National Institute on Drug Abuse (NIDA)

Medications to Treat Opioid Use Disorder

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Table of Contents

Overview

An estimated 2.1 million people in the United States had a substance use disorder related to prescription opioid pain medicines in 2016.[1] However, only a fraction of people with prescription opioid use disorders receive specialty treatment (17.5 percent in 2016).[1] Overdose deaths linked to these medicines were five times higher in 2016 than 1999.[2] There is now also a rise in heroin use and heroin use disorder as some people shift from prescription opioids to their cheaper street relative; 626,000 people had a heroin use disorder in 2016, and more than 15,000 Americans died of a heroin overdose in 2016.[1,3] Besides overdose, consequences of the opioid crisis include a rising incidence of infants born dependent on opioids because their mothers used these substances during pregnancy[4,5] and increased spread of infectious diseases, including HIV and hepatitis C (HCV), as was seen in 2015 in southern Indiana.[6]

Effective prevention and treatment strategies exist for opioid misuse and use disorder but are highly underutilized across the United States. An initiative of the Secretary of Health and Human Services (HHS)[7] began in 2015 to address the complex problem of prescription opioid and heroin use. In 2017, HHS announced five priorities for addressing the opioid crisis:

1. improving access to treatment and recovery services
2. promoting use of overdose-reversing drugs
3. strengthening our understanding of the epidemic through better public health surveillance
4. providing support for cutting-edge research on pain and addiction
5. advancing better practices for pain management

Effective medications exist to treat opioid use disorder: methadone, buprenorphine, and naltrexone. These medications could help many people recover from opioid use disorder, but they remain highly underutilized. Fewer than half of private-sector treatment programs offer medications for opioid use disorders, and of patients in those programs who might benefit, only a third

actually receive it.[9] Overcoming the misunderstandings and other barriers that prevent wider adoption of these treatments is crucial for tackling the problem of opioid use disorder and the epidemic of opioid overdose in the United States.

How do medications to treat opioid use disorder work?

Opioid Agonists and Partial Agonists (Maintenance Medications)

Studies show that people with opioid use disorder who follow detoxification with complete abstinence are very likely to relapse, or return to using the drug.[10] While relapse is a normal step on the path to recovery, it can also be life threatening, raising the risk for a fatal overdose.[11] Thus, an important way to support recovery from heroin or prescription opioid use disorder is to maintain abstinence from those drugs. Someone in recovery can also use medications that reduce the negative effects of withdrawal and cravings without producing the euphoria that the original drug of abuse caused. For example, the FDA recently approved lofexidine, a non-opioid medicine designed to reduce opioid withdrawal symptoms. **Methadone** and **buprenorphine** are other medications approved for this purpose.

Methadone is a synthetic *opioid agonist* that eliminates withdrawal symptoms and relieves drug cravings by acting on opioid receptors in the brain—the same receptors that other opioids such as heroin, morphine, and opioid pain medications activate. Although it occupies and activates these opioid receptors, it does so more slowly than other opioids and, in an opioid-dependent person, treatment doses do not produce euphoria. It has been used successfully for more than 40 years to treat opioid use disorder and must be dispensed through specialized opioid treatment programs.[12]

Buprenorphine is a *partial opioid agonist*, meaning that it binds to those same opioid receptors but activates them less strongly than full agonists do. Like methadone, it can reduce cravings and withdrawal symptoms in a person with an opioid use disorder without producing euphoria, and patients tend to tolerate it well. Research has found buprenorphine to be similarly effective as methadone for treating opioid use disorders, as long as it is given at a sufficient dose and for sufficient duration.[13] The U.S. Food and Drug Administration (FDA) approved buprenorphine in 2002, making it the first medication eligible to be

prescribed by certified physicians through the Drug Addiction Treatment Act. This approval eliminates the need to visit specialized treatment clinics, thereby expanding access to treatment for many who need it. Additionally, the Comprehensive Addiction and Recovery Act (CARA), which was signed into law in July 2016, temporarily expands eligibility to prescribe buprenorphine-based drugs for medication-assisted treatment (MAT) to qualifying nurse practitioners and physician assistants through October 1, 2021. Buprenorphine has been available for opioid use disorders since 2002 as a tablet and since 2010 as a sublingual film.[14] The FDA approved a 6-month subdermal buprenorphine implant in May 2016 and a once-monthly buprenorphine injection in November 2017. These formulations are available to patients stabilized on buprenorphine and will eliminate the treatment barrier of daily dosing for these patients. (Also see "What are misconceptions about maintenance treatment?")

Opioid Antagonists

Naltrexone is an *opioid antagonist*, which means that it works by blocking the activation of opioid receptors. Instead of controlling withdrawal and cravings, it treats opioid use disorder by preventing any opioid drug from producing rewarding effects such as euphoria. Its use for ongoing opioid use disorder treatment has been somewhat limited because of poor adherence and tolerability by patients. However, in 2010, an injectable, long-acting form of naltrexone (Vivitrol®), originally approved for treating alcohol use disorder, was FDA-approved for treating opioid use disorder. Because its effects last for weeks, Vivitrol® is a good option for patients who do not have ready access to health care or who struggle with taking their medications regularly.

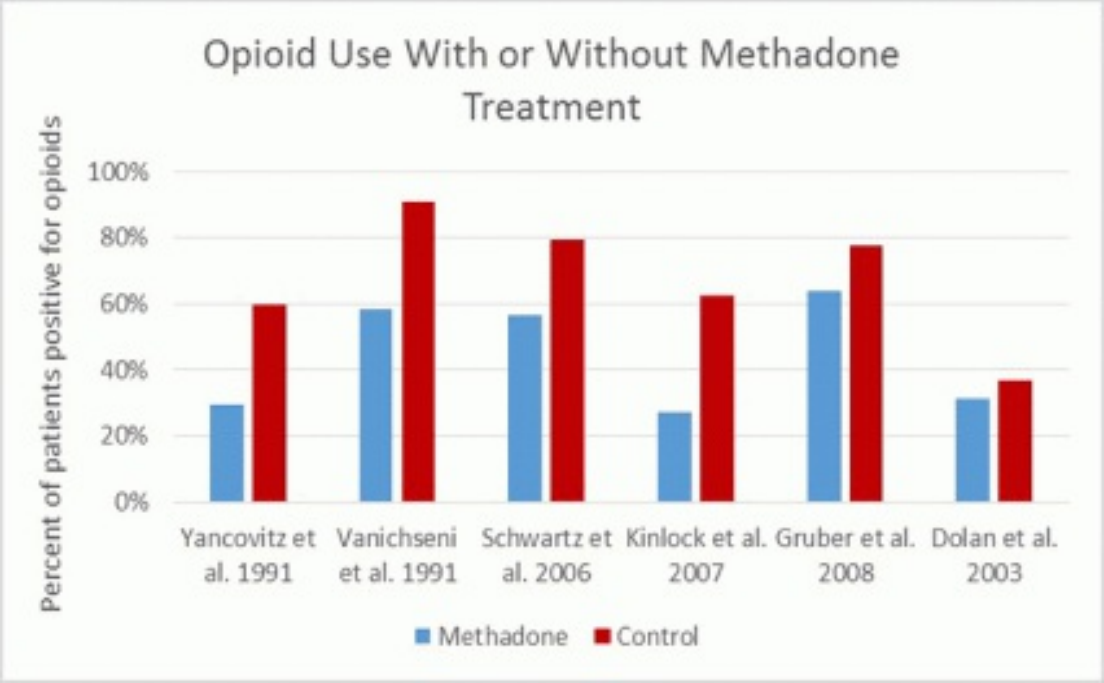
Because each medication works differently, a treatment provider should decide on the optimal medication in consultation with the individual patient and should consider the patient's unique history and circumstances.

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]

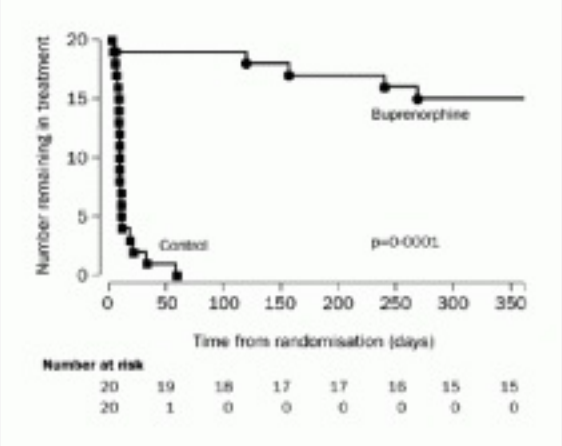
Methadone

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]

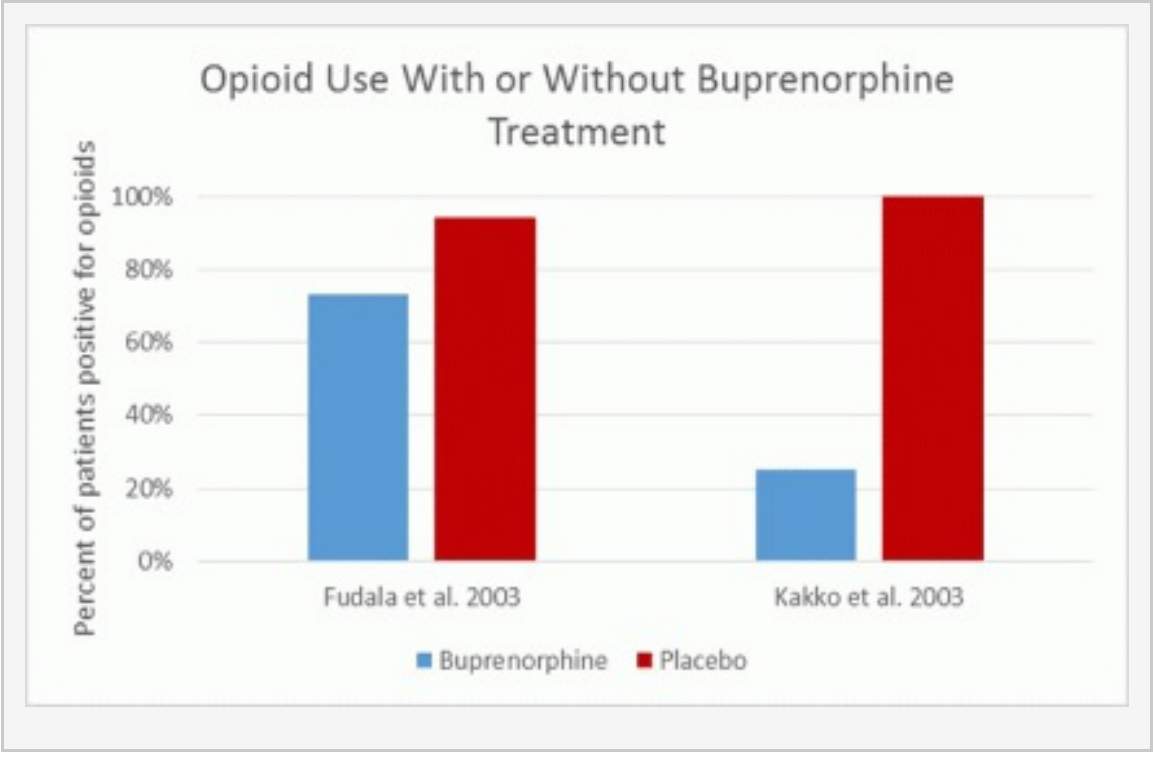


Source: Kakko et al., 2003

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.

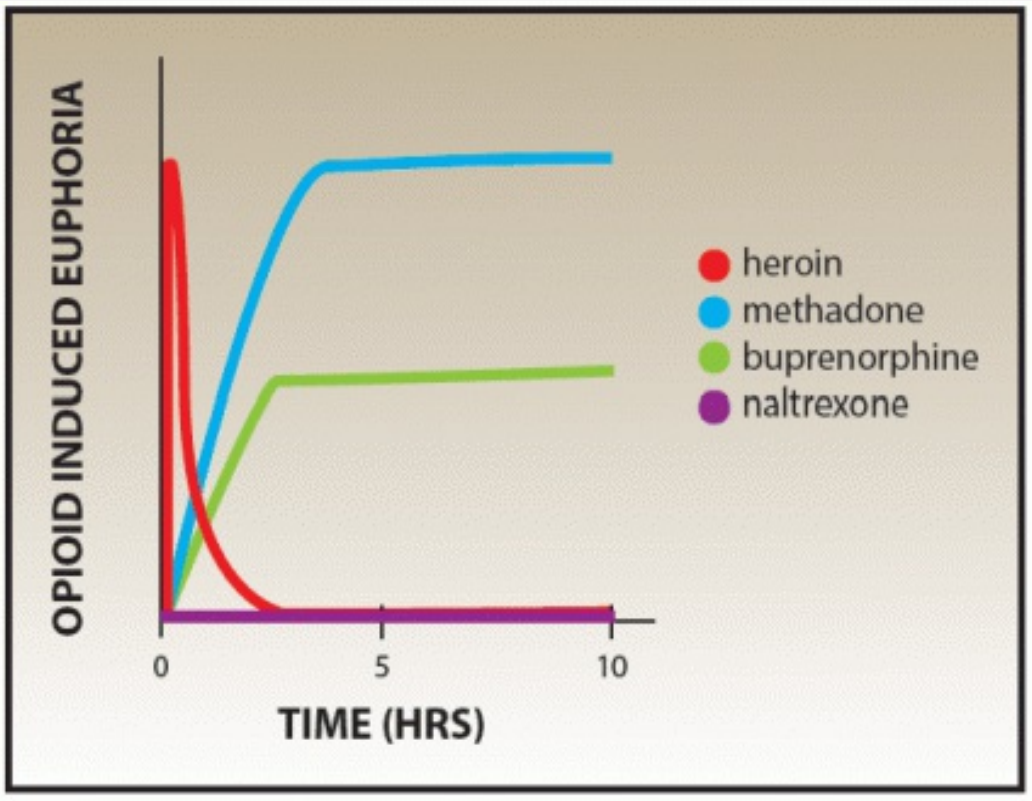
In 2005, methadone and buprenorphine were added to the World Health Organization's list of essential medicines, defined as medicines that are "intended to be available within the context of functioning health care systems at all times in adequate amounts, in the appropriate dosage forms, with assured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



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]

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

What is the treatment need versus the diversion risk for opioid use disorder treatment?

Like other opioid medications, buprenorphine and methadone are sometimes diverted and misused. However, most data suggest that the majority of buprenorphine and methadone misuse (use without a prescription) is for the purpose of controlling withdrawal and cravings for other opioids and not to get high. Among all opioid agonist medications, methadone and buprenorphine together make up 15 percent of diversion reports, while oxycodone and hydrocodone are responsible for 67 percent.[43] Naltrexone, an opioid antagonist used to treat opioid addiction, does not cause euphoric effects and is not a diversion risk.

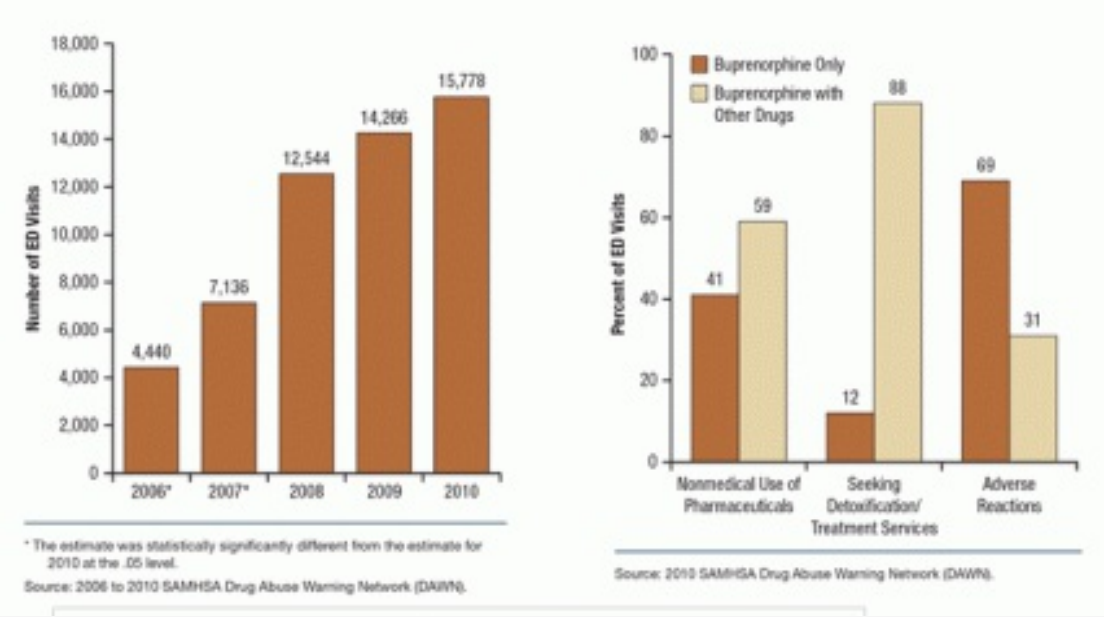
Diversion Risk of Buprenorphine

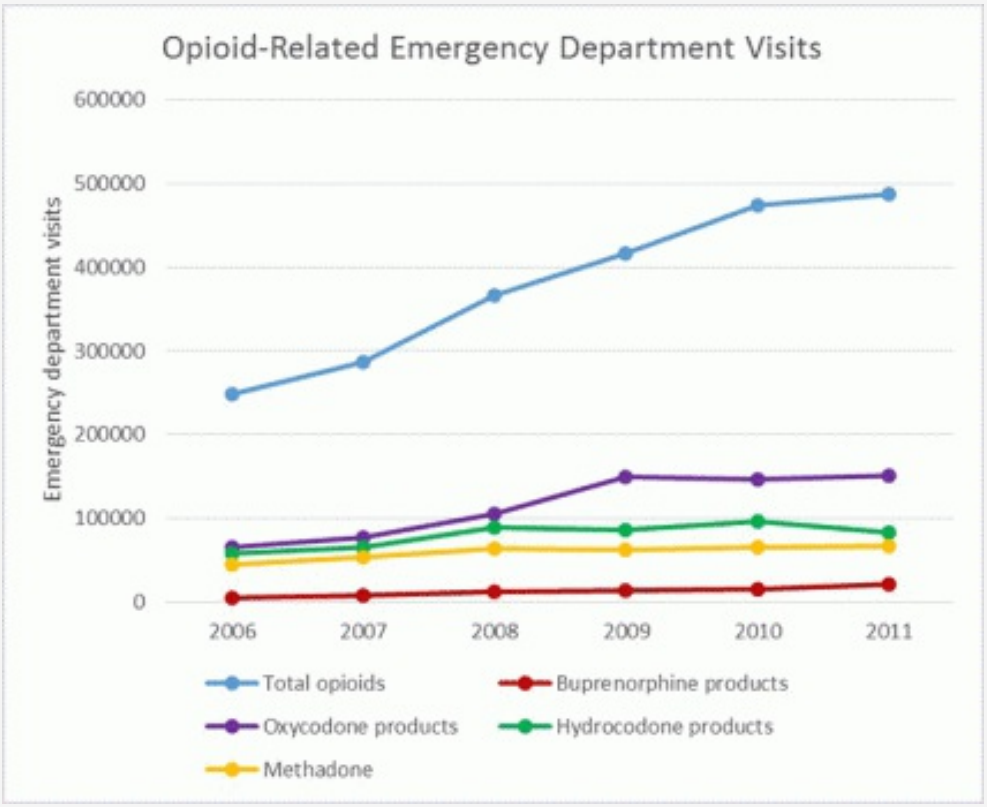
Both buprenorphine and buprenorphine/naloxone formulations can interfere with the effects of full opioid agonists, such as heroin, and can precipitate withdrawal in individuals with opioid dependence. Two U.S. surveys of people with opioid use disorder found that a majority of those who used illicit buprenorphine reported that they used it for therapeutic purposes (i.e., to reduce withdrawal symptoms, reduce heroin use, etc.).[44,45] Ninety-seven percent reported using it to prevent cravings, 90 percent to prevent withdrawal, and 29 percent to save money.[45] Illicit use of buprenorphine decreased as individuals had access to treatment.[45] The minority proportion of people who use buprenorphine illicitly to get high (ranging from 8 to 25 percent)[45,46] has been shown to decrease over time, which could suggest that people abandon this goal after they experience the drug's blunted rewarding effects.[46] Indeed, patients in treatment for opioid use disorder rarely endorse buprenorphine as the primary drug of misuse.[47]

While there is some risk associated with misuse of buprenorphine, the risk of harms, such as fatal overdose, are significantly lower than those of full agonist opioids (oxycodone, hydrocodone, heroin).[39,51] Overdoses and related deaths

do occur but are usually the result of combination with other respiratory depressant drugs such as benzodiazepines or alcohol. Emergency department (ED) visits involving buprenorphine increased from 3,161 in 2005 to 30,135 visits in 2010 as availability of the drug increased (buprenorphine was first approved in 2002); but ED visits for buprenorphine remain significantly less common than those for other opioids.[52] Fifty-two percent, or 15,778 visits (see left bar chart below), were related to nonmedical use in 2010; 59 percent of these visits involved additional drugs (see right bar chart below).[53,54]

Emergency department (ED) visits involving buprenorphine increased as drug availability increased, but ED visits for buprenorphine are far less common than those for other opioids.





Source: CBHSQ, 2011

Diversion Risk of Methadone

Methadone diversion is primarily associated with methadone prescribed for the treatment of pain and not for the treatment of opioid use disorders. Opioid treatment programs are required to maintain and implement a diversion control plan; they typically require patients to come in daily to receive their medication and strictly monitor take-home doses. In addition, evidence suggests that the diversion that does occur is associated with a lack of access to medication.[48] In one survey, giving methadone away was identified as the most common form of methadone diversion,[49] which aligns with other findings that 80 percent of people who report diverting methadone did so to help others who misused substances.[48,50] Among those using illicit methadone, the most common reason was a missed medication pick-up.[50]

Methadone, as a full opioid agonist that is metabolized slowly, poses a greater risk of overdose than buprenorphine. In 2010, 65,945 ED visits involved nonmedical use of methadone.[53] However, methadone that is dispensed for use as a pain reliever, not as an substance use disorder medication, is the main

source of the methadone involved in overdose deaths.[55]

What is the impact of medication for opioid use disorder treatment on HIV/HCV outcomes?

Injection drug use is still a primary driver of the HIV/AIDS epidemic across the world.[56] A recent example is the small community of Austin, Indiana, where 170 new HIV infections occurred in the 8 months between November 2014 and June 2015 among people misusing the prescription opioid pain reliever oxymorphone (Opana®) via injection.[6] People who inject drugs frequently share their needles and other injection equipment, enabling viruses such as HIV and hepatitis C (HCV) to spread between people.

Medications for opioid use disorder treatment can reduce transmission of HIV and HCV by reducing risk behaviors in people who inject drugs and can improve HIV- and HCV-related outcomes by treating those not engaged in injection opioid use who might otherwise transition to injection, linking those with HIV/HCV infection to appropriate treatment,[57,58] and improving adherence to HIV/HCV treatment.[59,60] These improvements depend on accessibility of medications for opioid use disorder to people who need it and coordinating medication delivery with HCV/HIV screening and treatment.

Treatment with methadone or buprenorphine is associated with reduced injection drug use risk behaviors. Meta-analyses have shown a reduction in risk behaviors including a 32 to 69 percent reduction in illicit opioid use, a 20 to 60 percent reduction in injection drug use, and a 25 to 86 percent reduction in sharing of injection equipment.[61,62] Treatment with extended-release naltrexone also reduced HIV risk behaviors compared to placebo.[31]

Methadone and buprenorphine treatment are also associated with lower HCV infection rates in young adults who inject drugs, while other treatments and detoxification alone are not.[63] Methadone treatment is associated with low rates of contracting HCV overall,[64] with mathematical modeling suggesting that it can prevent 22.6 new HCV infections per 100 treated people who engaged in injection drug use, per year.[65,66] Methadone treatment also reduces both HIV

risk behaviors and HIV infection, with better outcomes for people who inject drugs who are in treatment (3.5 percent contracting HIV vs. 22 percent), and better outcomes for longer treatment duration and for continuous (versus interrupted) treatment.[67–69]

A study comparing the effects of methadone and buprenorphine treatment on HIV risk from injection behaviors and HIV risk from sexual behaviors showed equal and significant reductions in risky injection behaviors. Risky sexual behaviors were reduced in both male and female methadone patients but were higher in male patients on buprenorphine.[70]

Mitigating Factors

There are several known interactions between medications used to treat HIV or HCV and both methadone and buprenorphine.[71,72] These could require an adjustment of dosage or revision of the treatment plan, and highlight the need for integrated care. For example, some patients are reluctant to begin highly active antiretroviral therapy (HAART) because of worries that it will interfere with their methadone treatment, so treatment providers should consider revised methadone doses for these patients.[72]

Contracting HCV while on methadone is associated with continued injection drug use.[73] Some studies have shown methadone detoxification alone to be associated with increased rates of contracting HIV, so ongoing treatment with this medication is key to reducing transmission of viral infection.[74]

Possibility of Dual Therapeutic Potential

One recent report demonstrates the potential of buprenorphine to counteract a neuroinflammatory process that is involved in HIV-associated neurocognitive disorders, suggesting that buprenorphine could potentially be simultaneously therapeutic for opioid use disorder and HIV.[75,76] Opioid use disorder medications are also associated with increased adherence to HAART for the treatment of HIV.[59,60] Some providers hesitate to treat HCV in people who inject drugs, but a naltrexone implantation clinic showed rates of sustained virologic response in their patients that were comparable to clinics treating non-injection-

drug-using patients.[77]

How is opioid use disorder treated in the criminal justice system?

Opioid use disorders are highly prevalent among criminal justice populations. According to data from the U.S. Department of Justice, approximately half of state and federal prisoners meet criteria for substance use disorder.[78] Even so, there has been reticence in criminal justice settings to using methadone, buprenorphine, and naltrexone to treat opioid use disorder. In national surveys, utilization of these medications is very low in criminal justice settings, including drug courts,[79] jails,[80] and prisons.[81] Thus, opioid use disorder goes largely untreated during periods of incarceration, and opioid use often resumes after release.

A former inmate's risk of death within the first 2 weeks of release is more than 12 times that of other individuals, with the leading cause of death being a fatal overdose.[82] Overdoses are more common when a person relapses to drug use after a period of abstinence due to loss of tolerance to the drug. One study found a reduction in post-incarceration deaths from overdose among individuals who had received medication for opioid use disorder in correctional facilities.[83] Untreated opioid use disorders also contribute to a return to criminal activity, reincarceration, and risky behavior contributing to the spread of HIV and hepatitis B and C infections (see "What is the impact of medication for opioid use disorder treatment on HIV/HCV outcomes?").[84]

The World Health Organization's Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence recommends that incarcerated individuals should receive adequate healthcare and that opioid withdrawal, agonist maintenance and naltrexone treatment should all be available in prison settings, and prisoners should not be forced to accept any particular treatment."[85]

Many states currently do not offer appropriate access to or utilize medications to treat opioid use disorder among arrestees or inmates even though research has shown many benefits of incorporating medication-assisted treatment into criminal justice treatment programs. Inmates who receive buprenorphine

treatment prior to release are more likely to engage in treatment after their release than inmates who only participate in counseling.[87] Participants who engage in methadone treatment and counseling in prison are more likely to enter community-based methadone treatment centers after their release (68.6 percent) than those receiving only counseling (7.8 percent) or those in counseling and referred to a treatment center (50 percent).[19]

In one study, inmates who began buprenorphine treatment while incarcerated engaged in post-release treatment sooner, averaging 3.9 days after release, compared to 9.2 days for participants referred to treatment post-release.[84] They were also likely to stay in treatment longer if they were initiated in treatment prior to release (20.3 weeks on average) than if they began treatment after their release (13.2 weeks).[84]

Inmates who participate in methadone treatment and counseling while in prison are less likely to test positive for illicit opioids at one month following their release (27.6 percent) compared to those who only receive counseling (62.9 percent) and those who receive counseling and a referral to a treatment center (41 percent).[19]

A randomized controlled trial was published in 2016, comparing prison-initiated extended-release naltrexone (XR-NTX) treatment to standard counseling protocols for prevention of opioid relapse. During the treatment phase, relapse was significantly lower in the group receiving XR-NTX (43 percent vs. 64 percent). The XR-NTX group also experienced no overdose events, while there were seven overdose events in the control group.[88]

A survey of community correction agents' views on using medications to treat opioid use disorder showed that more favorable attitudes toward medication use are associated with greater knowledge about the evidence base for these medications and greater understanding of opioid use disorder as a medical disorder.[89] Organizational linkage between correctional stakeholders and community treatment providers, along with training sessions, can be an effective way to change perceptions and increase knowledge about the efficacy of these medications, and can increase the intent within correctional facilities to refer individuals with opioid use disorder to treatment that incorporates

medications.[86]

A mechanism to reduce recidivism and divert nonviolent offenders from traditional jail and prison settings is the drug treatment court model, which provides treatment services in combination with judicial supervision.[90] Still, resistance to medications persists even in this area of the criminal justice system; a survey published in 2013 reported that 50 percent of drug courts did not allow agonist treatment for opioid use disorder under any circumstances.[79] In 2015, the Office of National Drug Control Policy announced that state drug courts receiving federal grants must not: 1) deny any appropriate and eligible client for the treatment drug court access to the program because of their use of FDA-approved medications that is in accordance with an appropriately authorized prescription; or 2) mandate that a drug court client no longer use medications as part of the conditions of the drug court if such a mandate is inconsistent with a medical practitioner's recommendation or prescription.[91]

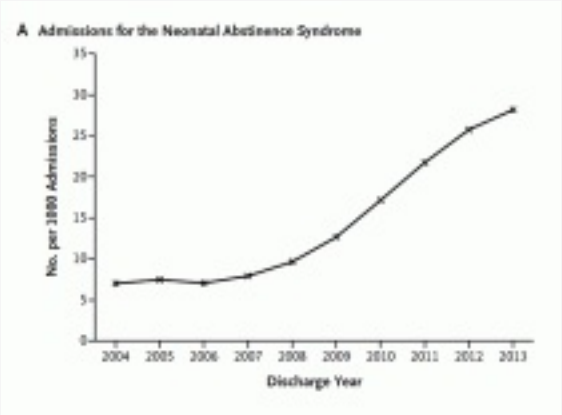
Is medication to treat opioid use disorder available in the military?

Rates of prescription opioid misuse are higher among service members than among civilians.[92] Survey results suggest drug use among returning soldiers is often a coping strategy to treat arousal symptoms of post-traumatic stress disorder.[93] Returning military personnel also experience higher rates of chronic pain and related medical use of opioid pain relievers compared to the civilian population. These data collectively suggest an unmet need for the assessment, management, and treatment of both chronic pain and opioid use disorder in this population.[94]

The Veterans Health Administration (VHA) acknowledges that treatment with opioid agonists (methadone or buprenorphine) is the first-line treatment for opioid use disorder and recommends it for all opioid-dependent patients. Notably, a 2015 revision of treatment guidelines for the U.S. Department of Veteran Affairs and U.S. Department of Defense shifted toward allowing these medications as a treatment option for active duty military members.[95] Still, only about a quarter of patients with an opioid use disorder treated at VHA facilities receive medication.[96] Barriers to opioid agonist medication among VHA providers include lack of perceived patient interest, stigma toward the patient population, and lack of education about opioid agonist treatment.[97]

In the past, lack of insurance coverage for opioid agonist medications was a barrier for use among active duty military; however, as of 2013, TRICARE included coverage for these medications, and a 2016 modification of TRICARE regulation included provisions for expanded coverage of opioid use disorder treatment.[98] This expanded coverage removed annual and lifetime limitations on substance use disorder treatment allowed for office-based opioid treatment, and established opioid treatment programs as a newly recognized category of institutional provider under TRICARE.

What treatment is available for pregnant mothers and their babies?



Source: Tolia et al., 2015

Paralleling the large recent increases in opioid use, use disorder, and overdose, the incidence of babies born dependent on opioids (neonatal abstinence syndrome, or NAS) as a result of the mother's opioid use during pregnancy has also greatly increased.[5] Incidence of NAS rose nearly fivefold between 2000 and 2012;[4] this increase was associated with increases in the prescription of opioids to pregnant women for pain, which doubled between 1995 and 2009.[99,100]

Untreated opioid use disorder during pregnancy can have devastating effects on the fetus. The fluctuating levels of opioids in the blood of mothers misusing opioids expose the fetus to repeated periods of withdrawal,[101] which can also harm the function of the placenta and increase the risk of:

- fetal growth restriction[101]
- placental abruption[101]
- preterm labor[101]
- fetal convulsions[101]
- intrauterine passage of meconium[101]

- fetal death[102]

In addition to these direct physical effects, other risks to the fetus include:

- untreated maternal infections such as HIV[103]
- malnutrition and poor prenatal care[104]
- dangers conferred by drug-seeking lifestyle, including violence and incarceration[102,104]

Methadone and Buprenorphine as the Standard of Care for Opioid Use Disorder in Pregnancy

To lessen the negative effects of opioid dependence on the fetus, treatment with methadone has been used for pregnant women with opioid use disorder since the 1970s and has been recognized as the standard of care since 1998.[102,103] Recent evidence, however, suggests that buprenorphine may be an even better treatment option.[105]

Both methadone and buprenorphine treatment during pregnancy:

- stabilize fetal levels of opioids, reducing repeated prenatal withdrawal[101,106]
- improve neonatal outcomes[104]
- increase maternal HIV treatment to reduce the likelihood of transmitting the virus to the fetus[102–104]
- link mothers to better prenatal care[102,104]

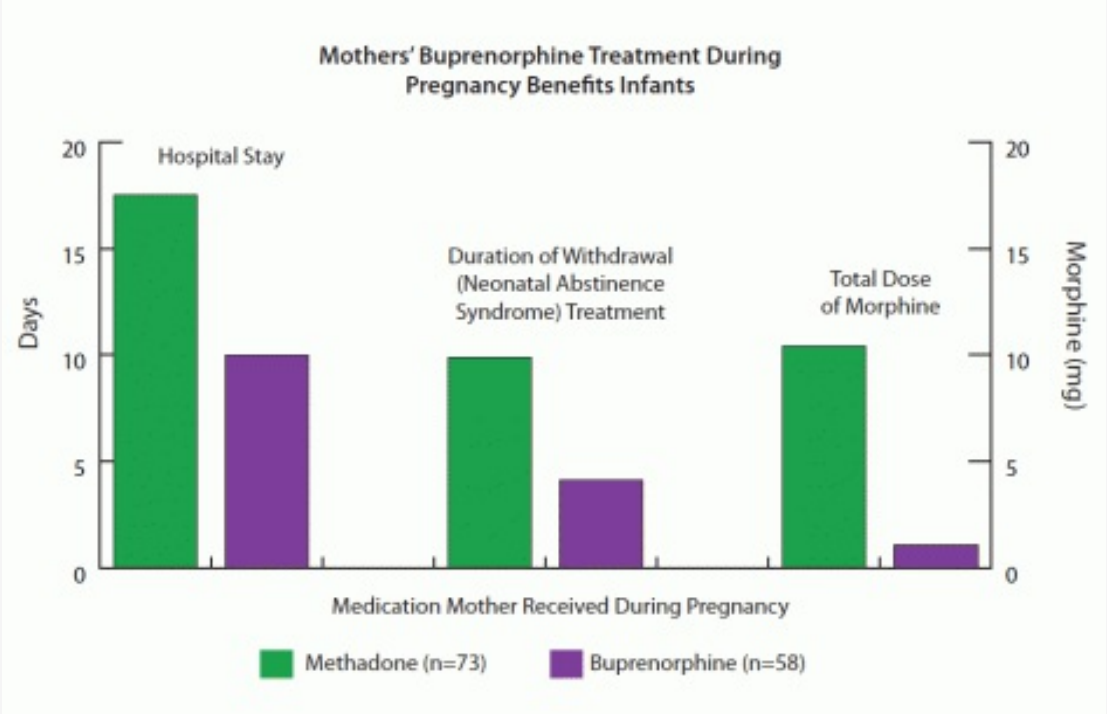
A meta-analysis showed that, compared to single-dose methadone treatment, buprenorphine resulted in:

- 10 percent lower incidence of NAS
- shorter neonatal treatment time (an average of 8.4 days shorter)

- lower amount of morphine used for NAS treatment (an average of 3.6 mg lower)
- higher gestational age, weight, and head circumference at birth[105]

Data from the NIDA-funded *Maternal Opioid Treatment: Human Experimental Research* study show similar benefits of buprenorphine.[107] Still, methadone is associated with higher treatment retention than buprenorphine.[105] Divided dosing with methadone has been explored as a way to reduce fetal exposure to withdrawal periods, and recent data show low levels of NAS in babies born to mothers treated with divided doses of methadone.[108] Larger comparison studies are needed to determine if split methadone dosing for opioid use disorders in pregnancy is associated with better outcomes.

NAS still occurs in babies whose mothers have received buprenorphine or methadone, but it is less severe than it would be in the absence of treatment.[109] Research does not support reducing maternal methadone dose to avoid NAS, as this may promote increased illicit drug use, resulting in increased risk to the fetus.[101]



Source: Jones et al., 2010

How Much Does Opioid Treatment Cost?

Although the price for opioid treatment may vary based on a number of factors, recent preliminary cost estimates from the U.S. Department of Defense for treatment in a certified opioid treatment program (OTP) provide a reasonable basis for comparison:[98]

- methadone treatment, including medication and integrated psychosocial and medical support services (assumes daily visits): $126.00 per week or $6,552.00 per year
- buprenorphine for a stable patient provided in a certified OTP, including medication and twice-weekly visits: $115.00 per week or $5,980.00 per year
- naltrexone provided in an OTP, including drug, drug administration, and related services: $1,176.50 per month or $14,112.00 per year

To put these costs into context, it is useful to compare them with the costs of other conditions. According to the Agency for Healthcare Research and Quality, annual expenditures for individuals who received health care are $3,560.00 for those with diabetes mellitus and $5,624.00 for kidney disease.[110]

It is also important to remember the costs associated with untreated opioid use disorders, including costs associated with:

- criminal justice
- treating babies born dependent on opioids
- greater transmission of infectious diseases
- treating overdoses
- injuries associated with intoxication (e.g., drugged driving)
- lost productivity

The amount paid for treatment of substance use disorders is only a small portion of the costs these disorders impose on society. An analysis suggested that the total costs of prescription opioid use disorders and overdoses in the United States was $78 billion in 2013. Of that, only 3.6 percent, or about $2.8 billion, was for treatment.[111]

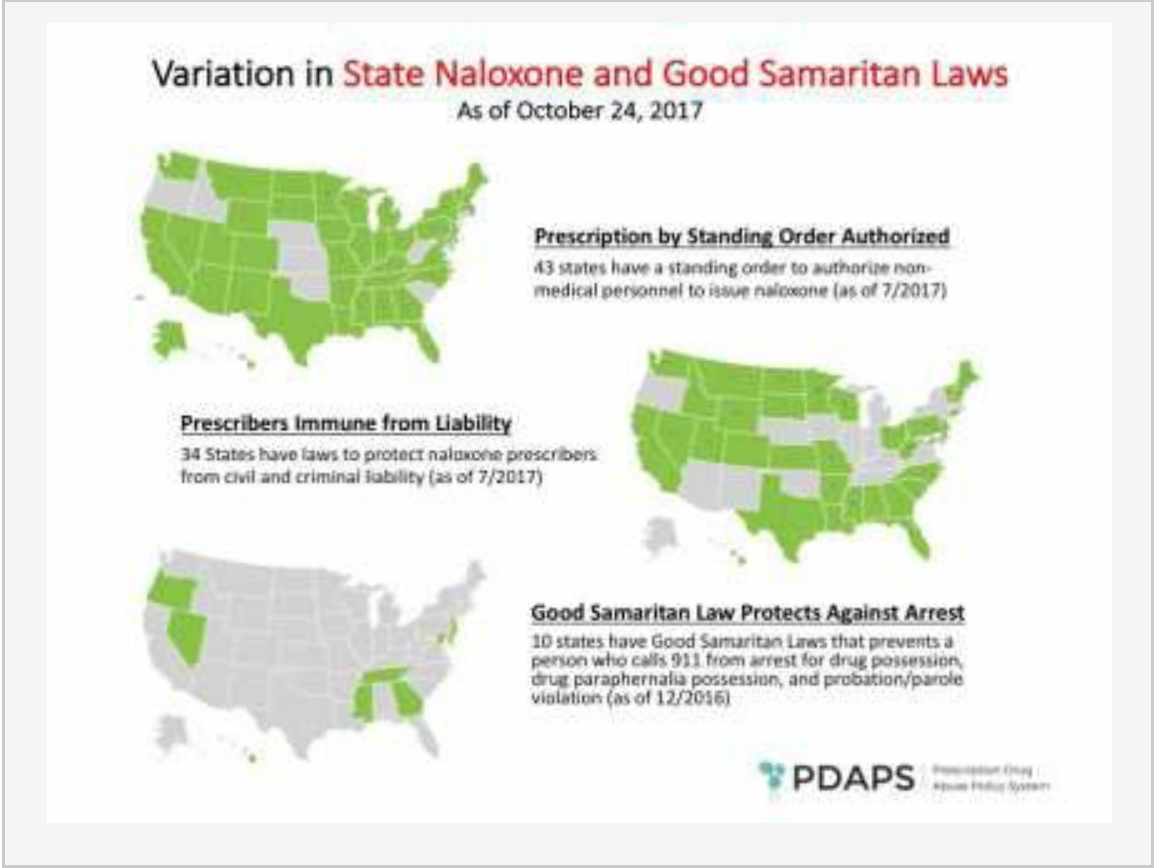
Is naloxone accessible?

Naloxone is an opioid antagonist that can reverse an opioid overdose. Naloxone access increased between 2010 and 2014, with:[8]

- more than three times the number of local sites providing naloxone (from 188 to 644)
- nearly three times the number of laypersons provided naloxone kits (from 53,032 to 152,283)
- a 94 percent increase in states (from 16 to 30), including Washington, DC, with at least one organization providing naloxone
- more than 2.5 times the number of overdose reversals reported (from 10,171 to 26,463)

Naloxone prescriptions dispensed from retail pharmacies increased nearly twelvefold between the fourth quarter of 2013 and the second quarter of 2015.[112]

Most states have passed laws to widen the availability to naloxone for family, friends, and other potential bystanders of overdose.



Naloxone has become widely used by emergency medical providers, with all 50 states and the District of Columbia, Guam, and Puerto Rico certifying and approving emergency medical service personnel at the paramedic level to administer naloxone. One step further, emergency medical technicians (EMTs) were explicitly permitted to administer naloxone in 12 of these 53 jurisdictions (23 percent—California, Colorado, District of Columbia, Massachusetts, Maryland, New Mexico, North Carolina, Ohio, Oklahoma, Rhode Island, Virginia, and Vermont) as of November 2013. Because non-paramedic EMTs are typically the first and sometimes only source of emergency care, providing authorization and training for them to administer naloxone is a promising strategy to reduce overdose deaths.[113]

After a naloxone training session, a majority of police officers reported that it would not be difficult to use naloxone at the scene of an overdose (89.7 percent) and that it was important that other officers be trained to use naloxone (82.9 percent).[114]

Effects of Naloxone Distribution

Overdose education and naloxone distribution (OEND) has been shown to increase the reversal of potentially fatal overdoses; one study showed opioid overdose death rates to be 27 to 46 percent lower in communities where OEND was implemented.[115] Among 4,926 people who used substances and participated in OEND in Massachusetts, 373 (7.6 percent) reported administering naloxone during an overdose rescue, with few differences in behavior between trained and untrained overdose rescuers.[116] A naloxone distribution study in San Francisco reported that 11 percent of participants used naloxone during an overdose; of 399 overdose events where naloxone was used, 89 percent were reversed.[117] Brief education is sufficient to improve comfort and competence in recognizing and managing overdose.[118] Prospective studies are needed to determine the optimal level of training and whether naloxone rescue kits can meet the standard for becoming available over the counter.[116]

In a probabilistic analysis, naloxone distribution programs were shown to prevent overdose deaths, increase quality-adjusted life years (QALYs) and be highly cost-effective. Naloxone distribution was predicted to prevent 6 percent of overdose deaths, 1 for every 227 naloxone kits distributed. Cost effectiveness, under markedly conservative predictions, was measured to be $14,000.00 per QALY, well within the standard favorable range of cost-benefit ratios (under $50,000.00 per QALY).[119]

Critics of naloxone distribution have claimed that it could lead to an increase in risky opioid use, but a study in Massachusetts showed rates of opioid-related emergency department visits and hospital admissions were not significantly different in communities with low or high implementation of OEND programs.[115]

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