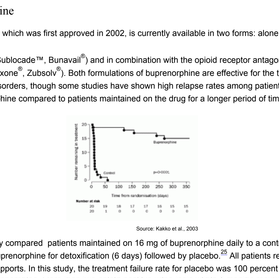
How effective are medications to treat opioid use disorder?

Abundant evidence shows that methadone, buprenorphine, and naltrexone all reduce opioid use and opioid use disorder-related symptoms, and they reduce the risk of infectious disease transmission as well as criminal behavior associated with drug use.[15] These medications also increase the likelihood that a person will remain in treatment, which itself is associated with lower risk of overdose mortality, reduced risk of HIV and HCV transmission, reduced criminal justice involvement, and greater likelihood of employment.[15]

Methadone

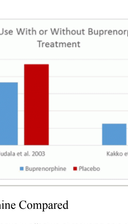
Methadone is the medication with the longest history of use for opioid use disorder treatment, having been used since 1947. A large number of studies (some of which are summarized in the graph below) support methadone's effectiveness at reducing opioid use. A comprehensive Cochrane review in 2009 compared methadone-based treatment (methadone plus psychosocial treatment) to placebo with psychosocial treatment and found that methadone treatment was effective in reducing opioid use, opioid use-associated transmission of infectious disease, and crime.[12,16–20] Patients on methadone had 33 percent fewer opioid-positive drug tests and were 4.44 times more likely to stay in treatment compared to controls.[12] Methadone treatment significantly improves outcomes, even when provided in the absence of regular counseling services;[18,19,21] long-term (beyond 6 months) outcomes are better in groups receiving methadone, regardless of the frequency of counseling received.[22,23]



Buprenorphine

Buprenorphine, which was first approved in 2002, is currently available in two forms: alone

(Probuphine®, Sublocade™, Bunavail®) and in combination with the opioid receptor antagonist naloxone (Suboxone®, Zubsolv®). Both formulations of buprenorphine are effective for the treatment of opioid use disorders, though some studies have shown high relapse rates among patients tapered off of buprenorphine compared to patients maintained on the drug for a longer period of time.[24]



Source: Kakko et al., 2003

A Swedish study compared patients maintained on 16 mg of buprenorphine daily to a control group that received buprenorphine for detoxification (6 days) followed by placebo.[25] All patients received psychosocial supports. In this study, the treatment failure rate for placebo was 100 percent vs. 25 percent for buprenorphine. More than two opioid-positive urine tests within 3 months resulted in cessation of treatment, so treatment retention was closely related to relapse. Of patients not retained in treatment, there was a 20 percent mortality rate.

Meta-analysis determined that patients on doses of buprenorphine of 16 mg per day or more were 1.82 times more likely to stay in treatment than placebo-treated patients, and buprenorphine decreased the number of opioid-positive drug tests by 14.2 percent (the standardized mean difference was -1.17).[13,25,26]

To be effective, buprenorphine must be given at a sufficiently high dose (generally, 16 mg per day or more). Some treatment providers wary of using opioids have prescribed lower doses for short treatment durations, leading to failure of buprenorphine treatment and the mistaken conclusion that the medication is ineffective.[13,27]

Methadone and Buprenorphine Compared

Methadone and buprenorphine are equally effective at reducing opioid use. A comprehensive Cochrane review comparing buprenorphine, methadone, and placebo found *no* differences in opioid-positive drug tests or self-reported heroin use when treating with methadone or buprenorphine at medium-to-high doses.[13]

Notably, flexible dose regimens of buprenorphine and doses of buprenorphine of 6 mg or below are less effective than methadone at keeping patients in treatment, highlighting the need for delivery of evidence-based dosing regimens of these medications.[13]

Naltrexone

Naltrexone was initially approved for the treatment of opioid use disorder in a daily pill form. It does not produce tolerance or withdrawal. Poor treatment adherence has primarily limited the real-world effectiveness of this formulation.[28] As a result, there is insufficient evidence that oral naltrexone is an effective treatment for opioid use disorder.[29] Extended-release injectable naltrexone (XR-NTX) is administered once monthly, which removes the need for daily dosing. While this formulation is the newest form of medication for opioid use disorder, evidence to date suggests that it is effective.[28,30]

The double-blind, placebo-controlled trial that was most influential in getting XR-NTX approved by the FDA in 2010 for opioid use disorder treatment showed that XR-NTX significantly increased opioid abstinence. The XR-NTX group had 90 percent confirmed abstinent weeks compared to 35 percent in the placebo group. Treatment retention was also higher in the XR-NTX group (58 percent vs. 42 percent), while subjective drug craving and relapse were both decreased (0.8 percent vs. 13.7 percent).[31] Improvement in the XR-NTX group was sustained throughout an open label period out to 76 weeks.[32] These data were collected in Russia, and additional studies are required to determine if effectiveness will be similar in the United States.[33]

Buprenorphine and Naltrexone Compared

A NIDA study showed that once treatment is initiated, a buprenorphine/naloxone combination and an extended release naltrexone formulation are similarly effective in treating opioid use disorder. Because naltrexone requires full detoxification, initiating treatment among active opioid users was more difficult with this medication. However, once detoxification was complete, the naltrexone formulation had a similar effectiveness as the buprenorphine/naloxone combination.

What are misconceptions about maintenance treatment?

Because maintenance medications (methadone and buprenorphine) are themselves opioids and are able to produce euphoria in people who are not dependent on opioids, many people have assumed that this form of treatment just substitutes a new substance use disorder for an old one. This belief has unfortunately hindered the adoption of these effective treatments. In the past, even some inpatient treatment programs that were otherwise evidence-based did not allow patients to use these medications, in favor of an "abstinence only" philosophy.

Although it is possible for individuals who do not have an opioid use disorder to get high on buprenorphine or methadone (see "What is the treatment need versus the diversion risk for opioid use disorder treatment?"), these medications affect people who have developed a high *tolerance* (see "Opioid Tolerance") to opioids differently. At the doses prescribed, and as a result of their *pharmacodynamic* and *pharmacokinetic* properties (the way they act at opioid receptor sites and their slower metabolism in the body), these medications do not produce a euphoric high but instead minimize withdrawal symptoms and cravings (see "Mechanisms of Opioid Dependence"). This makes it possible for the patient to function normally, attend school or work, and participate in other forms of treatment or recovery support services to help them become free of their substance use disorder over time.

The ultimate aim can be to wean off the maintenance medication, but the treatment provider should make this decision jointly with the patient and tapering the medication must be done gradually. It may take months or years in some cases. Just as body tissues require prolonged periods to heal after injury and may require external supports (e.g., a cast and crutches or a wheelchair for a broken leg), brain circuits that have been altered by prolonged drug use and substance use disorder take time to recover and benefit from external supports in the form of medication. In cases of serious and long-term opioid use disorder, a patient may need these supports indefinitely.

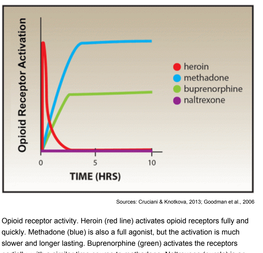
In 2005, methadone and buprenorphine were added to the World Health Organization's list of essential medicines, defined as medicines that are "intended to be available within the context of functioning health care systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford."[34,35]

Opioid Tolerance

People who take opioids for long periods of time typically develop *tolerance*, a state in which more of the drug is needed to produce the same effect. Receptor desensitization and downregulation are molecular processes that cause tolerance. In people with opioid use disorder, the brain is continually exposed to high levels of opioids as well as dopamine, which is released in the reward circuit following opioid receptor activation. Brain cells respond to this by reducing their response to receptor activation and by removing opioid and dopamine receptors from the cell membrane, resulting in fewer receptors that can be activated by the drug.[36,37] These mechanisms result in a lessened response to the drug, so higher doses are required to elicit the same effect. This opioid tolerance is the reason that people with opioid use disorder do not experience euphoric effects from therapeutic doses of buprenorphine or methadone, while people without opioid use disorder do.[38,39] It is also the reason why people are at increased risk of overdose when relapsing to opioid use after a period of abstinence: They lose their tolerance to the drug without realizing it, so they no longer know what dose of the drug they can safely tolerate.

Mechanisms of Opioid Dependence

The sustained activation of opioid receptors that results from opioid use disorder and causes tolerance also causes withdrawal symptoms when the opioid drugs leave the body. Drug withdrawal symptoms are opposite to the symptoms caused by drug taking. In the case of opioids, they include anxiety, jitters, and diarrhea.[40] Avoidance of these negative symptoms is one reason that people keep taking opioids, and in the early stages of treatment, medications such as methadone and buprenorphine reduce withdrawal symptoms.



Sources: Cruciani & Knotkova, 2013; Goodman et al., 2006

Opioid receptor activity. Heroin (red line) activates opioid receptors fully and quickly. Methadone (blue) is also a full agonist, but the activation is much slower and longer lasting. Buprenorphine (green) activates the receptors partially, with a similar time course to methadone. Naltrexone (purple) is an opioid receptor antagonist and therefore prevents receptor activation.[41,42]