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Buprenorphine and the Opioid Crisis: A Primer for Congress

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SUMMARY

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Buprenorphine and the Opioid Crisis: A Primer for Congress

Buprenorphine is a medication used to treat adults addicted to opioids (it is also used in the treatment of pain). Buprenorphine's effectiveness, safety, and availability in the treatment of opioid addiction are of considerable interest to policymakers seeking to address the ongoing opioid epidemic in the United States. Congressional actions taken in recent years to address the opioid crisis have included attempts to increase access to buprenorphine. This report addresses questions policymakers may have about the effectiveness of buprenorphine, the demand for buprenorphine, and access to buprenorphine.

Effectiveness of Buprenorphine

Overall, buprenorphine appears to be an effective medication for treatment of opioid dependence. When compared to other treatments for opioid addiction such as methadone, buprenorphine appeared equally as effective in promoting abstinence from drug use. Buprenorphine does not seem to retain individuals in treatment as well as methadone, however, though the reasons for this remain unclear. The research on buprenorphine suggests that it works better at higher daily doses (16mg or higher). The higher the dose of buprenorphine and the longer people used the drug, the more likely they were to remain in treatment, abstain from opioid use, and successfully complete treatment. Preliminary data suggest that buprenorphine may be safer and more cost effective than methadone; comparison of the safety and costs of buprenorphine with other treatments awaits further research.

Demand for Buprenorphine

Admissions to substance abuse treatment facilities involving prescription opioids nearly quadrupled between 2002 and 2014; in 2015 18% of individuals in need of treatment for opioid use disorders received it. In 2016, one-fifth (21.1%) of those with any opioid use disorder received specialty treatment, including 37.5% of those with heroin use disorder and 17.5% of those with prescription pain reliever use disorders. Despite marked increases in opioid abuse, deaths attributed to opioids, and related hospital admissions, the majority of individuals in need of treatment do not receive it.

Access to Buprenorphine

Buprenorphine is regulated differently when used to treat opioid use disorder than when used to treat pain. The Controlled Substances Act (CSA) limits who may prescribe (or administer or dispense) buprenorphine to treat opioid use disorders, and the circumstances under which they may do so. These limits have implications for how patients gain access to buprenorphine and how they pay for buprenorphine. Buprenorphine comes in different formulations, and these modes of administration have implications for how patients gain access to buprenorphine and how they pay for buprenorphine.

As of May 1, 2018, the Substance Abuse and Mental Health Services Administration has implemented capacity for health providers to treat with buprenorphine almost 3,000,000 patients. Nonetheless, access to substance abuse treatment such as buprenorphine has not kept pace with the mounting rates of opioid addiction in the United States.

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Introduction

Buprenorphine is one of three medications currently used in medication-assisted treatment of opioid use disorders. As such, buprenorphine's effectiveness, safety, and availability are of considerable interest to policymakers seeking to address the ongoing opioid crisis in the United States.[1] During the 115th Congress, committees have held hearings on opioid-related topics such as implementation of the Comprehensive Addiction and Recovery Act of 2016 (CARA, P.L. 114-198),[2] the effects of the opioid crisis on families,[3] and opioid use among veterans.[4] Members have introduced more than 150 bills related to opioids.[5] Congressional actions taken in recent years to address the opioid crisis have included attempts to increase access to buprenorphine.

Opioids and Medication-Assisted Treatment

Heroin and some prescription painkillers (such as morphine and oxycodone) belong to the class of drugs known as opioids, which act on receptors in the brain important in regulating pain and emotion. Natural opioids (sometimes referred to as "opiates") are derived from the opium poppy plant, while synthetic opioids are made entirely in a laboratory. Semi-synthetic opioids are synthesized from naturally occurring opium products, such as morphine and codeine.[6] Opioids have significant abuse liability and high potential for overdose.[7] Use of opioids can cause physical dependence, which results in uncomfortable and potentially dangerous withdrawal symptoms during periods of abstinence.

Medication-assisted treatment (MAT) is the combined use of medication and other services (such as counseling) to treat addiction. Three medications are currently used in MAT for opioid addiction: methadone, buprenorphine, and naltrexone.[8] Naloxone (e.g., Narcan®), a medication used to reverse opioid overdose, is not used to treat opioid use disorders.

Methadone and buprenorphine are both opioids; their use to treat opioid use disorders is often called *opioid agonist therapy*, *opioid substitution therapy*, or *opioid replacement therapy*. Methadone or buprenorphine may be used both in the short term to mitigate the immediate withdrawal symptoms associated with discontinuing use of the opioid of abuse and over extended periods to maintain abstinence and prevent relapse.

Naltrexone is not an opioid and carries no known risk of abuse or overdose. Naltrexone blocks the receptors in the brain that opioids activate, thereby preventing opioids from taking effect.

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[1] See also CRS Report R44987, *The Opioid Epidemic and Federal Efforts to Address It: Frequently Asked Questions*.

[2] U.S. Congress, House Committee on Energy and Commerce, *Federal Efforts to Combat the Opioid Crisis: A Status Update on CARA and Other Initiatives*, 115th Cong., 1st sess., October 25, 2017.

[3] U.S. Congress, Senate Special Committee on Aging, *Grandparents to the Rescue: Raising Grandchildren in the Opioid Crisis and Beyond*, 115th Cong., 1st sess., March 21, 2017.

[4] U.S. Congress, Senate Committee on Appropriations, Subcommittee on Military Construction and Veterans Affairs, and Related Agencies, *Hearing on VA Efforts to Prevent and Combat Opioid Over-Medication*, 115th Cong., 1st sess., November 15, 2017.

[5] Results of a search on congress.gov for bills using the word "opioid" in the 115th Congress conducted on May 31, 2018.

[6] U.S. Department of Justice, Drug Enforcement Administration, *Drugs of Abuse*, A DEA Resource Guide: 2017 Edition, 2017, pp. 38-47, https://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf.

[7] U.S. Department of Health and Human Services (HHS), National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA), *Buprenorphine: Treatment for Opiate Addiction Right in the Doctor's Office*, Topics in Brief, Bethesda, MD, August 2006.

[8] A new medication, Lucemyra™ (lofexidine hydrochloride) was approved in May 2018 for "the mitigation of withdrawal symptoms to facilitate abrupt discontinuation of opioids." However, this drug is only approved for short-term use (<14 days) and "is not a treatment for opioid use disorder (OUD)" according to the U.S. Food & Drug Administration (https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm607884.htm).

Among the U.S. population aged 12 or older, an estimated 11.8 million (4.4%) used heroin, misused prescription pain relievers, or did both in 2016.[9] This includes at least 2 million people (0.8% of the U.S. population aged 12 or older) who met full diagnostic criteria for an opioid use disorder.[10] A minority (21.1%) of those with any opioid use disorder received specialty treatment, including 37.5% of those with heroin use disorder and 17.5% of those with prescription pain reliever use disorders.[11]

Opioid Use Terminology

The terminology used to describe opioid use can be a source of confusion. The label *opioid use disorder* is the official diagnostic term for "a problematic pattern of opioid use leading to clinically significant impairment or distress," as defined in the current edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Prior editions of the DSM distinguished between *abuse* (less severe) and *dependence* (more severe), a distinction that is no longer used clinically but that still appears in research literature.

In common use, the term *opioid abuse* is used interchangeably with terms indicating a condition severe enough to warrant treatment (such as *opioid use disorder* or *opioid addiction*) as well as with terms indicating any use of prescription opioids other than as prescribed (such as *opioid misuse* or *non-medical use of prescription opioids*).[12]

The term *diversion*, which is used more often in a crime policy context than in a health policy context, refers to the movement of opioids (or other drugs) from the legitimate medical supply chain to illicit uses.

This report draws on numerous sources of information, which use all of these terms.

About This Report

This CRS report attempts to answer questions policymakers may have about the following topics:

- the effectiveness of buprenorphine as a treatment for opioid use disorder,
- the demand for buprenorphine as a treatment for opioid use disorder, and
- access to buprenorphine as a treatment for opioid use disorder.

The information about effectiveness in this report is based on a systematic review of research on buprenorphine. A systematic review is a comprehensive report collating all of the relevant empirical evidence on a specific topic. A more thorough explanation of the methodology for the systematic review of the literature, including all citations on which much of the information in this report is based, is available in the **Appendix**. The report focuses on buprenorphine as a treatment for opioid use disorder for adults. It does not provide a comprehensive overview of opioid abuse as a public health or criminal justice issue.

[9] HHS, Substance Abuse and Mental Health Services Administration (SAMHSA), *SAMHSA Shares Latest Behavioral Health Data, Including Opioid Misuse*, October 12, 2017, https://newsletter.samhsa.gov/2017/10/12/samhsa-new-data-mental-health-substance-use-including-opioids/. The data on heroin-related deaths reported in this source are drawn from HHS, Centers for Disease Control and Prevention (CDC), National Center for Health Statistics, National Vital Statistics System. All other data are drawn from SAMHSA's National Survey on Drug Use and Health (NSDUH).

[10] HHS, SAMHSA, *Key Substance Use and Mental Health Indicators in the United States: Results from the 2016 National Survey on Drug Use and Health*, HHS Publication No. SMA 17-5044, NSDUH Series H-52, 2017, https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.htm.

[11] HHS, SAMHSA, *SAMHSA Shares Latest Behavioral Health Data, Including Opioid Misuse*, October 12, 2017.

[12] Kathleen Brady, Jenna McCauley, and Sudie Back, "Prescription Opioid Misuse, Abuse, and Treatment in the United States: An Update," *American Journal of Psychiatry*, vol. 173, no. 1 (January 1, 2016), pp. 18-26.

Effectiveness of Buprenorphine

Whether buprenorphine (or any medication) is effective is not a simple "yes" or "no" answer, for several reasons. Buprenorphine comes in different formulations, each of which has been evaluated separately. Studies may define effectiveness in different ways and may compare buprenorphine to different treatments (e.g., another medication or a non-pharmacological treatment). Also, effectiveness is weighed against safety risks. Finally, buprenorphine may be more effective for some people, or in some circumstances, than in others. The following sections address these topics.

What is buprenorphine?

Buprenorphine is a partial opioid agonist, meaning it binds to the same opioid receptors in the brain as full opioid agonists (such as heroin or methadone) but activates the receptors less strongly. Similar to methadone, buprenorphine can reduce the cravings and withdrawal symptoms that often accompany discontinuation of the opioid of abuse, but buprenorphine does so without producing the same euphoria or "high."[13] As a partial agonist, buprenorphine offers less potential for abuse and has a lower overdose risk than methadone.[14]

Buprenorphine was first approved by the Food and Drug Administration (FDA) as a pain reliever in 1981.[15] Research on buprenorphine as a pain analgesic showed mixed effectiveness,[16] though the drug did demonstrate lower rates of abuse than other opioid pain medications such as oxycodone.[17] More than 20 years after it was first approved to treat pain, buprenorphine was approved by FDA as a treatment for opioid use disorder, under the trade names Subutex® and Suboxone®.[18] The difference between the two products is that Suboxone® combines buprenorphine with naloxone—an opioid antagonist that blocks opioid receptors from being activated and thereby reduces the risk of abuse. Since 2002, FDA has approved other forms of

[13] U.S. Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse, *Medications to Treat Opioid Addiction*, Research Report Series, Updated May 2017, pp. 1-44, https://www.drugabuse.gov/publications/research-reports/medications-to-treat-opioid-addiction/overview.

[14] Johan Kakko, Leif Gronbladh, and Kerstin Dybrandt Svanborg et al., "A Stepped Care Strategy Using Buprenorphine and Methadone Versus Conventional Methadone Maintenance in Heroin Dependence: A Randomized Controlled Trial," *American Journal of Psychiatry*, vol. 164, no. 5 (2007), pp. 797-803.

[15] HHS, FDA, *Approval Date(s) and History, Letters, Labels, Reviews for NDA 018401*, Buprenex, December 29, 1981, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=018401.

[16] See, for example, Mia Schmidt-Hansen, Nathan Bromham, and Mark Taubert et al., "Buprenorphine for Treating Cancer Pain," *Cochrane Database for Systematic Reviews*, March 31, 2015 retrieved from http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD009596.pub4/full; Kelly Yan Chen, Lucy Chen, and Jianren Mao, "Buprenorphine-Naloxone Therapy in Pain Management," *Anesthesiology*, vol. 120, no. 5 (May 2014), pp. 1262-1274; and Joyce Cote and Lori Montgomery, "Sublingual Buprenorphine as an Analgesic in Chronic Pain: A Systematic Review," *Pain Medicine*, vol. 15, no. 7 (2014), pp.1171-1178.

[17] U.S. Department of Justice, Drug Enforcement Administration, Office of Diversion Control, *National Forensic Laboratory Information System (NFLIS)*, 2013 Annual Report, Springfield, VA, August 2014, pp. 1-32, https://www.nflis.deadiversion.usdoj.gov/DesktopModules/ReportDownloads/Reports/NFLIS2013AR.pdf.

[18] HHS, FDA, *Approval Date(s) and History, Letters, Labels, Reviews for NDA 020732*, Subutex, October 8, 2002, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020732; and HHS, FDA, *Approval Date(s) and History, Letters, Labels, Reviews for NDA 020733*, Suboxone, October 8, 2002, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020733.

buprenorphine (with and without naloxone) for the treatment of opioid use disorders, as shown in **Table 1**.[19]

Table 1. Buprenorphine Formulations Approved to Treat Opioid Use Disorder

Brand Name (generic)	Form	Year Approved
Subutex® (buprenorphine)	Sublingual Tablet	2002
Suboxone® (buprenorphine + naloxone)	Sublingual Tablet/Film	2002/2010
Zubsolv® (buprenorphine + naloxone)	Sublingual Tablet	2013
Bunavail® (buprenorphine + naloxone)	Buccal Film	2014
Probuphine® (buprenorphine)	Subdermal Implant	2016
Sublocade™ (buprenorphine)	Injectable (Subcutaneous)	2017

Source: U.S. Department of Health and Human Services, U.S. Food & Drug Administration, Drugs@FDA: FDA Approved Drug Products, updated January 9, 2018, https://www.accessdata.fda.gov/scripts/cder/daf/.

Notes: Sublingual tablets and films are placed under the tongue to dissolve. Likewise, buccal films dissolve when placed inside the cheek. Both sublingual and buccal formulations are commonly administered daily. Subdermal implants—which are inserted under the skin—last for six months. Similarly, injectable buprenorphine is administered as a subcutaneous (under the skin) injection monthly.

Is buprenorphine an effective treatment for opioid abuse?

Overall, research on buprenorphine has found it to be an effective medication for maintenance treatment of opioid dependence. A 2014 review of buprenorphine efficacy trials conducted by Cochrane[20] found that buprenorphine can be useful in helping individuals discontinue opioid drug use and maintain abstinence. The efficacy of buprenorphine in reducing opioid use, however, appeared to be dependent on several factors. For example, buprenorphine effectiveness seems to be dose dependent. It was only found to be superior to placebo[21] when used at high doses. Buprenorphine was most effective when used at 16mg daily doses or higher, compared to low or medium doses of 15mg or less. The standard of care for buprenorphine treatment currently includes "flexible dosing" which involves individual clinicians determining dose based on each patient, rather than fixed dosing consisting of predetermined dosage regimens. Other factors influencing the effectiveness of buprenorphine include primary opioid of use (i.e., prescription pain medication versus heroin) and length of buprenorphine treatment (see questions below for further elaboration).

[19] Federal law regulates buprenorphine differently depending on whether it is being used to treat opioid use disorders or pain; see CRS In Focus IF10219, *Opioid Treatment Programs and Related Federal Regulations*.

[20] Richard P. Mattick, Courtney Breen, and Jo Kimber et al., *Buprenorphine Maintenance versus Placebo or Methadone Maintenance for Opioid Dependence*, The Cochrane Collaboration, Cochrane Database of Systematic Reviews 2014 Issue 2. Art. No.: CD002207, 2014. The Cochrane Collaboration is an independent not-for-profit organization of health researchers and professionals who provide summary reports of medical research findings. Cochrane collaborators primarily conduct systematic reviews that summarize and evaluate current scientific evidence on a variety of health care interventions.

[21] In clinical research a placebo consists of an inactive substance containing minimal or no medication used as a control to determine the effects of the drug in question.

How does buprenorphine compare to other treatments for opioid abuse?

When compared to methadone (the most common treatment for opioid abuse), buprenorphine appears to be equally as effective in promoting abstinence from drug use. Buprenorphine offers several benefits compared to methadone. Buprenorphine has less potential for abuse and overdose than methadone, and some research suggests it may be more cost effective. Abrupt discontinuation of buprenorphine leads to milder withdrawal symptoms than methadone. Individuals using buprenorphine, however, appear to drop out of treatment at higher rates than those using methadone. **Table 2** describes various opioid treatment modalities.

Table 2. Opioid Treatment Options

Treatment	Description
Buprenorphine	A synthetic opioid medication that acts as a partial agonist at opioid receptors. It does not produce the euphoria and sedation caused by full opioid agonists but is able to reduce or eliminate withdrawal symptoms and carries a low risk of overdose. It is available by prescription from qualified health providers who have obtained Drug Addiction Treatment Act of 2000 (DATA) waivers.[22]
Buprenorphine/Naloxone	A combination drug formulation of buprenorphine, a partial opioid agonist, and naloxone, a full antagonist used to block the effects of other opioids. Naloxone is included to discourage misuse of buprenorphine. The naloxone is only activated if the buprenorphine tablet is crushed and injected. Once activated it blocks any euphoric effects and instead produces mild discomfort.[a]
Methadone	A long-acting synthetic opioid agonist medication that can prevent withdrawal symptoms and reduce craving in opioid-addicted individuals. It is available through specially licensed opioid treatment programs or methadone maintenance programs.[b]
Naltrexone	A synthetic opioid antagonist that blocks opioids from binding to their receptors and thereby prevents any euphoric effect. It is typically taken orally and is commonly prescribed in outpatient medical settings. It has no potential for abuse and is not addictive.
Psychosocial Treatment	Behavioral counseling typically provided in a one-on-one or small group setting in which a trained provider helps engage individuals in substance abuse treatment to modify their attitudes and behaviors related to drug use.

a. Suzuki, Joji, *Buprenorphine Formulations: A Practical Summary for Clinicians*, Psychopharmacology Institute, Clinical Psychopharmacology Education for Prescribers CME/CE Program, September 11, 2017, https://psychopharmacologyinstitute.com/substance-use-disorders/buprenorphine-formulations-practical-summary-clinicians/.

b. U.S. Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse, *Principles of Drug Addiction Treatment: A Research-Based Guide (Third Edition)*, NIH Publication No. 12-4180, December 2012, https://www.drugabuse.gov/publications/principles-drug-addiction-treatment-research-based-guide-third-edition. Last updated on December 1, 2012.

How well does buprenorphine maintain people in treatment?

Treatment retention describes the rate in which individuals remain in substance abuse treatment. Retention is often essential to achieve the goals of the treatment, namely abstinence from drug use. Retention in treatment for individuals using buprenorphine increases linearly as both the dose

[22] Title XXXV of P.L. 106-310.

of buprenorphine and length of time spent weaning off the medication increase.[23] Put simply, research implies that as the dose of buprenorphine increases, retention in treatment improves. Similarly, with a longer period of tapering off the medication comes greater retention in the treatment. Taper length for buprenorphine is also associated with greater rates of abstinence from other opioids and successful completion of treatment. Therefore, the higher the dose of buprenorphine and the longer individuals are on the medication, the more likely they are to remain in treatment, abstain from opioid use, and successfully complete treatment.

Studies seem to indicate that methadone is better able to retain participants in treatment than buprenorphine, but it remains unclear why this is the case. It may be that buprenorphine, being a partial opioid agonist, is less satisfying than methadone because it does not produce a comparable euphoric effect. Also, buprenorphine may not typically be increased to effective doses quickly enough, resulting in more attrition early in treatment. It is also possible that buprenorphine does not retain people as well because mild withdrawal symptoms from the opioid of abuse may still be present for many patients while using the medication. Being only a partial opioid agonist, buprenorphine is also easier to discontinue without withdrawal symptoms of its own, which may make dropping out of treatment less difficult.

Efficacy vs. Effectiveness

Clinicians and policymakers often distinguish between the *efficacy* and the *effectiveness* of an intervention. Efficacy studies examine outcomes of an intervention under ideal circumstances. Often this equates to tightly controlled settings with specific populations—methods designed to isolate the effect of the treatment being studied. Effectiveness trials on the other hand measure the degree of beneficial effect in "real world" settings.[24] Effectiveness studies are based on conditions of routine clinical practice. They record outcomes essential for clinical and policy-relevant decisions. Participants in these trials often better reflect the targeted population, and the conditions are closer to actual clinical practice. While this design can make examining the effects of the treatment more challenging, it usually provides a more authentic assessment of how an intervention will perform in the real world. Retention and compliance with treatment are important outcomes in effectiveness trials, because poor compliance or low retention rates can render an efficacious treatment ineffective.

Are there any risks to buprenorphine?

Buprenorphine is an opioid itself and therefore carries a risk for addiction and overdose. As a partial opioid agonist, the euphoric effects of buprenorphine are low compared to full agonists like heroin, fentanyl, morphine, or methadone. Therefore, the abuse potential for buprenorphine is generally considered to be less than that of full opioid agonists.[25] Overdoses caused solely by buprenorphine are rare, with most overdoses occurring when the medication is used at the same time as other drugs such as benzodiazepines or other sedatives.[26] Other adverse events associated with buprenorphine diverted intravenously, such as the transmission of communicable diseases, are similar to those of other misused injected substances. When buprenorphine is combined with

[23] See **Table A-2** in the **Appendix** for list of citations.

[24] U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality (AHRQ), *Criteria for Distinguishing Effectiveness From Efficacy Trials in Systematic Reviews*, Technical Review Number 12, Rockville, MD, April 2006.

[25] Michael A. Yokell, Nickolas Zaller, and Traci Green et al., "Buprenorphine and Buprenorphine/Naloxone Diversion, Misuse, and Illicit Use: An International Review," *Current Drug Abuse Review*, vol. 4, no. 1 (March 2011), pp. 28-41.

[26] Ibid., and Leslie Amass, Vilma Pukeleviciene, and Emilis Subata et al., "Bringing Buprenorphine-Naloxone Detoxification to Community Treatment providers: The NIDA Clinical Trials Network Field Experience," *The American Journal on Addiction*, vol. 13, no. S1 (May-June 2004), pp. S42-S66.

naloxone, an opioid antagonist, it discourages misuse via injection which may contribute to buprenorphine's lower rates of abuse and overdose.

How safe is buprenorphine compared to methadone?

Preliminary evidence on buprenorphine suggests it may be a safer treatment compared to methadone. Buprenorphine has less abuse potential and appears to result in fewer fatalities than methadone. In one study, patients taking buprenorphine experienced half as many ambulatory care visits compared to those taking methadone, suggesting buprenorphine use was associated with fewer incidents endangering health and safety.[27] Only a few studies have compared mortality rates between buprenorphine and methadone treatments; however, existing data suggest that methadone is associated with a higher potential for mortality in the first few weeks of treatment. Research indicates that rates of opioid overdose with buprenorphine are lower than those associated with methadone.[28] Data from one study conducted in France showed that death rates attributable to methadone may be as much as three times greater than that of buprenorphine,[29] though other studies found no significant differences.[30] Comparison of the safety of these two treatments in the United States awaits further research.

Does buprenorphine work for everyone?

There appear to be differences in successful outcomes of treatment for opioid addiction based on whether an individual was primarily abusing prescription pain medication or heroin.[31] When using buprenorphine for addiction treatment, heroin users seem to have less positive outcomes compared to individuals who abuse prescription painkillers. While both groups are retained in treatment at similar rates, those abusing pain medication demonstrate greater improvement when using buprenorphine. Also, several of the studies noted that more than ever before, heroin users began their drug abuse with prescription opioid medications. The effectiveness of buprenorphine treatment, therefore, may depend in part on whether an individual with opioid use disorder has transitioned from misusing prescription opioids to using heroin.

Demand for Buprenorphine

Buprenorphine is one of three medications currently used to treat adults addicted to opioids. The precipitous rise in opioid misuse in the last decade and increasing financial burden of this epidemic highlight the need for effective treatments. Despite marked increases in opioid abuse,

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[27] Paul Barnett, "Comparison of Costs and Utilization Among Buprenorphine and Methadone Patients," *Addiction*, vol. 104, no. 6 (June 2009), pp. 982-992.

[28] Yokell et al., *Buprenorphine and Buprenorphine/Naloxone Diversion, Misuse, and Illicit Use*, 2011, and Pascal Kintz, "Deaths Involving Buprenorphine: A Compendium of French Cases," *Forensic Science International*, vol. 121, no. 1-2 (September 2001), pp. 65-69.

[29] Marc Auriacombe, Pascale Franques, and Jean Tignol, "Deaths Attributable to Methadone vs Buprenorphine in France," *JAMA*, vol. 285, no. 1 (January 3, 2001), p. 45.

[30] Yih-Ing Hser, Elizabeth Evans, and David Huang et al., "Long-term Outcomes after Randomization to Buprenorphine/Naloxone versus Methadone in A Multi-site Trial," *Addiction*, vol. 111, no. 4 (April 2016), pp. 695-705 and Marc Larochelle, Dana Bernson, and Thomas Land et al., "Medication for Opioid Use Disorder After Nonfatal Opioid Overdose and Association With Mortality," *Annals of Internal Medicine*, June 19, 2018, http://annals.org/aim/fullarticle/2684924/medication-opioid-use-disorder-after-nonfatal-opioid-overdose-association-mortality.

[31] See **Table A-2** in the **Appendix** for list of citations.

deaths attributed to opioids, and related hospital admissions, the majority of individuals in need of treatment do not receive it.

What are the costs of the opioid epidemic?

Opioid overdose deaths have increased significantly in the past 15 years (**Figure 1**). In 2015, an estimated 33,091 Americans died of opioid-related overdoses, almost three times as many as in 2002 around the advent of the epidemic.[32] In 2016, that number increased to 42,249.[33] Almost a third of patients prescribed opioid pain relievers misuse these medications, and an estimated 1 in 10 become addicted.[34] Misuse of opioid pain medications remains high (**Figure 2**). In 2016, an estimated 11.8 million people aged 12 and older misused opioids, including 11.5 million misusers of pain relievers and 948,000 heroin users.[35] While the majority of individuals who misuse prescription opioids will not progress to heroin use, they are 13 times more likely to use heroin in their lifetime than those who use pain medication as prescribed.[36]

[32] U.S. Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse, *Overdose Death Rates*, Updated September 2017, https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates.

[33] Centers for Disease Control and Prevention, *Opioid Overdose*, Drug Overdose Death Data, https://www.cdc.gov/drugoverdose/data/statedeaths.html. Last updated December 19, 2017,

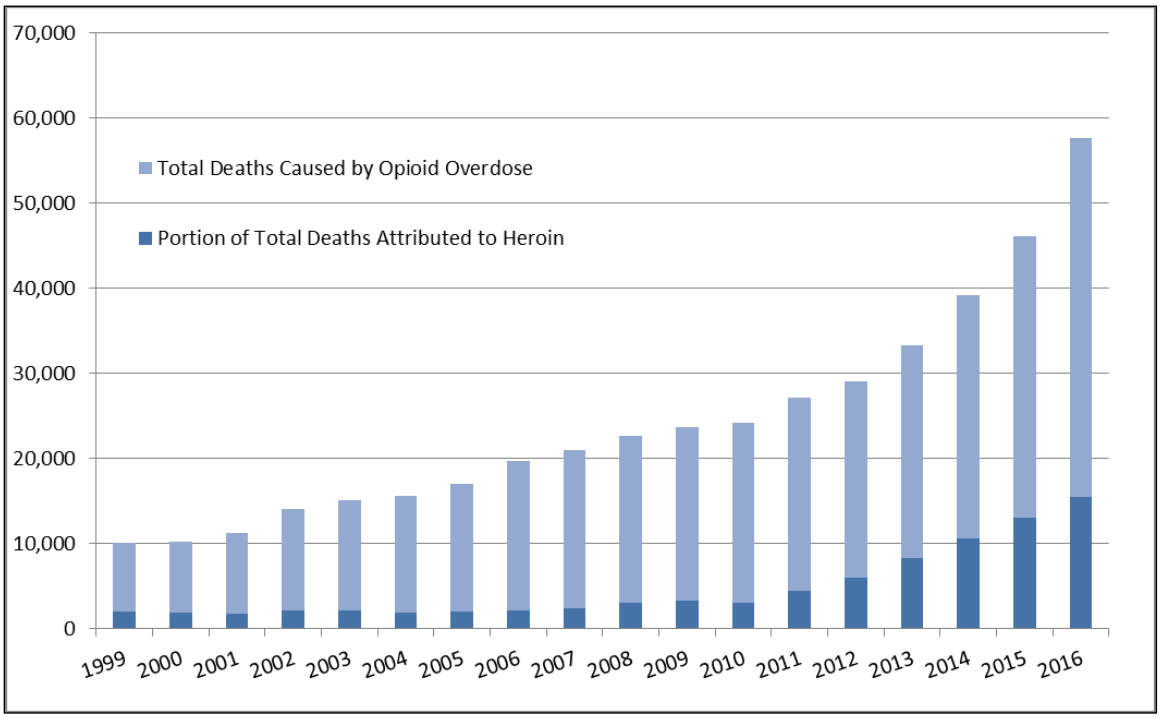
[34] Kevin Vowles, Mindy McEntee, and Peter Siyahhan Julnes et al., "Rates of Opioid Misuse, Abuse, and Addiction in Chronic Pain: A Systematic Review and Data Synthesis," *Pain*, vol. 156, no. 4 (April 2015), pp. 569-576.

[35] Some respondents fell into both categories, which is why the total (11.8 million) is lower than the two categories combined. See HHS, SAMHSA, *Results from the 2016 National Survey on Drug Use and Health: Detailed Tables*, September 2017. See Tables 1.1A and 1.27A at https://www.samhsa.gov/data.

[36] Magdalena Cerda, Julian Santaella, and Brandon Marshall et al., "Nonmedical Prescription Opioid Use in Childhood and Early Adolescence Predicts Transitions to Heroin Use in Young Adulthood: A National Study," *Journal of Pediatrics*, vol. 167, no. 3 (September 2015), pp. 605-612.

Figure 1. Annual U.S. Opioid Overdose Deaths (1999-2016)

Number of Deaths from All Opioid Drugs and Heroin



Source: U.S. Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse using data from CDC WONDER.

Notes: Data are based on death certificates for U.S. residents collected by the Centers for Disease Control and Prevention, National Center on Health Statistics, available in the CDC WONDER database. Each death certificate identifies a single underlying cause of death and demographic data. For more information about CDC Wonder, see https://wonder.cdc.gov/.

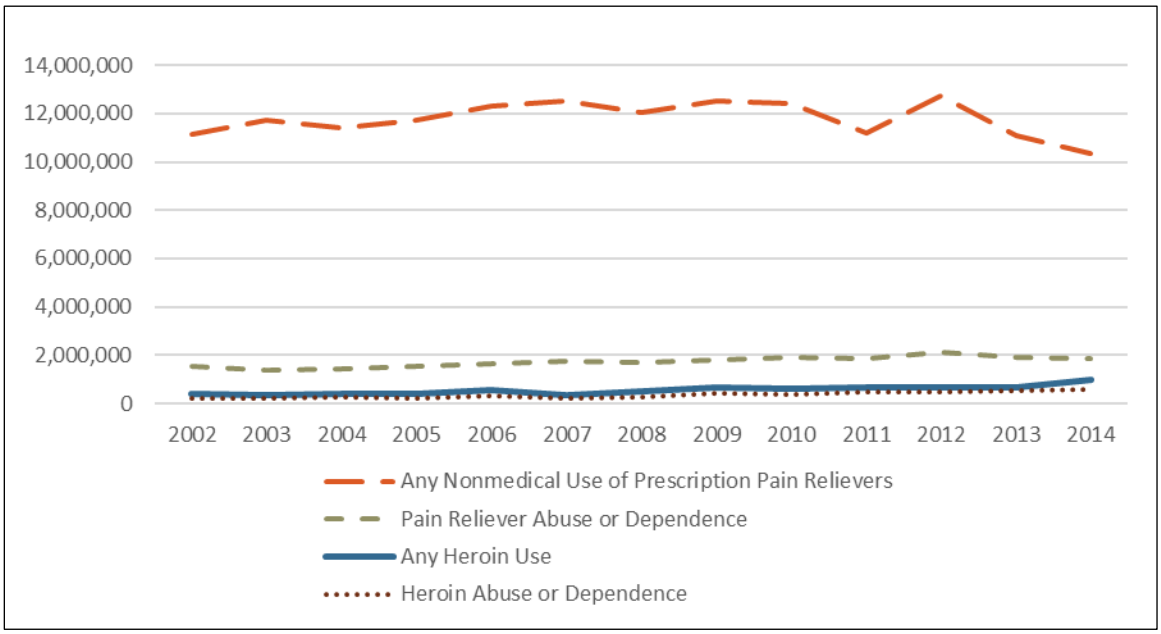
The financial costs of this epidemic have been substantial. The combined economic influence of the opioid epidemic (healthcare, labor, and criminal justice costs) was estimated at $92 billion in 2016, an increase of 67% from a decade ago.[37] Another analysis, which included the cost of opioid overdose fatalities, estimated the cost of the opioid epidemic at $504 billion in 2015.[38]

[37] Sean Murphy and Daniel Polsky, "Economic Evaluations of Opioid Use Disorder Interventions," *Pharmacoeconomics*, vol. 34, no. 9 (2016), pp. 863-887.

[38] White House Council of Economic Advisors, *The Underestimated Cost of the Opioid Crisis*, 2017, accessed at https://www.whitehouse.gov/briefings-statements/cea-report-underestimated-cost-opioid-crisis/.

Figure 2. Annual U.S. Opioid Use and Abuse (2002-2014)

Number of Individuals Reporting Use or Abuse of Prescription Pain Medication and Heroin



Source: Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, National Survey on Drug Use and Health (NSDUH) 2002-2015 accessed from the Substance Abuse and Mental Health Data Archive (SAMHDA) available at https://www.datafiles.samhsa.gov/

Notes: NSDUH is an annual nationwide survey of approximately 70,000 people age 12 and older in the United States. NSDUH employs a stratified multistage area probability sample designed to be representative of the nation as a whole. More information can be found at https://nsduhweb.rti.org/respweb/homepage.cfm

Access to Buprenorphine

Buprenorphine is regulated differently when used for opioid use disorder than when used for pain. The Controlled Substances Act (CSA)[39] limits who may prescribe (or administer or dispense) buprenorphine to treat opioid use disorder, and the circumstances under which they may do so. These limits have implications for how patients gain access to buprenorphine and how they pay for buprenorphine. The different forms of buprenorphine (e.g., implants vs. sublingual, etc.) also have implications for how patients gain access to buprenorphine and how they pay for it.

Who can prescribe buprenorphine?

Buprenorphine may be used to treat opioid use disorder in two settings: (1) within a federally certified opioid treatment program (OTP) and (2) outside an OTP pursuant to a waiver.[40] When used within an OTP, buprenorphine is administered or dispensed on site, rather than prescribed. That is, a patient does not receive a prescription to be filled at a retail pharmacy; instead, a patient receives the buprenorphine at the OTP, necessitating nearly daily visits to the OTP unless the

[39] 21 U.S.C. §§801 et seq.

[40] Federal law regulates buprenorphine differently depending on whether it is being used to treat opioid use disorders (as opposed to pain).

patient is using injectable or implantable forms of buprenorphine which can last up to several months.

A physician or other practitioner (i.e., physician assistant or nurse practitioner) may obtain a waiver to administer, dispense, or prescribe buprenorphine outside an OTP. This is commonly known as a DATA waiver, drawing its name from the law that established the waiver authority: the Drug Addiction Treatment Act of 2000 (DATA 2000).[41] Under DATA 2000, the requirement for separate Drug Enforcement Administration (DEA) registration as an OTP may be waived if both the medication and the physician meet specified conditions. To date, buprenorphine is the only medication to meet the conditions for the DATA waiver.

To qualify for a waiver, a physician must notify the Health and Human Services (HHS) Secretary of the intent to use buprenorphine to treat opioid use disorders and must certify that he or she

- is licensed under state law with expertise as evidenced by certification, training, or experience;
- can refer patients for appropriate counseling and other services; and
- will comply with a limit on the number of patients.

The patient limit is 30 during the first year, may increase to 100 after one year,[42] and may increase to 275 after two years (under certain conditions).[43]

Under a temporary authority (through October 1, 2021), qualifying nurse practitioners and physician assistants may obtain DATA waivers.[44]

Why are there limits on the number of patients that can be prescribed buprenorphine by a single provider?

In the 1990s, the makers of buprenorphine argued successfully that opioid substitution therapy with buprenorphine need not be limited to OTPs, primarily because the safety profile of buprenorphine compared favorably to that of methadone.[45] Congress remained convinced that opioid substitution therapy with buprenorphine should be subject to restrictions beyond those applicable when the same opioid medications are used to treat pain. The patient limit is one such restriction.

As originally enacted, DATA 2000 limited the number of patients a qualified physician could treat for opioid addiction using buprenorphine to 30. This patient limit remains in place for a physician during the first year he or she has a waiver; however, the law has been amended to allow a DATA-waived physician to increase the patient limit to 100 patients after one year.[46]

Pursuant to a statutory provision authorizing the HHS Secretary to raise the patient limit through rulemaking, in March 2016, HHS issued a notice of proposed rulemaking that would have

[41] Title XXXV of P.L. 106-310.

[42] Office of National Drug Control Policy Reauthorization Act of 2006 (P.L. 109-469).

[43] 21 C.F.R. Part 8 Subpart F.

[44] P.L. 114-198 §303.

[45] Jerome Jaffe and Charles O'Keefe, "From Morphine Clinics to Buprenorphine: Regulating Opioid Agonist Treatment of Addiction in the United States," *Drug and Alcohol Dependence*, vol. 70 (2003), pp. S3-S11.

[46] Office of National Drug Control Policy Reauthorization Act of 2006 (P.L. 109-469).

increased the patient limit to 200.[47] The proposed higher patient limit was intended to significantly increase patient capacity for practitioners qualified to prescribe at this level while also "ensuring quality of care and minimizing diversion."[48]

In response to public comments arguing that raising the patient limit to 200 was not likely to make a significant impact on addressing the treatment gap, HHS issued a final rule setting the patient limit at 275 after two years (subject to certain conditions).[49] Using survey data, HHS found that an OTP could manage, on average, 262 to 334 patients at any given time. HHS set the new DATA waiver patient limit near the low end of this range, a conservative estimate of the number of patients who could be treated by a single physician in "a high-quality, evidence-based manner that minimizes the risk of diversion."[50]

How has use of buprenorphine to treat opioid addiction changed?

As opioid abuse rates have increased, the federal government has made efforts to address this epidemic. Both Congress and the Administration have implemented policies intended to increase access to buprenorphine, such as changes to the DATA waivers described above.[51] Policy efforts to address the opioid epidemic have corresponded with increased treatment availability. Since 2003, treatment capacity has increased and continues to rise. The number of OTPs offering buprenorphine increased from 121 (11% of all OTPs) in 2003 to 779 (58% of all OTPs) in 2015.[52] The number of non-OTP substance abuse treatment facilities (non-OTPs) offering buprenorphine increased from 620 (5% of all non-OTPs) in 2003 to 2,625 (21% of all non-OTPs) in 2015.[53] In total, the proportion of facilities (either OTP or non-OTP) providing buprenorphine treatment increased from 11% in 2006 to 27% of all facilities in 2016.[54] This does not include practitioners with office-based (as opposed to facility-based) practices.

[47] HHS, SAMHSA, "Medication Assisted Treatment for Opioid Use Disorders," 81 *Federal Register* 17639-17662, March 30, 2016.

[48] HHS, SAMHSA, "Medication Assisted Treatment for Opioid Use Disorders," 81 *Federal Register* 44711-44739, July 8, 2016.

[49] Ibid.

[50] Ibid.

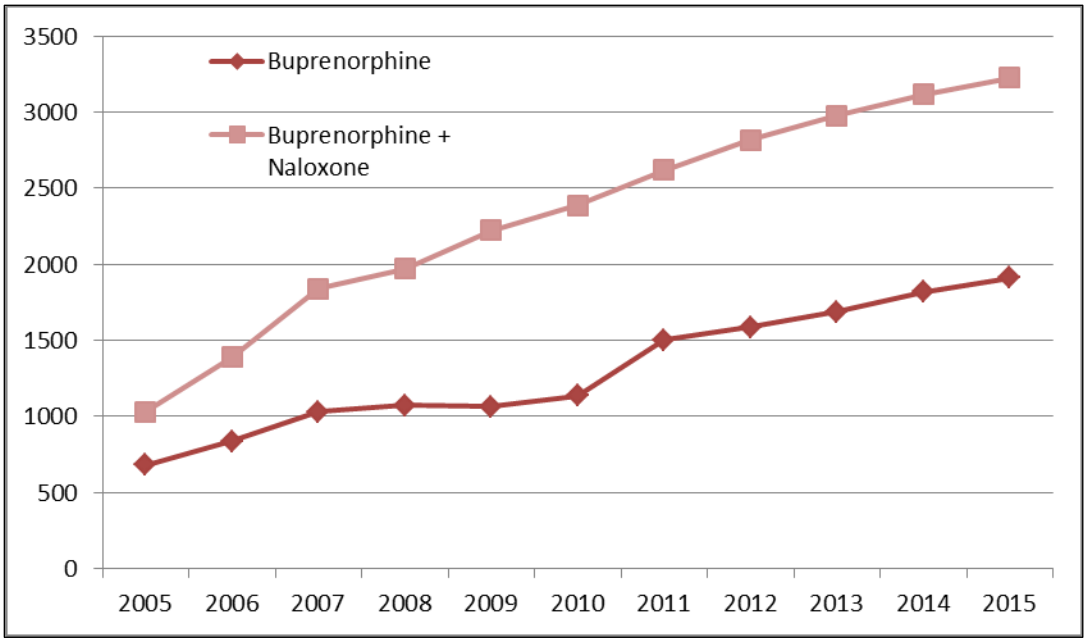
[51] Congress has authorized and funded grant programs aimed at increasing access to treatment for opioid addiction, including but not limited to medication-assisted treatment. For example, Section 1003 of the 21st Century Cures Act (P.L. 114-255, enacted in December 2016) authorizes the State Targeted Response to the Opioid Crisis grant program, which supports states in addressing the opioid abuse crisis. Another example is Section 103 of the Comprehensive Addiction and Recovery Act (P.L. 114-198) which authorized funding for Community-based Coalition Enhancement Grants to Address Local Drug Crises.

[52] U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, *Trends in the Use of Methadone, Buprenorphine, and Extended-Release Naltrexone at Substance Abuse Treatment Facilities: 2003-2015 (Update)*, The CBHSQ Report: August 22, 2017, p. 3.

[53] Ibid.

[54] U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, *National Survey of Substance Abuse Treatment Services (N-SSATS): 2016. Data on Substance Abuse Treatment Facilities*, BHSIS Series S-93, HHS Publication No. (SMA) 17-5039, Rockville, MD, 2017, p. 13.

Figure 3. U.S. Treatment Facilities Providing Buprenorphine (2005-2015)



Source: Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, National Survey of Substance Abuse Treatment Services (N-SSATS), 2003 to 2015

Notes: N-SSATS is an annual census of facilities providing substance abuse treatment in the United States. More information can be found at https://www.datafiles.samhsa.gov/study-series/national-survey-substance-abuse-treatment-services-n-ssats-nid13519.

The cumulative number of DATA-waived providers has increased also. The number of DATA-waived physicians with a 30-patient limit increased from 1,800 in 2003 to 16,095 by 2012, and those with a 100-patient limit expanded from 1,937 in 2007 to 6,103 in 2012. By 2012, the maximum number of patients who could be treated with buprenorphine in the United States was 1,093,150, a rate of 420.3 per 100,000 people aged 12 years and older.[55] Due to this increase in DATA-waivers for buprenorphine treatment, nearly 3.5 times as many patients could be treated with buprenorphine in 2012 as were receiving methadone in 2012.

The Substance Abuse and Mental Health Services Administration (SAMHSA), which oversees the buprenorphine waiver program, provides daily updates on the number of DATA waivers. As of May 1, 2018, the number of DATA-waived providers with a 30-patient limit exceeded 36,000 and those with a 100-patient limit totaled almost 10,000.[56] This provides the capacity for almost 3,000,000 patients to be treated with buprenorphine.[57]

Despite this increase, access to substance abuse treatment such as buprenorphine has not kept pace with the mounting rates of opioid addiction in the United States.[58] In 2012, the difference between the number of people experiencing opioid dependence and the combined methadone and

[56] HHS, SAMHSA, *Medication-Assisted Treatment: Physician and Program Data*, Last updated November 28, 2017, https://www.samhsa.gov/medication-assisted-treatment/physician-program-data.

[57] SAMHSA, *Physician and Program Data*.

[58] Christopher Jones, Melisa Campopiano, and Grant Baldwin et al., "National and State Treatment Need and Capacity for Opioid Agonist Medication-Assisted Treatment," *American Journal of Public Health*, vol. 105, no. 8 (August 2015), pp. e55-363.

buprenorphine treatment capacity in the U.S. was nearly one million.[59] Forty-eight states and the District of Columbia had higher rates of past-year opioid abuse than capacity for buprenorphine treatment in 2012. During that year, 82% of federally certified opioid treatment programs (OTPs) reported operating at 80% or greater capacity.[60]

An Alternative Approach to Buprenorphine Policy: France

In France, all registered medical doctors have been allowed to prescribe buprenorphine without any special education or licensing since 1995. This is in contrast to the strategies used by other countries using buprenorphine to treat opioid abuse, such as the United States and other European nations. The French example provides a test case for a more relaxed regulatory framework for this treatment, including possible benefits and drawbacks to this approach. Results from studies on this model show that allowing physicians to prescribe without much regulation led to a rapid increase in the number of opioid-dependent users receiving buprenorphine treatment in primary care.[61] In France, an estimated one half of all heroin users receive buprenorphine treatment from the 1 in 5 primary care providers who actively prescribe this medication. Studies have also reported a significant nation-wide decrease in heroin use following the introduction of buprenorphine in 1995.[62] Along with increased treatment utilization, the profusion of availability and absence of requirements for special training appears to also have resulted in increased misuse of the medication. Intravenous diversion of buprenorphine may occur in up to 20% of buprenorphine patients in France.[63] Overdoses involving buprenorphine remain rare, however, and are usually seen when the drug is combined with a sedative—a possible consequence of inappropriate prescribing practices. Overall, total opioid overdose deaths in France have declined substantially since buprenorphine's introduction.

The French approach to buprenorphine policy has both potential advantages and drawbacks. On one hand, making this medication easier to access has increased the number of individuals in treatment, to the point where most of those who need treatment receive it. On the other hand, fewer regulations may have increased clinically inappropriate prescribing practices and subsequent diversion, and possibly contributed to overdoses when buprenorphine was combined with sedatives. An increase in buprenorphine misuse may have actually contributed to a lower overall overdose mortality rate, likely from displacing use from other, more fatal opioids, such as heroin and fentanyl.

Admissions to substance abuse treatment facilities involving prescription opioids nearly quadrupled between 2002 and 2014; in 2015 18% of individuals in need of treatment for opioid use disorders received it.[64] In 2016, one-fifth (21.1%) of those with any opioid use disorder received specialty treatment, including 37.5% of those with heroin use disorder and 17.5% of those with prescription pain reliever use disorders.[65] A study conducted in Massachusetts found

[59] Ibid.

[60] Ibid.

[61] M. Fatseas and Marc Auriacombe, "Why Buprenorphine Is So Successful in Treating Opiate Addiction in France," *Current Psychiatry Reports*, vol. 9 (2007), pp. 358-364.

[62] Benedicte Lepere, Laurent Gourarier, and Mario Sanchez et al., "Reduction in the Number of Lethal Heroin Overdoses in France since 1994. Focus on Substitution Treatments." *Annales de Medecine Interne*, vol. 152, no. 3 (April 2001), pp. IS5-12.

[63] Fatseas & Auriacombe, "Why Buprenorphine Is So Successful," 2007.

[64] U.S. Department of Health and Human Services, Substance Abuse and Mental Health Service Administration, *Trends in the Use of Methadone, Buprenorphine, and Extended-release Naltrexone at Substance Abuse Treatment Facilities: 2003-2015 (Update)*, The CBHSQ Report: August 22, 2017, https://www.samhsa.gov/data/sites/default/files/report_3192/ShortReport-3192.pdf; and NIDA, *Medications to Treat Opioid Addiction*, p. 3.

[65] HHS, SAMHSA, *SAMHSA Shares Latest Behavioral Health Data, Including Opioid Misuse*, October 12, 2017, https://newsletter.samhsa.gov/2017/10/12/samhsa-new-data-mental-health-substance-use-including-opioids/. The data on heroin-related deaths reported in this source is drawn from HHS, Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS), National Vital Statistics System (NVSS). All other data are drawn from SAMHSA's National Survey on Drug Use and Health (NSDUH).

that of individuals recently hospitalized for a nonfatal opioid-related overdose, less than one-third received any medication-assisted treatment in the 12 months following the overdose.[66]

Geography may be relevant in understanding the treatment discrepancy: where services are located may be more important than the capacity for treatment in addressing the gap between need and availability. Other factors affecting the treatment gap besides location of services may include health insurance coverage, reimbursement for treatment services, transportation, stigma, and motivation for recovery among others.

How much does buprenorphine cost?

The cost of any prescribed medication is influenced by the pharmaceutical manufacturer, the insurer, the health plan or prescribing clinic, and the retail pharmacies that dispense the medication.[67] It is difficult, therefore, to identify a precise figure for the cost of buprenorphine. The Department of Defense (DOD) and the National Institute for Drug Abuse (NIDA) have estimated the following costs:

- methadone treatment: $126 per week ($6,552 per year)[68]
- buprenorphine treatment: $115 per week ($5,980 per year)[69]
- naltrexone: $1,176.50 per month ($14,122 per year)[70]

Most of the research comparing the costs of medication-assisted treatments has found similar results, suggesting buprenorphine may be cheaper than other medications. Some studies, however, have been inconclusive or suggest the opposite. In one study conducted at a Veterans Affairs (VA) medical center, the average cost of care for six months of buprenorphine treatment was $11,597.[71] The costs associated with methadone over that same time period were $14,921. The costs were not significantly different in subsequent months after the first six months of treatment, however. Indirect costs in that same study were also higher for the methadone group, which had twice as many ambulatory care visits as the buprenorphine group.[72] Other estimates suggest that the costs of buprenorphine treatments may be as much as 49% lower than those for methadone.[73] Preliminary studies on the subdermal formulation of buprenorphine approved in 2016 suggest that this type of treatment may have lower total costs than other forms.[74]

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[66] Marc Larochelle, Dana Bernson, and Thomas Land, et al., "Medication for Opioid Use Disorder After Nonfatal Opioid Overdose and Association with Mortality," *Annals of Internal Medicine*, June 19, 2018, http://annals.org/aim/fullarticle/2684924/medication-opioid-use-disorder-after-nonfatal-opioid-overdose-association-mortality.

[67] HHS, SAMHSA, *Medication-Assisted Treatment: Insurance and Payments*, Last updated September 28, 2015, https://www.samhsa.gov/medication-assisted-treatment/treatment/insurance-payments.

[68] Department of Defense, Office of the Secretary, "TRICARE; Mental Health and Substance Use Disorder Treatment," 81 *Federal Register* 61068-61098, September 2, 2016.

[69] Ibid.

[70] HHS, National Institutes of Health, National Institute on Drug Abuse, *Medications to Treat Opioid Use Disorder*, March 2018, https://www.drugabuse.gov/publications/research-reports/medications-to-treat-opioid-addiction/how-much-does-opioid-treatment-cost.

[71] Barnett, "Comparison of Costs," (2009).

[72] Indirect costs include expenses not directly attributable to the treatment, but that are otherwise associated with treatment usage. In this case, indirect costs include the total cost of treating a participant including ambulatory care visits and in-patient care.

[73] Onur Baser, Mady Chalk, and David Fiellin et al., "Cost and Utilization Outcomes of Opioid-Dependence Treatments," *American Journal of Managed Care*, vol. 17, no. 8 (June 2011), pp. S235-48.

[74] John Carter, Ryan Dammerman, and Michael Frost, "Cost-Effectiveness of Subdermal Implantable Buprenorphine

Other studies have found buprenorphine treatment costs equivalent to, or slightly higher than, those for methadone.[75] The findings of a few studies may not be representative of the costs of buprenorphine (or methadone) in other VA medical centers or other settings. Determination of the cost effectiveness of buprenorphine, particularly compared to other treatment options such as methadone, awaits further research.

Does Medicare pay for buprenorphine treatment?

Medicare reimbursement for prescription drugs depends on the setting in which the drugs are used and how they are administered.[76] In general, Medicare Part A covers drugs used as part of an in-patient medical treatment; Medicare Part B covers prescription drugs that are not usually self-administered and are furnished and administered as part of a physician service; and Medicare Part D covers FDA-approved drugs that (1) are available only by prescription, (2) are used for a medically accepted indication, and (3) are not covered under Parts A or B.[77]

As noted previously, buprenorphine may be administered or dispensed (but not prescribed) in an OTP, and also may be administered, dispensed, or prescribed outside an OTP pursuant to a DATA waiver. Medicare does not recognize OTPs as covered providers, and does not provide Medicare reimbursement for buprenorphine dispensed in an OTP.

Medicare Part B has no separate benefit category for drugs used in the management of opioid use disorder. However, Part B will cover long-acting injectable and implantable forms of buprenorphine if administered by a physician and used in the management of opioid use disorder (referred to as "incident to a physician's services" by Medicare). Since January 1, 2018, Medicare Part B has provided a separate payment for insertion, removal, and removal with reinsertion of buprenorphine subdermal implants.[78]

Part B does not pay for self-administered drugs used during a provider visit. For example, if a physician's office stocks sublingual buprenorphine, its use would not be paid under Part B because such forms of the drug are considered self-administered (thus not payable under the "incident to" benefit). Payment to a physician for the observation of self-administration of the drug by the patient (such as initial induction doses, for example) may be possible under Part B.[79]

Medicare Part D plans must cover buprenorphine and other self-administered drugs used in MAT for opioid use disorder, either on their formularies (list of covered drugs) or via a coverage exception request by an enrollee. Part D plans also must provide a transition supply of drugs for

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versus Sublingual Buprenorphine to Treat Opioid Use Disorder," *Journal of Medical Economics*, vol. 20, no. 8 (August 2017), pp. 893-901.

[75] Heide Jackson, Kara Mandell, and Kimberly Johnson et al., "Cost Effectiveness of Injectable Extended Release Naltrexone Compared to Methadone Maintenance and Buprenorphine Maintenance Treatment for Opioid Dependence," *Substance Abuse*, vol. 36, no. 2 (2015), pp. 226-231.

[76] CRS In Focus IF10875, *Medicare Coverage of Opioid Addiction Treatment Services*, by Suzanne M. Kirchhoff and Johnathan H. Duff.

[77] Centers for Medicare & Medicaid Services, "Medicare Drug Coverage Under Part A, Part B, Part C, & Part D," Revised August 2017, https://www.cms.gov/outreach-and-education/outreach/partnerships/downloads/11315-p.pdf. Part B also covers certain vaccines, oral cancer drugs, and other products.

[78] Medicare and other payers use Healthcare Common Procedure Coding System (HCPCS) to identify reimbursable procedures; the HCPCS codes for these specific procedures are G0516, G0517, and G0518.

[79] Although payment for HCPCS code H0033, "Oral medication administration, direct observation," is not available under the Medicare Physician Fee Schedule, evaluation and management codes could be used to pay for the supervision of MAT under Part B, so long as all required elements to bill the code are met.

new enrollees who are already in treatment for opioid use disorder. Part D plans are to place MAT drugs on lower-cost-sharing tiers, although beneficiary cost sharing might vary depending on the Part D plan.[80] Medicare Part D does not cover oral buprenorphine or buprenorphine-naloxone combination products for the treatment of opioid dependency when they are administered or dispensed by OTPs. The Centers for Medicare & Medicaid Services has told Part D plan sponsors that they are expected to set low enrollee cost-sharing for MAT drugs, including buprenorphine.[81]

Does Medicaid pay for buprenorphine treatment?

All 48 states that responded to a 2017 survey (Arkansas and Illinois did not respond) indicated that their Medicaid programs covered buprenorphine.[82] Analysis of 2013-2014 survey data found that all 50 states and the District of Columbia covered buprenorphine and that 49 respondents imposed some limits, such as prior authorization requirements, duration of treatment, or per-day maximum doses.[83] Even though state Medicaid programs cover buprenorphine, states may only cover certain buprenorphine forms or may only cover buprenorphine under certain conditions.[84] For instance, a state Medicaid program may use a formulary that requires beneficiaries to enroll and attend MAT therapy or counseling before they can receive buprenorphine. States also may use a preferred drug list to require providers to use specific products first.[85]

Concluding Comments

Buprenorphine is one of three medications currently used to treat adults addicted to opioids. The rise in opioid abuse in the last decade and substantial financial burden of this epidemic highlight the need for effective treatments. Overall, buprenorphine appears to be an effective medication for treatment of opioid dependence. Despite marked increases in opioid abuse, related hospital admissions, and overdose deaths, the majority of individuals in need of treatment do not receive it. Prescribing practices for buprenorphine as a treatment for opioid use disorder are carefully regulated and include provisions that limit the number of patients certain providers can treat simultaneously. Congress and the executive branch have made efforts to increase access to buprenorphine treatment while balancing potential risks of this opioid-replacement therapy. Congress is likely to continue grappling with the opioid crisis for some time, as policymakers and medical and public health professionals wait for new data to indicate whether existing efforts have changed the trajectory of the opioid epidemic. Striking a balance between providing access to buprenorphine and maintaining quality standards for those who prescribe or dispense it may prove challenging.

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[80] CMS, "Announcement of Calendar Year (CY) 2019 Medicare Advantage Capitation Rates and Medicare Advantage and Part D Payment Policies and Final Call Letter," April 2, 2018, Access to Medication-Assisted Treatment, p. 253; and CMS, "Medicare Coverage of Substance Abuse Services," April 28, 2016, https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/Downloads/SE1604.pdf.

[81] CRS In Focus IF10875, *Medicare Coverage of Opioid Addiction Treatment Services*.

[82] The Henry J. Kaiser Family Foundation, *States Reporting Medicaid Coverage of Medication Assisted Treatment (MAT) Drugs*, state fiscal year 2017, https://www.kff.org/medicaid/state-indicator/states-reporting-medicaid-coverage-of-medication-assisted-treatment-mat-drugs.

[83] Colleen M. Grogan, Christina Andrews, and Amanda Abraham et al., "Survey Highlights Differences in Medicaid Coverage for Substance Use Treatment and Opioid Use Disorder Medications," *Heath Affairs*, vol. 35, no. 12 (December 1, 2016), pp. 2289-2296.

[84] CRS Report R43778, *Medicaid Prescription Drug Pricing and Policy*.

[85] Ibid. States are required to have a process by which providers can request non-preferred drugs.

Appendix. Systematic Review

Report Methodology

Much of the information in this CRS report is based on a systematic review of the scientific literature on buprenorphine. A systematic review is a single comprehensive report collating all of the relevant empirical evidence on a specific topic. Systematic reviews use explicit, systematic methods to identify studies that fit pre-specified eligibility criteria.[86] Systematic reviews have become an increasingly important source of information for clinical practice and policymaking. They synthesize large amounts of information and provide better estimations of performance and generalizability than individual studies.[87]

CRS' systematic review aimed to determine how well buprenorphine works in the treatment of opioid dependence compared to other treatments (such as methadone) or no treatment at all. Studies were included if they were comparisons of buprenorphine with other interventions in outpatient community settings in the United States and were published in the past five years. These included primary and secondary analyses of randomized control trials, quasi-experimental studies, and cohort studies. The CRS review concentrated on effectiveness rather than efficacy (see textbox under "How well does buprenorphine maintain people in treatment?"). Therefore, studies were excluded from this review if they examined efficacy, occurred in inpatient settings, focused on withdrawal, or occurred outside the United States. To identify original articles that met the inclusion criteria, we developed a search strategy for each of the three scientific databases used. We searched PubMed life science and biomedical database, PyscINFO behavioral sciences and mental health database, and CINAHL nursing journal database.

Article Summaries

Table A-1 provides full citations and abbreviated references to the 16 articles identified above. **Table A-2** summarizes each article, including its participants, study design and aims, and conclusions.

Table A-1. Article Citations and Abbreviations

Abbreviation	Full Citation
Crits-Christoph et al., 2016	Paul Crits-Cristoph, Hannah Markell, and Mary Beth Connolly Gibbons et al., "A Naturalistic Evaluation of Extended-Release Naltrexone in Clinical Practice in Missouri," *Journal of Substance Abuse Treatment*, vol. 70 (2016), pp. 50-57.
D'Onofrio et al., 2015	Gail D'Onofrio, Patrick O'Connor, and Michael Pantalon et al., "Emergency Department-Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence: A Randomized Clinical Trial," *JAMA,* vol. 313, no. 16 (2015), pp. 1636-1644.

[86] Alessandro Liberati, Douglas Altman, and Jennifer Tetzlaff et al., "The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies that Evaluate Health Care Interventions: Explanation and Elaboration," *PLoS Medicine*, vol. 6, no. 7 (July 2009), pp. 1-28.

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Abbreviation	Full Citation
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Fiellin et al., 2014	David Fiellin, Richard Schottenfeld, and Christopher Cutter et al., "Primary Care-Based Buprenorphine Taper vs Maintenance Therapy for Prescription Opioid Dependence: A Randomized Clinical Trial," *JAMA Internal Medicine*, vol. 174, no. 12 (2014), pp. 1947-1954.
Hser et al., 2014	Yih-Ing Hser, Andrew Saxon, and David Huang et al., "Treatment Retention Among Patients Randomized to Buprenorphine/Naloxone Compared to Methadone in a Multi-Site Trial," *Addiction*, vol. 109, no. 1 (January 2014), pp. 79-87.
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Marsch et al., 2016	Lisa Marsch, Sarah Moore, and Jacob Borodovsky et al., "A Randomized Controlled Trial of Buprenorphine Taper Duration Among Opioid-Dependent Adolescents and Young Adults," *Addiction*, vol. 111, no. 4 (August 2016), pp. 1406-1415.
Matson et al., 2014	Steven Matson, Gerrit Hobson, and Mahmoud Abdel-Rasoul et al., "A Retrospective Study of Retention of Opioid-Dependent Adolescents and Young Adults in an Outpatient Buprenorphine/Naloxone Clinic," *Journal of Addiction Medicine*, vol. 8, no. 3 (May/June 2014), pp. 176-182.
Nielson et al., 2013	Suzanne Nielson, Maureen Hillhouse, and Christie Thomas et al., "A Comparison of Buprenorphine Taper Outcomes Between Prescription Opioid and Heroin Users," *Journal of Addiction Medicine*, vol. 7, no. 1 (January 2013), pp. 33-38.
Potter et al., 2015	Jennifer Sharpe Potter, Jessica Dreifuss, and Elise Marino et al., "The Multi-Site Prescription Opioid Addiction Treatment Study: 18-month Outcomes," *Journal of Substance Abuse Treatment*, vol. 48, no. 1 (January 2015), pp. 62-69.
Proctor et al., 2014	Steven Proctor, Amy Copeland, and Albert Kopak et al., "A Naturalistic Comparison of the Effectiveness of Methadone and Two Sublingual Formulations of Buprenorphine on Maintenance Treatment Outcomes: Findings from a Retrospective Multisite Study," *Experimental and Clinical Psychopharmacology*, vol. 22, no. 5 (2014), pp. 424-433.
Rosenthal et al., 2013	Richard Rosenthal, Walter Ling, and Frank Vocci et al., "Buprenorphine Implants for Treatment of Opioid Dependence: Randomized Comparison to Placebo and Sublingual Buprenorphine/Naloxone," *Addiction*, vol. 108, no. 12 (December 2013), pp. 2141-2149.
Rosenthal et al., 2016	Richard Rosenthal, Michelle Lofwall, and Sonnie Kim et al., "Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults with Opioid Dependence Treated with Sublingual Buprenorphine: A Randomized Clinical Trial," *JAMA*, vol. 316, no. 3 (2016), pp. 282-290.
Sigmon et al., 2013	Stacey Sigmon, Kelly Dunn, and Kathryn Saulsgiver et al., "A Randomized, Double-Blind Evaluation of Buprenorphine Taper Duration in Primary Prescription Opioid Abusers," *JAMA Psychiatry*, vol. 70, no. 12 (December 2013), pp. 1347-1354.
Vo et al., 2016	Hoa Vo, Erika Robbins, and Meghan Westwood et al., "Relapse Prevention Medications in Community Treatment for Young Adults with Opioid Addiction," *Substance Abuse*, vol. 37, no. 3 (2016), pp. 392-397.

Source: CRS analysis.

a. Same data from D'Onofrio et al., 2015.

b. Same data from Hser et al., 2014.

Table A-2. Article Summaries

Reference/Study	Participants	Study Design & Aims	Conclusions
Crits-Christoph et al., 2016	8,996 individuals who participated in substance abuse treatment for opioid use in Missouri	Naturalistic study that compared extended-release naltrexone (XR-NTX) with oral naltrexone, buprenorphine/naloxone, and psychosocial treatment on a composite outcome of employment, abstinence, duration of treatment, self-help participation, and arrests	XR-NTX-treated patients had significantly higher scores on composite outcome compared to buprenorphine/naloxone, however, the effect size was small (*d*=.17). All groups improved. Patients receiving buprenorphine/naloxone-remained in treatment longer than those receiving XR-NTX or psychosocial treatment. There were no differences in abstinence, participation in self-help, or arrest rates between groups.
D'Onofrio et al., 2015	329 opioid-dependent patients treated at an urban teaching hospital emergency department	A randomized clinical trial that compared the efficacy of ED-initiated buprenorphine/naloxone treatment with a referral to treatment or a brief (15-minute) intervention	More patients in the buprenorphine group were engaged in treatment at 30 days (78%) compared to the brief intervention group (45%) and the referral group (37%). The buprenorphine group self-reported greater reductions in number of days of illicit opioid use per week. Rates of urine samples negative for opioids did not differ across groups. Fewer patients in the buprenorphine group (11%) used inpatient addiction treatment services compared to the referral group (37%) and brief intervention group (35%).
D'Onofrio et al., 2017	290 opioid-dependent patients treated at an urban teaching hospital emergency department	A randomized clinical trial that compared the efficacy of ED-initiated buprenorphine/naloxone treatment with a referral to treatment or a brief intervention at 6- and 12-month follow-up	A greater number of patients in the buprenorphine group (74%) were engaged in addiction treatment at 2 months compared to the referral (53%) and brief intervention (47%) groups, but no differences existed at 6 months or 12 months.
Fiellin et al., 2014	113 opioid-dependent patients treated at a primary care center	A 14-week randomized clinical trial that compared the efficacy of buprenorphine taper (2-mg	The percentage of urine samples negative for opioids was lower for patients in the taper group (35%) than the

Reference/Study	Participants	Study Design & Aims	Conclusions
		decrease every 3 days for 3 weeks after 6 weeks of stabilization) vs. ongoing buprenorphine maintenance therapy using stable dosing in primary care-based treatment	maintenance group (53%). Patients in the taper group had fewer consecutive weeks of opioid abstinence compared with those in the maintenance group. Patients in the taper group were less likely to complete the trial. They also reported more days per week of illicit opioid use than those in the maintenance group once they were no longer receiving buprenorphine.
Hser et al., 2014	1,267 opioid-dependent individuals participating in 9 opioid treatment programs randomized to receive buprenorphine or methadone for 24 weeks	A secondary analysis of data from a randomized clinical trial that compared the effectiveness of buprenorphine/naloxone and methadone treatment for retention and opioid use	Treatment completion was higher for the methadone group (74%) compared to the buprenorphine group (46%). The completion rate for the buprenorphine group increased linearly with higher doses, reaching 60% with doses of 30-32mg/day. Higher medication dose was also related to lower opiate use, particularly among the buprenorphine group. Lower medication dose (<16mg) was associated with higher dropout. Of those remaining in treatment, opiate use was lower among the buprenorphine group in the first 9 weeks of treatment.
Hser et al., 2016	1,080 opioid-dependent individuals participating in 7 opioid treatment programs randomized to receive buprenorphine/naloxone or methadone	Follow-up study on data from a randomized clinical trial that compared the effectiveness of buprenorphine/naloxone and methadone on opioid use and mortality up to 4.5 years after treatment	Mortality was not different between the two conditions with 3.6% of the buprenorphine group having died compared to 5.8% of the methadone group. Opioid use was higher among participants in the buprenorphine group (43% vs 32% position urine screens). Individuals in the buprenorphine group had less treatment participation after initial 24-week treatment than those in the methadone group.

Reference/Study	Participants	Study Design & Aims	Conclusions
Jacobs et al., 2015	740 opioid-dependent individuals previously randomized to the buprenorphine arm of a clinical trial	A secondary analysis of data from a randomized clinical trial that compared opioid-use, retention, and safety of various doses of buprenorphine at 7 days, 28 days, and 6 months	Participants who started on moderate (between 8 and 24mg) doses of buprenorphine and shifted to high doses (>24mg) were three times less likely to drop out of the first 7 days of treatment than those receiving consistent low doses (<8mg). At 28 days, participants dosed at >16mg were less likely to drop out of treatment compared to those who received <16mg. Dropout during the first 28 days was highest in the group receiving the lowest dose of buprenorphine (<8mg/day). At 6 months, participants receiving >8mg/day had fewer opioid using days than the lowest dose group. The longer it took to reach maintenance dose of buprenorphine, the more days of opioid use at 6 months. There was no difference in safety between the groups.
Marsch et al., 2016	53 opioid-dependent individuals between the ages of 16 and 24 (n=11 under age 18) being treated at two urban hospital-based research clinics randomized to one of two buprenorphine taper lengths	A randomized controlled trial comparing the effects of a 28-day taper off of buprenorphine versus a 56-day taper on retention in treatment and abstinence from opioid use of over a 2-month period	Participants who received a 56-day taper had a lower percentage of positive urine drug tests compared to those in the 28-day taper group. On average, participants in the 56-day taper remained in treatment longer than those in the 28-day group (37.5 days vs. 26.4 days).
Matson et al., 2014	103 opioid-dependent young adults and adolescents who received medication-assisted treatment at a hospital-based outpatient clinic	A retrospective chart review of all qualified patients receiving buprenorphine/naloxone treatment at the clinic that examined retention and compliance rates after one year	Opioid abstinence (85%) and compliance with buprenorphine/naloxone treatment (86%) were high while participants were engaged in treatment. 75% of patients returned for a 2nd visit and 45% remained in treatment at 60 days. By 1 year, 9% were still retained in treatment. There was no difference in retention rates for those with heroin/prescription opioid dependence compared to prescription opioid dependence alone. Female

Reference/Study	Participants	Study Design & Aims	Conclusions
			sex and negative THC urine screen were associated with higher retention in treatment
Nielson et al., 2013	516 opioid-dependent individuals randomized to one of two buprenorphine taper lengths across 11 sites in the U.S.	A secondary analysis of data from a multisite randomized clinical trial that compared two buprenorphine taper schedules (7 days vs 28 days) on opioid use. The analysis compared characteristics and outcomes for subgroups reporting prescription opioid use vs. heroin use	A higher percentage of the prescription opioid group (49%) provided an opioid free urine screen at the end of taper compared to the heroin group (35%). There was no difference between these groups in the 28-day taper however. Individuals primarily using prescription opioids were almost twice as likely to provide opioid negative urine samples at the end of tapering than those who primarily use heroin.
Potter et al., 2015	252 opioid-dependent participants treated at 10 sites who were previously randomized to receive standard care, counseling, or buprenorphine-naloxone	A follow-up analysis at 18 months of in a large multisite randomized clinical trial that compared standard care (weekly brief physician meetings), counseling (1-2x weekly), brief treatment (2 weeks + 2-week taper) using buprenorphine-naloxone, or extended treatment (12 weeks of buprenorphine-naloxone stabilization). The study used a two-phase adaptive design meaning participants who did not improve after receiving one treatment were randomized again to receive a different treatment	No differences were found between the treatments in abstinence, opioid dependence diagnosis, or participation in agonist treatment at 18-month follow-up. Overall, the average number of days of prescription opioid use decreased by almost two-thirds and 77% of participants used less often than when they began treatment. The average number of days of heroin use increased slightly. Individuals who successfully completed extended treatment were more likely to maintain abstinence. Participants receiving agonist treatment after the study were more likely to report opioid abstinence than those who did not (63% vs. 39%).
Proctor et al., 2014	3,233 patients receiving medication-assisted treatment for opioid use at an outpatient substance use treatment facility during a one-year period	A retrospective longitudinal study that compared the effectiveness of methadone, Suboxone® (buprenorphine + naloxone), and Subutex® (buprenorphine) on retention in treatment and opioid use	The average number of days in treatment (retention) was longer for the methadone group (170 days) compared to the Subutex® (69 days) and Suboxone® (119 days) groups. The prevalence rates of opioid use were similar across all three groups.

Reference/Study	Participants	Study Design & Aims	Conclusions
Rosenthal et al., 2013	287 opioid-dependent individuals randomized to one of three groups receiving buprenorphine implants, placebo implants, or buprenorphine-naloxone tablets over 24 weeks	A randomized placebo-controlled trial that compared buprenorphine implants with placebo implants and buprenorphine-naloxone tablets (12-16mg fixed dose) for the treatment of opioid dependence	Buprenorphine implants were more effective at reducing opioid use than placebo implants. 27% of the buprenorphine implant group had more than half negative urine screens vs. 6% in the placebo group. There was no difference found between the buprenorphine implants and the buprenorphine-naloxone tablets in retention in treatment or percent of negative urine screens.
Rosenthal et al., 2016	177 opioid-dependent individuals randomized to one of two groups receiving buprenorphine implants + sublingual placebo or placebo implants + sublingual buprenorphine over 24 weeks	A randomized clinical trial that compared buprenorphine implants (plus sublingual placebo) with sublingual buprenorphine (plus placebo implants) for the treatment of opioid dependence	More participants in the buprenorphine implant group (96%) obtained at least 4 months of negative urine drug screens compared to the sublingual group (88%). A larger proportion of participants receiving buprenorphine implants (86%) demonstrated abstinence through 6 months compared to the sublingual buprenorphine group (72%)
Sigmon et al., 2013	70 prescription opioid-dependent individuals randomized to receive 1-, 2-, or 4-week tapers of buprenorphine followed by naltrexone therapy	A double-blind randomized clinical trial that compared 1-, 2-, and 4-week buprenorphine tapering regimens on opioid use and retention in treatment	Opioid abstinence was higher in the 4-week taper group (63%) compared with the 1-and 2-week taper conditions (29% each) after 5 weeks and again after 12 weeks (50% vs. 20% and 16%). There were more treatment responders in the 4-week taper condition (50%) than in the 1-week (21%) or 2-week (17%) groups. Retention in treatment was also greater in the 4-week taper than the other two groups.
Vo et al., 2016	56 young adults (19-26 years old) admitted to an outpatient community treatment program for opioid use disorders	A naturalistic retrospective chart review that compared buprenorphine with extended release naltrexone (XR-NTX) on opioid use over 24 weeks	There were no differences found in rates of opioid-negative urine tests between the two treatment groups. About half of the participants in each group had opioid-negative urine tests at 12 weeks and slightly less than half (39%) at 24 weeks. The XR-NTX group had greater retention in treatment after 12 weeks,

Reference/Study	Participants	Study Design & Aims	Conclusions
			however there were no differences found in retention to treatment at the end of 24 weeks.

Source: CRS analysis.

Note: A placebo is an inactive substance containing minimal or no medication used as a control in an experiment to determine the effects of a medicinal drug.

a. Same data from D'Onofrio, O'Connor, Pantalon, Chawarski, Busch, Owens, Bernstein & Fiellin, 2015.

b. Same data from Hser, Saxon, Huang, Hasson, Thomas, Hillhouse, Jacobs, Teruya, McLaughlin, Wiest, Cohen, & Ling, 2014.

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