given weekly (16, 24, or 32 mg) for 12 weeks followed by a monthly injection (64, 96, 128, or 160 mg), or to sublingual buprenorphine/naloxone. The

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TABLE 1 Health Care Sector Perspective Results for Probuphine, Brixadi, and Vivitrol Cost-Effectiveness

Intervention	Discounted				Versus No Prophylaxis
	MAT Drug Costs $	Other Costs $	Total Costs: U.S. Health System Perspective $	QALYs	Incremental Cost-Effectiveness Ratio (per QALY), $
Brixadi	–	66,100	–	3.26	–
Probuphine	11,000	66,900	77,900	3.38	265,000
Vivitrol	15,900	65,500	81,500	3.25	More costly, less effective

Note: Total costs are the sum of "MAT Drug Costs" drug and "Other Costs." All costs are rounded to the nearest $100. Incremental cost-effectiveness ratios are rounded to the nearest $1,000.
MAT = medication-assisted treatment; QALY = quality-adjusted life-year.

administered doses of Brixadi were determined based on individual patient circumstances. The percentage of opioid-negative urine samples for Brixadi was 35.1% and 28.4% for buprenorphine/naloxone over 24 weeks. Based on the study's noninferiority margin of -11%, the mean difference of 6.7% (95% confidence interval [CI] = 0.1%-13.6%) was interpreted as demonstrating noninferiority. By 28 weeks (after the safety follow-up), a similar proportion of patients discontinued in the Brixadi arm as in the buprenorphine/naloxone arm (41% vs. 43%).

Vivitrol. We included data on Vivitrol from 1 phase 4 trial comparing Vivitrol with sublingual buprenorphine/naloxone.[8] The trial included 570 participants aged 18 years or older with OUD who had used nonprescribed opioids within 30 days of the trial. Patients were randomized either during or after detoxification to once-monthly injections of Vivitrol or to sublingual buprenorphine/naloxone. During weeks 3-24, a higher proportion of participants in the intent-to-treat group relapsed after 20 days on Vivitrol than on sublingual buprenorphine/naloxone film (65% vs. 57%, $P = 0.036$). More participants discontinued Vivitrol than buprenorphine/naloxone (28% and 22%), but significantly more discontinued during induction in the Vivitrol arm (28% vs. 6%, $P < 0.0001$).

Harms. Serious adverse events were uncommon and similar in the trials of all 4 extended-release treatments. Discontinuations due to adverse events were generally low in all trials. The most common adverse events reported were injection/implant site pain, gastrointestinal issues, headaches, and insomnia.

Limitations of the Clinical Evidence

The evidence presented is limited by variations in trial designs, outcome measures that vary across agents and trials, and lack of long-term efficacy and safety data. Uncertainty remains in whether comparing the proportion of opioid-negative urine samples with differences in frequency of collection represents a meaningful measure of success, even in such short-term trials. Participants with psychiatric comorbidities, such as depression, post-traumatic stress disorder, and personality disorders were excluded from the trials, limiting the generalizability of these findings. One important limitation of Vivitrol is that patients need to complete detoxification before initiating treatment, which may be difficult in a real-world setting.

Long-Term Cost-Effectiveness

We compared the cost-effectiveness of Probuphine, Brixadi, and Vivitrol with sublingual buprenorphine/naloxone using a Markov model. Due to a lack of trial evidence comparing Sublocade to sublingual buprenorphine/naloxone, we reserved this analysis to a scenario built on assumptions.

The model had a 4-week cycle and was run over a 5-year time horizon from a U.S. health care sector perspective. High rates of treatment discontinuation and uncertainty in subsequent lines of therapy limited the modeling of this analysis over a longer time horizon. We did not assume retreatment among those who relapsed to illicit use nor did we assume subsequent lines of therapy following discontinuation of MATs. We assumed long-term abstinence in a fraction of patients who remained abstinent from illicit use while on treatment for at least 1 year. Background health care costs when abstinent were lower than when illicitly using opioids. We attributed higher health-related quality of life estimates to those who abstained from illicit use compared with those who did not. We included an estimate of overdose-related mortality and mortality from hepatitis C virus or human immunodeficiency virus infections among injection drug users. Complete information on model assumptions, design, and results can be found in the final ICER report.[4]

The baseline characteristics of the population in the model reflected the weighted average across the key clinical trials for the interventions, with a mean age of 36 years, 30% female, 50% of the population being injection drug users, and 50% using prescription drugs. Treatment-specific efficacy estimates and discontinuation rates were derived from key relevant clinical trials.[5-8] MAT drug costs were sourced from the Federal Supply Schedule database for all except Vivitrol, whose net price was provided to us by its manufacturer. Other model inputs such as non-drug health care costs, mortality estimates and health-related quality of life estimates were sourced from

TABLE 2 Other Benefits or Disadvantages

Does treating with 1 of the extended-release interventions (Brixadi, Sublocade, Probuphine, or Vivitrol) offer 1 or more of the following potential "other benefits" versus transmucosal formulations of buprenorphine/naloxone?

Potential Benefit	Panel Votes[a]
a. ***Brixadi and Sublocade*** offer reduced complexity that will significantly improve patient outcomes.	10
b. ***Probuphine*** offers reduced complexity that will significantly improve patient outcomes.	4
c. ***Vivitrol*** offers reduced complexity that will significantly improve patient outcomes.	8
d. Intervention will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.	7
e. This intervention will significantly reduce caregiver or broader family burden.	6
f. ***Brixadi and Sublocade*** offer a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	7
g. ***Probuphine*** offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	3
h. ***Vivitrol*** offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	8
i. These interventions will have a significant impact on improving patients' ability to return to work and/or their overall productivity.	5
j. There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	7

[a]*Thirteen NE CEPAC panelists voted.*

NE CEPAC = New England Comparative Effectiveness Public Advisory Council.

the published literature. We were unable to calculate the cost-effectiveness for Brixadi, since its price is currently not known. Total health care costs over 5 years were $77,900 for Probuphine and $81,500 for Vivitrol. All cost and health-related quality of life outcomes are shown in Table 1. Further details are available in the final ICER report.[4]

Limitations of the Cost-Effectiveness Model

Our analyses were limited by a lack of evidence on therapeutic pathways upon MAT discontinuation and how patients cycle through different therapies. Furthermore, treatment-specific quality of life estimates were not reported in the trials, and robust data on diversion and change in opioid treatment regimens were unavailable.

Policy Discussion

The NE CEPAC is one of the independent appraisal committees convened by ICER to engage in the public deliberation of the evidence on clinical and cost-effectiveness of health care interventions. The NE CEPAC is composed of medical evidence experts, including practicing clinicians, methodologists, and leaders in patient engagement and advocacy. Input from clinical experts and patient representatives for the specific condition under review is discussed, as well as formal comment from public and manufacturers. A policy roundtable concludes each meeting, during which representatives from insurers and manufactures join with clinical experts and patient representatives to discuss how best to apply the findings of the evidence presented to clinical practice, insurance coverage, and pricing negotiations.

The ICER report on extended-release opioids was the subject of a NE CEPAC meeting in November 2018. Following the discussion, the CEPAC panel members voted that the evidence was inadequate to demonstrate that the net health benefit of Sublocade, Probuphine, Brixadi, and Vivitrol were each superior to transmucosal buprenorphine/naloxone: 13-0 for Sublocade, 12-1 for Probuphine, 9-4 for Brixadi, and 11-2 for Vivitrol. The CEPAC voted 12-1 that the evidence was inadequate to distinguish the net health benefit among the 4 interventions.

The CEPAC panel also voted on "other potential benefits" and "contextual considerations" of these treatments as part of a process intended to signal to policymakers whether there are important considerations when making judgments about long-term value for money that are not adequately captured in the analyses of clinical effectiveness and cost-effectiveness. The results are displayed in Tables 2 and 3, which highlight several factors that the NE CEPAC panel felt were influential when making judgments about value.

The policy roundtable explored how best to translate the evidence and broader perspectives discussed into clinical practice and into pricing and insurance coverage policies. The full set of policy recommendations can be found in the final evidence report;[4] several key policy recommendations follow:

- All stakeholders should decrease stigma by aligning efforts around education that enhance awareness that OUD is a chronic disease requiring long-term treatment.
- Manufactures should bring the price of extended-release medications into alignment with their clinical value.
- For treatments of OUD whose prices are aligned with clinical value, payers should create coverage that present no barriers to access.

TABLE 3 Contextual Considerations

Are any of the following contextual considerations important in assessing the long-term value for money of extended-release interventions (Brixadi, Sublocade, Probuphine, or Vivitrol)?

Contextual Consideration	Panel Votes[a]
a. These interventions are 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.	11
b. These interventions are intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	12
c. These interventions are the first to offer any improvement for patients with this condition.	0
d. There is significant uncertainty about the long-term risk of serious side effects of ***Brixadi***.	2
e. There is significant uncertainty about the long-term risk of serious side effects of ***Sublocade***.	3
f. There is significant uncertainty about the long-term risk of serious side effects of ***Probuphine***.	3
g. There is significant uncertainty about the long-term risk of serious side effects of ***Vivitrol***.	3
h. There is significant uncertainty about the magnitude or durability of the long-term benefits of ***Brixadi***.	9
i. There is significant uncertainty about the magnitude or durability of the long-term benefits of ***Sublocade***.	9
j. There is significant uncertainty about the magnitude or durability of the long-term benefits of ***Probuphine***.	2
k. There is significant uncertainty about the magnitude or durability of the long-term benefits of ***Vivitrol***.	9
l. There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	6

[a]*Twelve NE CEPAC panelists voted due to 1 member's early departure as a result of a medical emergency.*
NE CEPAC = New England Comparative Effectiveness Public Advisory Council.

- Based on available evidence and clinical expert testimony at the CEPAC meeting, the following prior authorization (PA) considerations should guide the development of payer policies for coverage of Sublocade and similar extended-release OUD treatments:
  1. *Concomitant behavioral health counseling.* Although counseling has been shown to be important in supporting beneficial outcomes of OUD treatment, PA criteria requiring documentation of ongoing counseling may present a barrier to treatment. Instead, payers may wish to ask prescribers to attest that they have a relationship through which they can refer their patients to counseling or care management. If this is not available, the payer should consider reaching out to the provider/patient to help arrange these services.
  2. *Medical necessity for Sublocade versus buprenorphine.* In an environment with a significant price difference between transmucosal buprenorphine therapy and extended-release formulations, payers may consider requiring that patients attempt treatment with transmucosal therapy before transitioning to extended-release formulations. This would likely not be necessary if the price for extended-release formulations were to align with value.

     For patients for whom Sublocade treatment is being considered, stabilization on buprenorphine at a dose ≤ 24 mg per day for at least 7 days is a reasonable PA criterion to ensure that patients can be adequately managed with Sublocade alone. The medical necessity for Sublocade over less expensive buprenorphine can also be supported by specific home and life situations. For example, patients with unstable home and life situations, where storage of the daily transmucosal doses is challenging, are likely to have greater chance to benefit from OUD treatment through an extended-release agent. Similarly, patients who desire treatment but have demonstrated that they cannot easily maintain the commitment to daily treatment are viewed as good candidates for Sublocade.

Conclusions

These extended-release treatments offer more options for medicated treatment of chronic OUD and therefore add importantly to the ability of combating the opioid epidemic. After the review of the evidence and the discussion of wide-ranging potential benefits and contextual considerations associated with critical treatment, the pricing of Sublocade, Probuphine, and Vivitrol in the U.S. health care system was judged to represent low value for the money. Greater efforts are necessary to aid in the alignment of the price of treatments with their demonstrated benefits to ensure sustainable access to high-value care for all patients.

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REFERENCES

1. U.S. Department of Health and Human Services. What is the U.S. opioid epidemic? 2018. Available at: https://www.hhs.gov/opioids/about-the-epidemic/index.html. Accessed March 26, 2019.

2. Substance Abuse and Mental Health Services Administration. Medications for opioid use disorder. Treatment Improvement Protocol 63. 2018. Available at: https://store.samhsa.gov/system/files/sma18-5063fulldoc.pdf. Accessed March 26, 2019.

3. U.S. Food and Drug Administration. Information about medication-assisted treatment (MAT). 2018. Available at: https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm600092.htm. Accessed March 26, 2019.

4. Banken R, Otuonye I, Kumar V, et al. Extended-release opioid agonists and antagonist medications for addiction treatment (MAT) in patients with opioid use disorder: effectiveness and value. Final evidence report. Institute for Clinial and Economic Review. December 3, 2018. Available at: https://icer-review.org/material/mat-final-report/. Accessed April 10, 2019.

5. Indivior. Treatment seeking participants with opioid use disorders assessing tolerability of depot injections of buprenorphine. ClinicalTrials.gov Identifier: NCT02357901. Last updated February 20, 2018. Available at: https://clinicaltrials.gov/ct2/show/results/NCT02357901. Accessed March 26, 2019.

6. 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):282-90.

7. Lofwall MR, Walsh SL, Nunes EV, et al. Weekly and monthly subcutaneous buprenorphine depot formulations vs daily sublingual buprenorphine with naloxone for treatment of opioid use disorder: a randomized clinical trial. *JAMA Intern Med*. 2018;178(6):764-73.

8. 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):309-18.

The Individualized Treatment of Opioid Use Disorder

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COMMENTARY

The treatment of opioid use disorder (OUD) has progressed substantially over the past 50 years. We now have an excellent arsenal of therapies to combat this chronic but deadly disease. OUD, like other substance use disorders, can be successfully managed, but there is no cure. Relapse is always a threat. Like other chronic diseases, the clinical progression of substance use disorders, including OUD, can be best characterized by periods of exacerbation and periods of remission, but the patient is never disease-free. It is not uncommon for a simple trip to the dentist or the emergency department to precipitate a full-blown exacerbation of drug-seeking behavior. Just a few hydrocodone or alprazolam tablets from a legal prescription can quickly escalate to a life-threatening relapse.

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Patients in recovery should consider themselves "allergic" to self-administered controlled substances. When controlled substances are used, they should be administered under strict supervision and surveillance of an addiction medicine specialist or addiction psychiatrist.

Use disorders are not a substance-specific disease. Patients may transition through the abuse of many different substances throughout the course of the disease process. Many patients may start with heavy alcohol use then find that their alcohol consumption decreases as they move into opioids as their drug of choice. Patients may go through a methamphetamine phase and then a heroin phase; drug use is often determined by drug availability. Recovery from OUD can be sabotaged by benzodiazepines or other dopamine-releasing chemicals, even when prescribed by well-meaning clinicians who fail to consider a substance use disorder as part of the patient's medical history.