

Extended-Release Opioid Agonists and Antagonists for Medication-Assisted Treatment (MAT) of Opioid Use Disorder: Effectiveness and Value

Draft Background and Scope

April 26, 2018

Background

Opioid use disorder (OUD) has become a public health crisis in the United States. OUD is defined as meeting the following Diagnostic and Statistical Manual of Mental Disorders (DSM-5) characteristics: impaired control, social impairment, risky use, increased tolerance, and withdrawal.^{1,2} Many experts feel that it should be considered a chronic disease that requires long-term maintenance treatment.³

In addition to its health and social impacts, OUD can lead to death from drug overdose. The number of deaths from drug overdose has increased continuously since 1999⁴ and reached around 70,000 deaths over the last 12 months.⁵ Around 2.4 million persons in the US suffer from OUD; two-thirds of this prevalence relates to prescription opioid painkillers and one-third relates to heroin or other illicit opioids.⁶

A variety of treatment approaches are available for treating OUD. Medicated-Assisted Treatment (MAT) is one of the approaches that is increasingly used. MAT is defined as the use of medications approved by the Food and Drug Administration (FDA), generally in combination with counseling and behavioral therapies.⁷ Treatment of OUD with an MAT component has been shown to be effective^{3,8}, and three types of medications are approved by the FDA: the opioid agonists methadone and buprenorphine, as well as the opioid antagonist naltrexone.^{9,10}

In 2014, ICER conducted an assessment on clinical, delivery system, and policy options for the management of patients with opioid dependence.¹¹ The report found that “long-term maintenance treatment approaches using methadone or Suboxone® 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.

Over the last two years, the number of patients treated with MAT in the US has approximately doubled overall;¹² part of this increase is due to better access to MAT for Medicaid patients through provisions in the Patient Protection and Affordable Care Act (ACA).¹³ On February 24, 2018, the US

Secretary of Health and Human Services announced that the Trump administration will expand access to MAT.^{14,15} Current work in the US Senate and congress involves enabling more medical professionals to prescribe buprenorphine medications and to increase the Medicare reimbursement for prescribing these medications.¹⁶

Still, access to MAT remains a challenge for many individuals. Two long-acting buprenorphine formulations have been approved recently and a third is currently under review by the FDA, as listed below:

- Buprenorphine subcutaneous extended-release injection (Sublocade[®], Indivior, FDA approved November 30, 2017)
- Buprenorphine implant (Probuphine[®], Braeburn/Titan, FDA approved May 26, 2016)
- Buprenorphine intramuscular extended-release injection (CAM2038, Braeburn, investigational, currently under FDA review)

There is interest in understanding whether these new delivery mechanisms might expand access to patients and providers who are not able to make optimal use of the current forms of MAT. In addition, there are additional data now available for long-acting naltrexone (Vivitrol[®], Alkermes, FDA approved October 13, 2010) that may also serve to expand the policy discussions around MAT. The purpose of this review is to expand on the original 2014 review, with a focus on the effectiveness and value of newer long-acting medications.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patients and patient advocacy groups, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders, who noted the difficulties that persist in accessing MAT and other treatments. Different patients may need different types of treatment with different emphasis on medication, counseling, and peer support. Some patients may enter recovery without needing MAT. A particular lack of social skills in adolescents with OUD call for strong peer support services for this particular patient group.

Stakeholders also mentioned that complete absence of non-medical opioid use (abstinence) should not be the only measure of effectiveness. Diminishing non-medical opioid use and better daily functioning should also be considered as measures of treatment success. Considering a broader set of outcomes in measuring effectiveness of MAT has also been stressed in a public meeting on Patient-Focused Drug Development for Opioid Use Disorder convened on April 17, 2018.¹⁷

A final scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Report Aim

This project will evaluate the health and economic outcomes of several new options for MAT in OUD. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms - including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs - are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

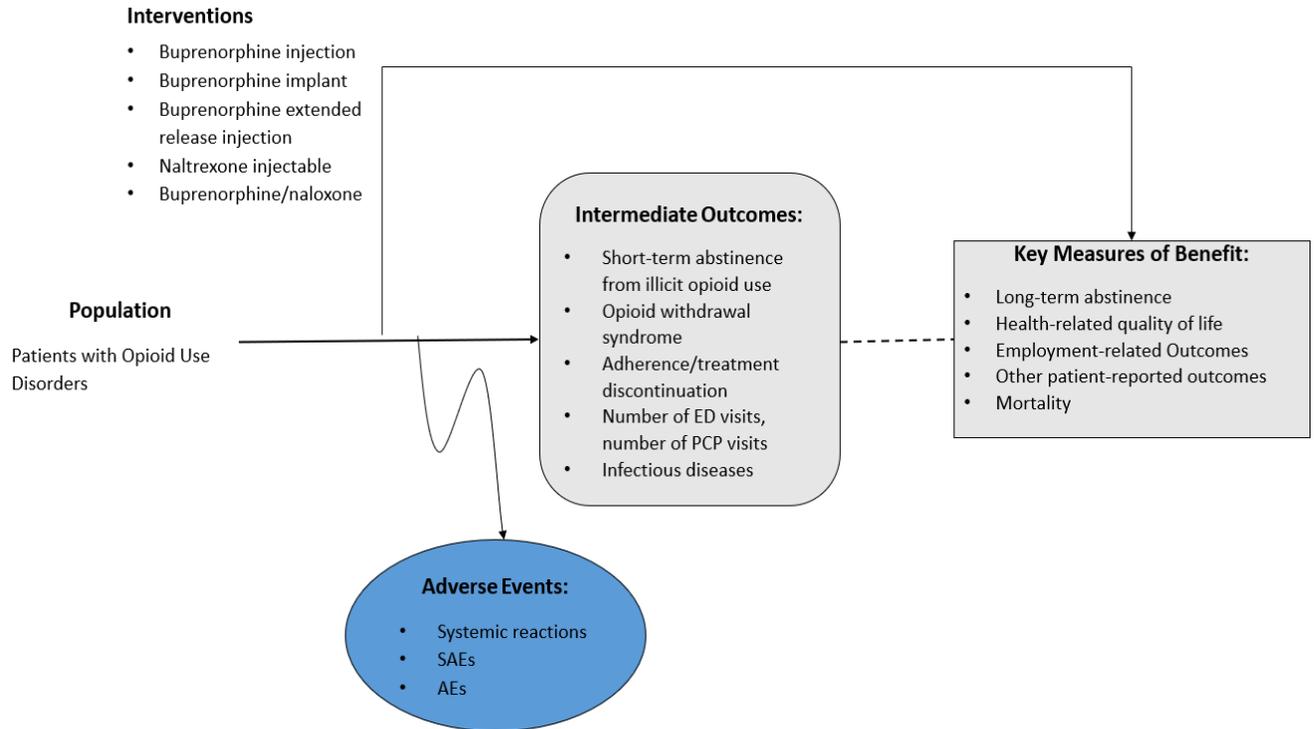
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see <https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/>).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the finalized scope in a research protocol published on the Open Science Framework website (<https://osf.io/7awvd/>).

Analytic Framework

The general analytic framework for assessment of therapies for OUD is depicted in Figure 1.

Figure 1. Analytic Framework: Opioid Agonists and Antagonists for MAT of Opioid Use Disorder



AE: adverse event, SAE: serious adverse event

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 adverse events of an action (typically treatment), which are listed within the blue ellipsis.¹⁸

Populations

The key populations of interest for the review will be patients aged 16 and above with OUD seeking outpatient treatment in office-based settings. We will consider a subpopulation that focuses on adolescents if there is available data. Input from stakeholders suggests that the greatest potential for expansion of access is in outpatient, office-based settings, given longstanding concerns with current access via the requirement for directly observed administration of methadone in clinic-based settings.

We will focus attention on two distinct populations, given different patient incentives for seeking treatment and differing mechanisms of action for the treatments themselves:

- Population 1: Patients with OUD seeking MAT for “harm reduction” (long-term MAT in the setting of current opioid use).
- Population 2: Patients with OUD seeking MAT for withdrawal from opioid use.

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 for each population:

Population 1:

- Buprenorphine subcutaneous extended-release injection (Sublocade[®], Indivior)
- Buprenorphine implant (Probuphine[®], Braeburn/Titan)
- Buprenorphine intramuscular extended-release injection (CAM2038, Braeburn)

Population 2:

- Naltrexone intramuscular extended-release injection (Vivitrol[®], Alkermes)

Comparators

Data permitting, we intend to compare all the agents to each other within each population and to therapies commonly used in MAT, such as a buprenorphine/naloxone in both the sublingual and buccal formulations. Although we do not intend to include methadone in the formal list of comparators for either population, given the setting of interest for the evaluation, we will nevertheless summarize historical data on its effectiveness, safety, and access challenges, and also highlight individual studies of methadone that match our intended scope (e.g., US trials of outpatient-administered methadone conducted using a legal waiver).

Outcomes

The outcomes of interest are described in the list below.

- Short-term and long-term abstinence from illicit opioid use
- Opioid withdrawal syndrome
- Number of emergency department (ED) visits, number of primary care physician (PCP) visits
- Infectious diseases (HIV, hepatitis) through continued use of injectable opioids
- Mortality (overdose deaths)
- Health-related quality of life
- Employment-related outcomes
- Other patient-reported outcomes
- Adherence/treatment discontinuation (number of times treated in detox/rehab, duration of abstinence)
- Harms/adverse events

Timing

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

Settings

The setting of interest will be outpatient, office-based settings in the US.

Other Benefits and Contextual Considerations

Our reviews seek to provide information on 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.

Table 1.1. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.
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 “the comparator,” there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to “the comparator,” 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.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop a simulation model to assess the lifetime cost-effectiveness of MAT. As described in the proposed scope, we will consider this differently for the two populations of interest. In population 1 (“harm reduction”), interventions of interest will include buprenorphine extended-release injection (CAM2038 - investigational), buprenorphine extended-release injection (Sublocade®), and buprenorphine implant (Probuphine®), each compared to buprenorphine/naloxone (sublingual and buccal formulations) in patients diagnosed with OUD. In population 2 (“opioid withdrawal”), the comparison of interest will involve extended-release injectable naltrexone (Vivitrol®) and oral immediate-release naltrexone. We will also consider a comparison of the two treatment strategies as evidence allows.

A detailed economic model analysis plan with proposed methodology, model structure, parameters, and assumptions is forthcoming. The model structure will be based in part on a literature review of prior published models of MATs¹⁹⁻²³, as well as clinical trials and observational studies of MATs. The base case analysis will take a health system perspective (i.e., focus on direct medical care costs only). Data permitting, a modified societal perspective will be considered in a separate analysis. The target population will consist of adult patients in the US diagnosed with OUD seeking MAT in an office-based outpatient setting. The model will potentially consist of health states including being on MAT and off opioids, off MAT and off opioids, on MAT and opioid relapse, off MAT and opioid relapse, and death. A cohort of patients will transition between states during predetermined monthly cycles over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness will be estimated for shorter time horizons (e.g., two years and five years).

Key model inputs will include clinical probabilities such as relapsing to opioid use after a period of abstinence, quality of life values, and health care costs that include drug and non-drug MAT costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Data permitting, findings from a potential network meta-analysis or other systematic reviews will be used to estimate treatment effectiveness.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of number of days of abstinence from opioid use, life-years, and quality-adjusted life years (QALYs) gained. Quality of life weights will be applied to each health state, including potential quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, productivity loss costs and outcomes, and costs and outcomes associated with criminal justice and incarceration will be included in a separate analysis if available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per life-year gained, and cost per period of opioid abstinence.

In separate analyses, we will explore the potential health system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions.

More information on ICER's methods for estimating potential budget impact can be found at: <http://icer-review.org/wp-content/uploads/2018/01/ICER-value-framework-v1-21-18.pdf>.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see <https://icer-review.org/material/final-vaf-2017-2019/>). These services are ones that would not be directly affected by MAT (e.g., infectious diseases), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of OUD beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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