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Correctional Medication-Assisted Treatment Research Compendium

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Correctional Medication-Assisted Treatment Research Compendium

Note to Readers:

The compendium is organized by specific questions related to medication-assisted treatment (MAT). Each section provides a response to the question posed and is followed by a list of the supporting research. Summaries of each of the cited studies are provided alphabetically by author in the Appendix. Readers can refer to source documents included at the end of each summary for more details.

The compendium is not intended to be inclusive of all MAT-related studies, but rather to present the current science in support of each of the topics covered. All studies included in the compendium have been published in peer review journals from 2002 through early 2023. The date on the cover page reflects the last update to compendium.

And while all the studies in this publication are relevant and contribute to our understanding of medication-assisted treatment (MAT), the studies that involve justice-involved individuals are of special relevance because they looked at individuals that more closely resemble those found in the nation's jails and prisons. Many of the study subjects in the research that does not specifically focus on justice-involved individuals involve individuals who may have only abused prescription pain pills, are not polydrug abusers, are more likely to be employed, have residential stability and familial support unlike many justice-involved persons with opioid use disorder (OUD).¹ The studies that specifically involved justice-involved populations are in **RED**.

Readers should note that almost all the research presented pertaining to the agonist medication buprenorphine specifically involves a buprenorphine/naloxone combination, the most common formulation of buprenorphine OUD medication prescribed.² The addition of naloxone does not affect the buprenorphine but is added to decrease the likelihood of diversion and misuse of the combination drug product. When taken together, buprenorphine's opioid effects dominate naloxone. The research below pertaining to naltrexone, unless specifically indicated otherwise, involves extended-release injectable naltrexone.³

Readers should also note that the studies included in the compendium do not employ consistent outcome measures. Some are concerned with opioid overdose deaths, some with the number of positive or negative drug tests indicating continued use or abstinence, others with patient satisfaction or treatment retention, and so on. ("Treatment retention," unless otherwise specified, refers in these studies to continuation of the medication, not concurrent counseling or other psychosocial or behavioral treatment modalities.) Nor are the studies consistent in terms of time of outcome measurements. Some are limited, for example, to one month after a person began taking the medication. Others look at outcomes up to 42 months after medication was begun.

¹ For example, a study of 6,756 patients on buprenorphine for OUD found that those who had chronic or acute prescription opioid use prior to treatment were more likely to be successfully stabilized on buprenorphine than those who had no prescription opioid use (e.g., heroin) prior to buprenorphine treatment (Varisco, T., Shen, C., Thornton, D. (2020) **Chronic prescription opioid use predicts stabilization on buprenorphine for the treatment of opioid use disorder**. *Journal of Substance Abuse Treatment*. <https://doi.org/10.1016/j.jsat.2020.10873>).

² Buprenorphine/naloxone is marketed as Suboxone®, Bunavail®, Zubsolv®, and Cassipa® as either a sublingual tablet or film. Long-acting injectable buprenorphine is marketed as Sublocade®; it does not contain naloxone.

³ Extended-release injectable naltrexone is marketed as Vivitrol®.

Lastly, readers should note that the studies employ different research methodologies. Some are qualitative, based on surveys or interviews with data subjects, others are quantitative, based on various sized data sets collected from various sources, like a state's Medicaid records. Some of the studies are descriptive of what researchers found studying a specific program or event, while others report the results of experimental studies. Readers should also note that many of the studies only looked at one of the FDA-approved medications, so the findings do not necessarily suggest the medication studied is unique, better or worse than other medications.

The compendium is organized by specific questions related to medication-assisted treatment (MAT). Each is introduced by a brief discussion of the specific research reviewed that addresses each question. For a more complete understanding of the specific research, readers are encouraged to read the more detailed summaries of each study, which is included alphabetically by author in the Appendix. Readers can refer to source documents included at the end of each summary for more details. All the studies included in the compendium have been published in peer reviewed journals. The studies included are not exhaustive, but what we have been able to access over the last several years. This means that where there is a widespread consensus based on previous research, more recent research on the same topic is not included in this manual as it is not being done. We will continue to update this compendium.

1 What is the evidence for the use of the three FDA approved medications (Buprenorphine, Methadone, and Naltrexone) for the treatment of individuals with opioid use disorder (OUD)?

Buprenorphine, methadone, and naltrexone are the three FDA approved medications to treat OUD. The studies presented in this section address the impact of these medications on mortality, short- and long-term OUD recovery, recidivism, and the quality of life of individuals with OUD. Additionally, this section includes studies on their medical contraindications and their relative cost effectiveness. In considering the impact of medications on mortality, it should be understood that persons released from incarceration are at an extremely high risk for nonfatal and fatal overdoses (Hartung, D. 2023).

a) Mortality

The research overwhelmingly finds that using the three FDA approved medications for OUD lowers the risk of mortality amongst individuals with OUD, including those previously incarcerated (Chatterjee, 2023; Jones, C., 2024; Laroche, M. 2018; Pearce, L. 2020; Russolillo, A. 2018; Santo, T. 2021; Sordo, L. 2017; Stone, A. 2020; Stone, J. 2021; Watts, B. 2021; Wakeman, S. 2020). For example, a systematic review and meta-analysis found that pooled all-cause mortality rates were 11.3 and 36.1 per 1,000 person years in and out of methadone treatment and 4.3 and 9.5 in and out of buprenorphine treatment. Overdose mortality rates were 2.6 and 12.7 per 1,000 person years in and out of methadone treatment and 1.4 and 4.6 in and out of buprenorphine treatment (Sordo, L. 2017). Another systematic review and meta-analysis similarly found that compared to patients receiving agonist as well as naltrexone, untreated patients had significantly higher risk for both all-cause and overdose mortality (Ma, J. 2019). Persons on Medicare Disability who suffered a nonfatal overdose who were given buprenorphine in an inpatient or emergency department had a 62% reduction in the risk of another opioid overdose over the next year, despite the fact that fewer than one in 20 continued to receive buprenorphine during the year (Samples, H. 2023).

Retention on opioid agonist treatment has been found to be associated with substantial reduction of risk of mortality for people with OUD and its protective effect on mortality has increased as fentanyl and other synthetic opioids have become common in the illicit drug supply (Pearce, L. 2020).

Reduced mortality associated with OUD medications has been specifically found to be true among justice-involved individuals (Russolillo, A. 2018; Cates, 2023), including incarcerated persons with OUD (Green, T. 2018; Lim, S. 2022; Macmadu, A. 2020; Marsden, A. 2016; Marsden, A. 2017), and veterans (Watts, B. 2021). A microsimulation study based on 55,000 incarcerated individuals in Rhode Island between 2017 and 2024 at risk for opioid overdose deaths compared what the results would be for those receiving standard care (methadone for pregnant), extended-release naltrexone, and all three FDA approved medications. It projected that extended-release naltrexone would avert 103 deaths and all three would avert 139 deaths. Within the first-year post-release, extended-release naltrexone would reduce overdose deaths by 22.8% and all three medications would reduce it by 31.6% (Macmadu, A. 2021).

A Connecticut study found that methadone reduced risk of OD deaths by 38% and buprenorphine by 34% compared to people who received neither. It also found that individuals who were previously incarcerated were at especially high risk of OD deaths as they were less likely to have received treatment (Heimer, 2024).

Studies have found that the first month after release from prison has the highest rate for overdose deaths (Binswanger, I. 2007; Ranapurwala, S. 2018). For example, a North Carolina prison study found the risk of overdose deaths were 40 times higher two weeks after release than in the general North Carolina public and 70 times higher specifically for heroin overdose deaths (Ranapurwala, S. 2018). Similarly, a hospital study in England found that discharge from the hospital is associated with an acute increase in the risk of opioid-related death with one in 14 opioid-related deaths in England occurring in the two weeks after hospital discharge (Lewer, 2021). An English national prison study found that opioid substitution therapy (agonist medication) provided in prison was associated with a 75% reduction in deaths, including an 85% reduction specifically for fatal drug-related poisoning in the first month after release (Marsden, 2017). A Rhode Island study found that post-release overdose deaths were reduced by 60.5% after persons about to be released were provided extended-release injected naltrexone (Green, 2018). A study of individuals with OUD released from New York City's jail, Rikers Island, between 2011 and 2017 found seven died of overdoses who received agonist medication compared to 47 without it. After one year, 41 died who received MOUD in jail compared to 70 who did not receive MOUD in jail (Lim, S. 2022).

Individuals with OUD are also at a higher risk of death and suicide than those without OUD (Ali, 2021; Carlson, 2020; Carson, 2021; Watts, B. 2021; Schepis, T. 2019). Additionally, one study found that a history of prior overdoses significantly increases the likelihood that an individual with OUD will die by overdose or suicide (Carlson, 2020). Among veterans with OUD, those who are White and have multiple psychiatric conditions are more likely to die by suicide (Watts, B. 2021). Past year misuse of prescription opioids and benzodiazepines was significantly associated with suicidal ideation for persons 50 or older -- only 2.2% of older persons not misusing these medications reported suicidal ideation compared to 25.4% misusers who reported suicidal ideation (Schepis, T. 2019). Opioid agonist treatment has been found to be associated with reduced risk of self-harm (Padmanathan, P. 2022). A study of veterans with OUD found that all three medications were associated with reduced risk of suicide or all-cause mortality over five years when the veterans were taking their medication. Among the three medications, buprenorphine was most associated with reduced suicide mortality and methadone most associated with reduced all-cause mortality (Watts, B. 2021). A large Swedish study found all three opioid medications to be associated with reduced suicidality (Molero, Y. 2018).

Buprenorphine provided in a transmucosal film or extended-release injection was associated with a seven-year increase in life expectancy compared to no medication for OUD (Falm-Ross, J. 2023).

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b) Short and Long-Term Recovery

The research does not reveal how long opioid medications must be taken to have maximum effectiveness regarding either short or long-term recovery. One study, for example, found risk of overdose was high following discontinuation of buprenorphine irrespective of medication duration, but superior outcomes became significant with treatment duration beyond 15 months (Williams, A. 2020). Additional research agrees that stopping any of the OUD medication after their effects have worn off increases risk of overdose deaths, including extended-release injected naltrexone (Saucier, R. 2018) as well as methadone (Santo, T. 2021).

The positive short-term impact of OUD medication, however, has been consistent. A review of 13 studies involving incarcerated persons found that “interventions that initiated medication-assisted treatment early and throughout incarcerations had significant positive effects on opioid use outcomes,” calling in-custody MAT “an effective method of improving post release outcomes with individuals with criminal justice involvement.” Study outcomes included both overdoses and need for “serious opioid-related acute care” after three and then twelve months of medication (Sugarman, O. 2020). A review of the literature on post release outcomes associated with the use of opioid medications in correctional settings found “compelling evidence” that the medication provided during incarceration increased community-based treatment engagement post-release and decreased opioid use (Cates, 2023). A methadone study found persons receiving only counseling while incarcerated were much more likely to test positive for opioids one month after release compared to those who also received counseling with methadone while incarcerated or those who received methadone upon release. Those who received methadone and counseling while incarcerated were the least likely to test positive (28%) compared to 63% for counseling only and 41% for methadone post release (Kinlock, 2007). In a follow up study, it was found that the counseling with methadone during incarceration had an average of 166 days enrolled in community treatment post release with 36.7% staying in treatment for one year. Counseling

and methadone maintenance after incarceration individuals had an average of 91.3 days enrolled in treatment with 17.3% in treatment for a year. The counseling only group were enrolled in community treatment for an average of 23.1 days with 0% in treatment for a full year (Kinlock, 2009). A meta-analysis of methadone found methadone maintenance significantly reduced illicit opioid use (Marsch, L., 1998).

Extended-release naltrexone has been found to be associated with increased number of opioid free days, improved adherence rates in treatment, and reduced craving and drug-seeking behavior for both heroin and non-heroin users (Cousins, S. 2015; Ndegwa, S. 2017). A Swedish random control trial found that persons provided cognitive behavioral therapy, with one group also receiving 16 mg of buprenorphine and the other no medication, found 75% of the former remained in treatment for a year. None of the latter remained in treatment for the year (Kakko, 2003). A multistate retrospective cohort study of 16,386 individuals found after one year of methadone, there was a 22% reduction in the likelihood of a positive tests for fentanyl, 49% reduction in heroin, but cocaine and methamphetamine use did not significantly decrease (Whitley, 2023).

Studies are also consistent in their findings that without continued medication post-release, mortality rates increase, and the benefits attributed to the medication decrease (Marsden, J. 2016; Green, T. 2018). A random clinical study of persons treated for opioid prescription addiction found reduction of opioid use while on buprenorphine. If tapered off, even after 12 weeks, the likelihood of successful outcomes was low, even if participants received counseling (Weiss, R. 2011). The follow up found at month 42, engagement in agonist therapy was associated with a greater likelihood of illicit-opioid abstinence, with 31.7% abstinent and no longer on agonist therapy, 29.4% on agonist therapy but not meeting criteria for current opioid dependence, 7.5% on agonist therapy but also using illicit opioids, and 31.4 % using opioids not on opioid therapy (Weiss, R. 2015). A systemic review and meta-analysis found overall a “high level of evidence” that buprenorphine treatment improved treatment retention and decreased illicit opioid use compared to individuals not receiving buprenorphine, although higher doses were more “efficacious than lower” (Thomas, C. 2014). A naltrexone study found long term (two year) naltrexone use compared to shorter term use had similar or better rates of retention, opioid-negative urines, opioid craving reduction, mental health functional quality of life improvement and re-employment (Early, P. 2017). Another naltrexone randomized control experiment comparing extended-release injected naltrexone to placebo injections found the treatment group was more likely to complete treatment (53.2% v. 37.9%), have increased opioid free weeks (90% v. 35%), and more confirmed abstinence (35.7% v. 22.6%). Significant differences were also found for the treatment group having lower opioid craving scores and “relapses to physiological opioid dependence” (Krupitsky, E. 2011).

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c) Recidivism

Providing medication for OUD reduces the likelihood of justice-involved individuals with OUD reoffending (Evans, E. 2022; Finigan, M, 2011, Krebs, E. 2017; Moore, K. 2018). One study looked at persons in methadone maintenance treatment during incarceration and compared them to individuals with OUD who did not receive methadone while incarcerated. Those who continued methadone after release were associated with reduced risk of arrest, new charges, and reincarceration (Moore, K. 2018). A meta-analysis on methadone maintenance found it significantly reduced drug and property crimes (Marsch, L., 1998).

Another study comparing persons receiving buprenorphine while incarcerated compared to persons not receiving it, found the former were less likely to be arraigned on new charges (Evans, E. 2022). A third looked at agonist treatment in general and found it associated with reduced criminal justice costs (Krebs, E. 2017). A literature review, however, found medication for OUD during incarceration “did not increase criminal involvement (Cates, 2023).”

Similarly, individuals under legal supervision in the community were also less likely to be reincarcerated when provided injectable naltrexone (Coviello, D. 2012). A Swedish study looked at persons released from prison who had been diagnosed positive for mental illness, including schizophrenia, many with co-occurring substance use disorders. It found rates of violent reoffending were significantly lower when medications for OUD, antipsychotics and psychostimulants were dispensed compared when they were not. The difference for the OUD medications was 36.4 fewer violent offenses per 1000 person-years (Swanson, J. 2016). A study of two drug courts found a re-arrest rate of eight percent those receiving extended-release naltrexone compared to 26% who did not receive naltrexone. The former had 57 percent fewer missed drug court sessions (Finigan, M, 2011).

There is one outlier study that found greater retention of buprenorphine after release was not associated with decreased criminal behavior outcomes up to one year later. The same study, however, found that despite longer retention on buprenorphine, there was no decrease in days of heroin use among the men and women released from the two Baltimore pre-release prisons (Gordon, M. 2017). And in another study of mostly Black Maryland heroin users recruited to use buprenorphine after hospitalization also found that for those who continued to take the medication their quality of life improved as did their treatment outcomes, there was no impact on criminal charges (Sittambalam, C. 2014).

A large Swedish study found all three medications reduce suicidality and crime during treatment (Molero, Y. 2018).

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d) Other Outcomes (quality of life, HIV, discipline within prison/jail, client satisfaction, etc.)

Medications for OUD have been found to be associated with many other positive outcomes. Buprenorphine, methadone, and extended-release naltrexone all have been found to be associated with improving HIV viral suppression (Korthuis, P. 2021, Marsch, L., 1998), including a study of incarcerated persons provided extended-released injected naltrexone (Springer, 2018); although there is no consensus on the preferred medication to

improve HIV suppression. The most effective medication appears to be the medication individuals are most likely to continue to take. One study, for example, found methadone to be superior to buprenorphine in improving HIV viral suppression because users had higher retention rates, thus experiencing less adverse events (Korthuis, P. 2021).

A jail MOUD program found those that participated had lower overdose rates up to 180 days after release than those not enrolled, 10% vs. 14.5%. After a year, those who were in the jail MOUD program overdose rate was 12.8% but 18.2% for those not enrolled when they were jailed (Wiest, D., 2023).

A study found that patients receiving buprenorphine reduced general healthcare costs compared to those who received little addiction treatment (Lynch, F. 2014). Extended-release naltrexone and buprenorphine have both been found, according to reports of users, to improve “quality-of-life” for individuals, with the latter specifically decreasing depression and increasing employment (Ling, W. 2020; Saxon, A. 2018; Sittambalam, C. 2014) and the former decreasing opioid cravings (Earley, P. 2017).

Studies also suggest that medication satisfaction is also influenced by ease of access to the medication, specifically for methadone and buprenorphine. One found patients were more satisfied when they could pick up buprenorphine at a clinic rather than a pharmacy (Kolb, E. 2021); another found patients were more satisfied with office-based methadone and pharmacy dispensing than OTP access (McCarthy, D. 2021).

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e) OUD Medication Contraindications

As with most medications, the two agonist medications for OUD have been found to have adverse consequences if taken with other medications and substances, as well as if the patient has specific medical conditions (Park, T. 2020; Olfson, M. 2017; Xu, K. 2021; Ferrant, O. 2011).

One of the most common additional medications persons with OUD often are prescribed (or otherwise obtain) are benzodiazepines. According to the DEA Fact Sheet (https://www.dea.gov/sites/default/files/2020-06/Benzodiazepenes-2020_1.pdf), benzodiazepines are depressants that produce sedation and hypnosis, relieve anxiety, muscle spasms and reduce seizures. While concurrent use of benzodiazepines with buprenorphine has been found to be associated with increased buprenorphine retention, concurrent use of both medications has also been found to be associated with increased risk of death from overdoses (Park, T. 2020; Olfson, M. 2017), especially higher doses of benzodiazepine (Xu, K. 2021). Adding alcohol, as well as central nervous system depressants (benzodiazepines, barbiturates, and certain sleep medications), have also been found to be associated with increased risk for overdoses and death for those taking buprenorphine. The same study found that administration of buprenorphine through injection or nasal spray (snorting) is specifically related to adverse effects (Ferrant, O. 2011).

Another study that looked at mixing benzodiazepines with methadone also found that while concurrent use of prescribed benzodiazepines does not impede a patient's retention on methadone, non-prescribed use of benzodiazepines is associated with methadone non-retention. However, the researchers concluded that alternatives to even clinical benzodiazepines should be encouraged to avoid benzodiazepine use disorder and risks of negative interactions with opioids (Eibi, J. 2019).

The Food and Drug Administration (FDA) has concluded that buprenorphine tablets and film are associated with dental problems although its delivery by injection or skin patches is not. It has suggested that rinsing one's mouth after use and seeing a dentist may lessen dental problems (Food and Drug Administration, 2022).

With careful monitoring and induction dose adjustment, buprenorphine has been found to be safe administered to patients with acute Hepatitis A Virus (Oller, D. 2021). Another study that looked at different dose levels of buprenorphine injections found treatment was “well tolerated,” with most common adverse events being headaches, constipation, nausea, and injection site pruritis, all never effecting more than nine present of the users. The adverse effects were the same as for oral buprenorphine except for itchy skin around the injection site (Haight, B. 2019). Sublingual buprenorphine as opposed to oral or transdermal buprenorphine significantly increases risk of adverse dental events (Etminan, E. 2022).

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f) Costs

OUD medications have been found to be more cost effective than providing treatment without medication (Connock, M. 2007; Krebs, E. 2017), but studies are not consistent as to which medication is the most cost effective. One study also found that a flexible dosing strategy with methadone maintenance was “somewhat more effective” in maintaining

individuals in treatment than flexible-dose buprenorphine maintenance therapy (Connock, M. 2007).

Among the limited research, one study found buprenorphine provided in jails as cost effective as providing it in community settings along with other forms of opioid agonist treatment in jails (Dunlop, A. 2021), another found injectable naltrexone to be as cost effective as methadone based on opioid-free days (Jackson, H. 2015), while still another found injectable naltrexone is not equally cost effective as agonist treatment because this study considered the longer period of detoxification needed before persons can begin naltrexone treatment which increased costs (Murphy, S. 2019). Providing buprenorphine and harm reduction services with standard primary care improved clinical outcome and increased life expectancy proving to be cost effective over a five-year span. Just providing buprenorphine without harm reduction services provided more costly as life expectancy decreased marginally but resulted in less deaths than primary care alone (Jawa, 2023). A simulation model for all of Massachusetts prisons and jails found that offering all three opioid medications would decrease the odds of overdose, increase the likelihood of treatment in the community but increase costs per person while incarcerated. Giving individuals a choice of all three medications less expensive than providing only extended-release naltrexone (Chatterjee, 2023).

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2 What is the evidence how the three medications compare with each other?

This section presents studies that specifically compare the three FDA approved medications. There is no consensus among the studies as to which medication overall is better than the others. Contrasting findings become most evident in studies of specific subpopulations of patients. It may be that the most effective medication for one subgroup may not be the same for another. Few of the following studies compared all three medications, so the research is broken down by which medication is compared to which medication or type of medication. Comparisons are also complicated because the medications can be administered in different manners. User retention, for example, may be associated with receiving an extended-release medication compared to daily medication irrespective of the specific medications involved.

a) Agonist v Antagonist Medications for OUD

A study of 17,568 Massachusetts adults without cancer who survived an opioid overdose between 2014 and 2014 compared both all cause and opioid-related mortality rates for those who were then treated with methadone, buprenorphine, or naltrexone. Those receiving either methadone or buprenorphine had reduced all cause and opioid-related mortality compared to individuals not receiving these medications. Those receiving naltrexone did not have reduced all-cause or opioid-related mortality compared to those not receiving this medication. However, the patients in this study that were prescribed naltrexone received a median of only one month of medication, compared to a median of five months for those receiving methadone and four months for those receiving buprenorphine (Laroche, M. 2018). A Norwegian randomized clinical study comparing buprenorphine medication taken daily with naltrexone injected monthly found in a 12-week trial that both medications were effective in reducing use of heroin, opioids and other illicit substances, but the naltrexone participants showed significantly lower use of heroin and other illicit opioids, but not for other illicit substances (Tanum, L. 2017). An Australian study found rates of fatal and non-fatal opioid overdose were not significantly different in patients treated with methadone, buprenorphine or implant naltrexone (Kelty, E. 2017).

Another found that extended-release naltrexone promotes abstinence from opioids better than the other medications for OUD but found no differences in employment or arrests in the relatively short time period reviewed (Crits-Christoph, P. 2015). Other studies, including two experimental trials, found extended-release naltrexone to be “noninferior” to buprenorphine (Institute for Clinical and Economic Review, 2018). However, another randomized experiment comparing 24 weeks of buprenorphine and extended-release naltrexone with 12 weeks of follow up found the latter was not associated with significantly better outcomes measured in quality-adjusted life years or abstinent years gained. The buprenorphine treatment was also less expensive even with its need for fewer follow up visits (Murphy, S. 2019).

A large Medicaid study found persons were more likely to discontinue antagonist medication compared to agonist opioid medication (Zhang, P. 2022). However, a systemic review of randomized trials, some of which included incarcerated persons, found antagonist medications were associated with longer treatment retention than agonist medications when coupled with contingency management (Chan, B. 2021). Another study determined that

once initiated, injectable naltrexone and buprenorphine were equally retained and effective. The same study also found that persons who signed up for OUD medication were more likely to fail to initiate antagonist medications than agonist medications (Lee, 2018). However, a Norwegian study found retention rates were the same for persons taking buprenorphine daily and injectable naltrexone monthly and persons preferred injectable naltrexone to daily buprenorphine/naloxone pills and switched medications given the option in this test comparison. The preference for naltrexone may have been influenced because, at the time of the study, naltrexone was a novel medication and only available to study participants (Tanum, L. 2017). Another study has found each medication was associated with different significant outcomes- naltrexone (antagonist) with reduced accidental overdoses, buprenorphine with reduced arrest rates for all crime categories as well as accidental overdoses, methadone for reduced suicidal behavior as well as crime reductions in all categories. Methadone has been found to be associated with increased risk of accidental overdoses (Molero, Y. 2018). A large study based on insurance claims of persons with OUD and co-occurring SUD found both buprenorphine and naltrexone treatments were associated with decreased poisonings compared to days without the medications (Xu, K. 2022).

A retrospective cohort study compared prescribed buprenorphine, oral naltrexone and extended-release naltrexone in outpatient and office settings. There were 2,755 opioid overdoses during the study period, 2,020 occurred when the patients were not in treatment. Participants who were prescribed buprenorphine were significantly at a lower risk of opioid related overdose compared to participants who were treated with oral naltrexone and extended-release buprenorphine. However, in the first four weeks following discontinuation of the medications, those who had received buprenorphine were at higher risk for overdose over those who had received naltrexone in any formulation (Morgan, J., 2019).

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b) Methadone v Buprenorphine

The use of methadone and buprenorphine has significantly increased over the years (Alderkes, C. 2017), but studies on which medication is better differ. Even the same studies have found different results depending upon the specific outcomes measured. For example, one study found methadone to be superior in terms of rates of retention for persons with OUD and mental disorders, but buprenorphine to be superior in terms of reduction of illicit opioid use (Hser, Y. 2021). Other studies agreed, finding methadone to be the more effective medication because it improves treatment retention better than buprenorphine (Burns, L. 2014; Degenhardt, 2023, Garcia-Portilla, M. 2014, Kinsky, S. 2019). An Australian study of 15,600 OUD treatment entrants found on average only 44% of those inducted on buprenorphine continued for three or more months while 70% of those inducted on methadone continued treatment three or more months. Although, during the study period, 2001 to 2010, retention rates for buprenorphine improved while the rates for methadone retention were stable (Burns, L. 2014).

While a large United Kingdom study of 11,033 opioid-dependent patients found buprenorphine was associated with a lower all-cause mortality and drug-related mortality than methadone, patients remained on methadone for a median of 111 days compared to a median of only 40 days on buprenorphine. Researchers concluded, despite the different mortality rates found, “Buprenorphine is unlikely to give greater overall protection because of the relatively shorter duration of treatment” (Hickman, M. 2018). A systemic review and meta-analysis comparing methadone and buprenorphine found that the efficacy of buprenorphine is dose dependent. However, comparing medium-dose ranges, it found the evidence to be mixed with some studies finding both medications comparable in terms of

illicit opioid use while some found methadone better at retention and buprenorphine with reduced adverse events. An Australian prison study found oral methadone and extended-release buprenorphine had similar high retention rates, significant decline in injection drug use and non-prescribed opioid use (Dunlop, A. 2022).

In Indian study compared individuals receiving methadone with those receiving buprenorphine. The relapse rate was higher for those on buprenorphine than methadone, 42% v 35%. Those on methadone had a drop out rate of 15% compared to 17% for those on buprenorphine (Bala, N. 2023).

A meta-analysis that included 10 randomized studies compared methadone and buprenorphine retention rates. It found that retention rates varied significantly for both medications in the studies, but there were no significant differences between when examining length of time of retention (Kilmas, J., 2021).

Rates of neonatal abstinence syndrome were similar for mothers treated with either medication during pregnancy, but symptoms were less severe for infants whose mothers received buprenorphine (Suarez, E. 2022; Thomas, C. 2014). A Finish study comparing pregnancies, births, and newborn outcomes of women treated with methadone, buprenorphine and buprenorphine with naloxone found the buprenorphine medications were better for increasing the likelihood of health newborns (Kanervo, M. 2022). A cohort study in the U.S. involving 13,000 pregnancies for women on methadone or buprenorphine found the latter was associated with lower risk of malformation in infancy (Suarez, 2024). While adherence to treatment was higher for those on methadone after one month, adherence while in treatment was the same for both medications. Those treated with buprenorphine were less likely to test positive for extra medical opioid use (Degenhardt, 2023). A retrospective study found infants with neonatal withdrawal syndrome treated with buprenorphine required less hospitalization stays and treatment than those treated with morphine (Analagan, S. 2024).

A study in Vietnam of patients in a HIV clinic with OUD being treated with either methadone or buprenorphine found those treated with methadone had greater viral suppression, greater treatment retention (65% v. 40%), and less serious adverse events (Korthuis, P. 2021).

In a jail study, buprenorphine and methadone were equally effective during incarceration but individuals who received buprenorphine were more likely to access continued treatment in the community post-release than individuals who received methadone (Magura, S. 2009). A large Medicaid study found utilization shift from inpatient to outpatient “added to evidence of clinical utility of buprenorphine compared with methadone, including reduced mortality, crime and personal costs...” (Kessel, J. 2018). Another state Medicaid study, just looking at length of time between starting and stopping buprenorphine or methadone found that buprenorphine was associated with a higher risk of discontinuation during the first year, but both were similar after the first year (Zhang, P. 2022). A retrospective chart review found at six months, methadone had the highest retention at 80% followed by extended-release buprenorphine at 78% and sublingual buprenorphine at 62%. Most nonfatal overdoses were those receiving methadone (18) and the least were those on extended-release buprenorphine (1) (Lee, K., 2023).

Sleep disturbance is common in OUD patients receiving agonist medication. A study found that patients treated with methadone versus buprenorphine did not differ “on any measure of sleep continuity or architecture” (Finan, P. 2020). Switching from methadone to buprenorphine has been found to increase the rate of discontinuing treatment (Chung, K. 2019).

Methadone and buprenorphine have both been found in a qualitative study equally affected by peer pressure, which often leads to discontinuation of both medications. Individuals report stopping both methadone and buprenorphine “to prevent medication or

health service” dependence; due to stigma and external pressure to stop (not experienced with naltrexone) as well as relapse and termination by health care providers or the criminal justice system (Randall-Kosich, O. 2019).

A study comparing the costs of methadone compared to buprenorphine treatment found methadone to be less expensive with pharmacy costs \$23 compared to \$219 (Kinsky, S. (2019).

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c) Methadone, Buprenorphine and/or Naltrexone for special populations, including person who are homeless, adolescents, pregnant, those with co-occurring mental illness and SUD, and fentanyl users

Different subpopulations of people respond to buprenorphine, methadone, and naltrexone in different ways. Among individuals with OUD and depression or anxiety, buprenorphine and naltrexone have been found to reduce suicidal ideation and improve sleep. These studies did not include methadone (Ahmadi, 2018; Latif, 2019). Cannabis use is associated with reduced exposure to fentanyl among people on opioid agonist therapy. Naltrexone was not studied (Socias, M. 2020). Buprenorphine, which is the only agonist medication approved for adolescents (16 and older), has been found to be effective in promoting abstinence among adolescents who abuse heroin. While the research involving adolescents is limited, a study found those who received at least 56 days of buprenorphine were more likely to remain in treatment longer than adolescents who received only 28 days of the medication (Borodovsky, J. 2018; Smyth, B. 2018). Homeless individuals who receive extended-release buprenorphine have been found to retain treatment longer and are less likely to use illicit opioids than the other medications (Nunes, E. 2021). Alaska Natives and Native Americans' retention rates on buprenorphine decrease over time, from 51% at six months to 40% at one year. Those with the highest risk for discontinuing treatment were younger people and polydrug abusers (Lillie, K. 2020).

Post-partum women have been found to benefit from taking methadone, buprenorphine, or naltrexone but outcomes vary. Methadone and buprenorphine are likely to help retain post-partum women in treatment (Schiff, D. 2021), whereas naltrexone is associated with reduced risk of newborns experiencing symptoms of neonatal abstinence syndrome if taken throughout pregnancy (Towers, C. 2019; Liu, J. 2022). A Finnish study comparing pregnancies, births, and newborn outcomes of women treated with methadone or buprenorphine with and without buprenorphine found the latter to be the safest pharmacological treatment for women to receive during pregnancy to increase the likelihood of a healthy newborn. The study found half of the women on the agonist medication abused drugs during their pregnancy, significantly common among women on methadone (80%) while 20 to 22% among women on buprenorphine with and without naloxone. The need for pharmacological treatment for their newborns for withdrawal syndrome was 87% if their mothers were on methadone and 56% if their mothers were in buprenorphine with or without naloxone (Kanervo, M. 2022).

Research has found that while buprenorphine is associated with mild respiratory depression compared to fentanyl that causes notable depression and apnea (a sleep disorder when breathing stops and starts), high buprenorphine doses can negate respiratory depression of fentanyl (Olofsen, E. 2022).

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d) Abuse, diversion, illicit use, and harm reduction

Comparing the three medications for OUD, the studies below find buprenorphine to be the most likely to be diverted, abused, and used illicitly. Diversion of buprenorphine has significantly increased over the years particularly in the 2010's (Buttram, M. 2021). Although naloxone was added to buprenorphine to stop diversion and injection of buprenorphine,

research confirms that buprenorphine-naloxone “retains some potential for abuse intravenously” (Thomas, C. 2014). These studies focus on buprenorphine taken daily as a pill or sublingual film. Another study has found long-acting injectable buprenorphine in correctional centers in Australia did not increase risk for diversion (Dunlop, A. 2021).

A study of reports from 896 opioid or opiate users collected by community-based residential treatment centers revealed that only 4% to 7% obtain their buprenorphine solely through prescriptions. Those who obtained buprenorphine through prescriptions reported it provided relief from withdrawal. A quarter said buprenorphine helped them with their substance use, while three-quarters said it had no effect on their substance use or had a negative effect. Most or 80%, who obtained buprenorphine without prescriptions reported using illicit buprenorphine until their preferred drug could be obtained and used it for its euphoric effect. Ten percent of recent buprenorphine users reported overdosing on buprenorphine and other drugs. The reports of users varied whether they were still using buprenorphine, used it over their lifetime, or within the past six months (Walker, R. 2018). Another review suggested from the literature that the most common form of buprenorphine diversion is self-treatment due to treatment services being unavailable. Individuals who self-treat with diverted buprenorphine likely to enter treatment when it becomes available (Grande, 2023).

Other study surveys suggest half of clients who use opioid drugs and seek treatment have used illicit buprenorphine, typically for withdrawal management and in attempts to control other opioid use symptoms, stop themselves from using heroin or fentanyl, or because they are unable to afford OUD treatment (Bazazi, A. 2011; Cicero, T. 2014). Although, another study finds nonprescribed opioid use has also been found to be associated with increased likelihood of risky behavior and risky decision making (Konova, A. 2019). This study examined the use of non-prescribed buprenorphine, revealed by drug testing before patients were prescribed buprenorphine. It found that it didn't make a difference in terms of risk for treatment discontinuation, suggesting that those with illicit buprenorphine use prior to treatment were treatment ready when prescribed buprenorphine (Williams, A. 2022).

A large study of persons receiving prescriptions for buprenorphine for pain and for OUD treatment found illicit buprenorphine use was higher for those receiving prescribed buprenorphine for OUD treatment. However, patients who were positive for buprenorphine were less likely to be positive for other opioids compared to those who tested negative for buprenorphine (Saloner, B. 2021).

Illicit use of buprenorphine poses a special challenge for prisons and jails, as illicit buprenorphine before incarceration is associated with increased risky behaviors, polydrug abuse, and increased rates of hepatitis C and B, as well as poor treatment outcomes after release (Bunting, A. 2021; Smith, K. 2020). Interviews with Australian prisoners after their release found 25% admitted removing all or part of their supervised dose at least once, 44% reported using non-prescribed opioids, and a third reported sharing or selling medication with others in the prison. The researchers found the introduction of buprenorphine-naloxone film presented “particular challenges with respect to supervised dosing in this setting” (White, N. 2016).

Individuals who experience pain have been found to be at high risk of seeking out illicit opioids (Mun, C. 2020). Studies find that persons prescribed opioid pain medications are likely to try and receive additional opioid prescriptions, mainly other painkillers (Daubresse, M. 2017).

A few studies have specifically looked at buprenorphine diversion in jails/prisons, one where buprenorphine was not available for in-jail or prison treatment and one where it was available in jails for treatment. Interviews with 150 recently incarcerated adults in Baltimore, Maryland and New York with OUD found 63% admitted to illicit/non-prescribed opioid use

while incarcerated and 39% reported non-prescribed buprenorphine use. Non-prescribed buprenorphine was considered the most widely available opioid in jails and prisons in both states with 81% classifying it as “very” or “somewhat” easy to get. While most said they used buprenorphine to get “high/mood alteration” while incarcerated, they said they used it for “therapeutic” purposes in the community. Use of illicit buprenorphine while imprisoned was associated with younger age and longer incarceration history (Gryczynski, J. 2021). A survey of jail staff in seven Massachusetts jails that provided buprenorphine found they believed that buprenorphine treatment disrupted the illicit market for buprenorphine in their jails and reduced violence related to its use. Most diversion was the result of intimidation by other incarcerated persons (Evans, E. 2022).

A cross-sectional investigation found 4,550 out of 58,476 patients (7.7%) treated with buprenorphine directly added buprenorphine to their urine samples. Opioid-positive with and without stimulant-positive specimens were associated with the direct addition of buprenorphine to specimens, while opioid-negative/stimulant-positive specimens were negatively associated. The adulterated samples were most likely obtained in primary care as opposed to behavioral health or substance use treatment clinics with highest number found in South Atlantic census region and lowest in New England (Pytell, J. 2023).

A retrospective cohort study looked at more than 20,000 patients prescribed agonist medication for OUD. A little more than 4,500 experienced nonfatal overdoses. Patients co-prescribed benzodiazepines, antipsychotics, gabapentinoids, and z-drugs with opioid agonist treatment were at an elevated risk of overdose, but not those prescribed anti-depressants (Domzaridou, 2023).

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3 What is the evidence regarding appropriate dosage and length of treatment required for each medication?

The studies presented in this section provide information of the preferred dosage levels and the length of treatment with OUD medications that will yield the most positive outcomes. Across all three medications for OUD, the studies agree that long term use of the medications with high dosages is associated with better treatment outcomes (Burns, L. 2002; Hser, Y. 2014). For example, a study of 1,267 participants in multiple OTPs found over 24 weeks completion rates were 74% for methadone and 46% for buprenorphine. However, when doses of each medication were increased, 60 mg/day for methadone and 30-32mg/day for buprenorphine, completion rates increased to 80% for methadone and 60% for buprenorphine (Hser, Y. 2014). However, none of the studies has determined the optimal length of treatment or dosage required to maintain long term abstinence. A multistate study of 293,180 Medicaid enrollees treated for OUD found that for every 50 days individuals continued medication for OUD, their risk of overdose decreased by 10% (Burns, L. 2022).

a) Methadone

The research agrees that high doses of methadone are more effective than lower doses for more positive outcomes (Hser, Y. 2014), specifically higher doses are associated with reduced opioid cravings and increased treatment retention for persons with co-occurring opioid and alcohol use disorders (Nava, F. 2008). Individuals who discontinue methadone during the first four weeks are at a high risk of mortality (Santo, T. 2021). Researchers have also found that if there is a waitlist to receive OUD medication treatment, even the temporary provision of methadone reduces drug-related adverse events compared to not receiving medication while awaiting entry into treatment (McCarty, D. 2021). A retrospective cohort study of more than 16,000 treated with methadone from 2017 to 2021 in ten states found from urine tests that the percent who tested positive for fentanyl increased from 13.1% to 53%, methamphetamines from 10.6% to 27.2%, cocaine from 12.8% to 19.5%. Heroin rates went from 6.94% in 2017 to 9.71% in 2020 and decreased to 6.45% in 2021 (Saloner, B. 2023).

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b) Buprenorphine

The same studies that found higher doses of methadone more effective than lower found the same for buprenorphine (Chambers, L. 2023, Hser, Y. 2014, Nava, F. 2008). A meta-analysis and systematic review of buprenorphine found a high level of evidence for its positive impact when dosed adequately (Thomas, C. 2014). By contrast, low doses of buprenorphine have been found to be associated with an elevated risk of discontinuation of treatment (Samples, H. 2019). However, a randomized experiment of long-acting injected buprenorphine comparing six injections of 300 mg with two injections of 300mg and four injections of 100 mg found abstinence in both groups significantly higher than in a group receiving placebo (no buprenorphine), but both groups received the same high doses initially in this experiment (Haight, B. 2019).

Individuals who receive buprenorphine for a longer period of time have also been found to be more likely to achieve stable health compared to those who receive buprenorphine for a short period of time. A large study compared outcomes among four groups of persons taking buprenorphine for: a) 6-9 months; b) 9-12 months; c) 12-15 months; and d) 15-18 months. The 15- to 18-month cohort was significantly less likely to be seen in an emergency department, to be hospitalized, or to receive a prescription for an opioid analgesic during the 6-month post-discontinuation period compared with the 6- to 9-month, but all cohorts had high rates of emergency department visits following discontinuation (>40%), and all cohorts had indistinguishable rates of nonfatal drug overdose at approximately 5.6% of the sample (Connery, H. 2020). Other studies similarly have found continuous use of buprenorphine for at least 15 months or more lowers the risk of inpatient hospitalizations, emergency department visits, and hospital use related to opioid use (Samples, H. 2020; Williams, A. 2020). A long term, four year follow up study of a clinical trial of long-acting injected buprenorphine found 55% of participants reported continued abstinence and 69% report abstinence over the last 30 days. They also reported low levels of depression and distress (Craft, W. 2022). A randomized control study of adolescents also found longer term use of buprenorphine was associated with better opioid abstinence outcomes (Borodovsky, J. 2018).

But, even short-term use of buprenorphine has been found useful, with a study finding that retaining buprenorphine for at least four weeks can reduce the risk of mortality compared to the absence of buprenorphine (Santo, T. 2021). Similarly, researchers have also found that if there is a waitlist to receive OUD medication treatment, even the temporary provision of buprenorphine reduces drug related adverse events compared to not receiving medication while awaiting entry into treatment (Sigmon, S. 2016).

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c) Naltrexone

A study, similarly, has found that higher doses of naltrexone are associated with longer treatment retention. After two months, retention was only 39% for those receiving placebo, 60% for those receiving 192 mg and 68% for those receiving 382 mg of naltrexone (Comer, S. 2006). A higher dose of naltrexone for AUD, 50 mg v 25mg, reduced reduce alcohol related hospitalizations from 42.9% to 25.5% (Ayyala, D. 2022). Another study found longer treatment duration with naltrexone was associated with lower relapse rates and improved outcomes generally (Saxon, A. 2018).

The longest period of naltrexone treatment studied was 78 weeks. This justice-involved study compared persons receiving extended-release naloxone to treatment as usual (i.e., no medication). During 24 weeks of treatment, the extended-release participants had longer median time to relapse, 10.5 vs 5 weeks, and a lower level of relapse, 43% vs. 64%. A year later, the differences between the two groups were extinguished in terms of opioid-negative urines or self-report drug use, although there were seven overdose events in the no medication group and none in the extended-release naltrexone group (Lee, J. 2016).

A study that included persons who switched after three months from buprenorphine to naltrexone and then had nine months of naltrexone found opioid abstinence rates of 53.7% for those who received naltrexone for the full 12 months and 44.4% for those who switched to naltrexone (Solli, K. 2018).

Extended-release naltrexone treatment reduced the high depression found among persons with heroin use disorder and reduced it below that found in a comparison control group of persons without OUD but does not effect on anhedonia symptoms or dopamine transporter availability (Zaaijer, 2015).

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4 What is the evidence regarding the impact of the delivery systems of these medications?

The research in this section focuses on oral, injection, and implanted formulations of buprenorphine and naltrexone as well as take home doses. While all delivery forms are viable ways to administer the medications to individuals, the studies below have arrived at different findings of which method is better based upon their performance, cost, and patient satisfaction.

a) Oral daily v. extended-release medication

Studies have found that extended-release injectable naltrexone is associated with significantly better outcomes than provision of it daily in terms of retention and abstinence (Crits-Christoph, P. 2015; Sullivan, M. 2018). In the latter study, the retention rate was twice as high after six months.

A randomized clinical trial compared weekly or monthly buprenorphine injections with daily buprenorphine over 24 weeks and found that treatment satisfaction was significantly higher in the injection group (Lintzeris, N. 2021). Another randomized clinical trial comparing weekly or monthly buprenorphine injected with daily buprenorphine for 24 weeks for opioid negative urines for illicit opioids found the former to be noninferior (Lofwall, M. 2018).

A random assigned comparison of incarcerated persons taking extended-release injected buprenorphine and those daily sublingual films found the former had fewer in jail clinic visits and increased community buprenorphine treatment after release, but participants preferred the sublingual buprenorphine (Lee, J. 2021). A study comparing sublingual buprenorphine-naloxone and extended-release injections for both opioid use disorder patients some of whom used fentanyl and some who had not found that while both formulations were effective for both populations, the extended-release formulation was more effective in decreasing opioid and fentanyl use. After 24 weeks, 74.6% of individuals who received extended-release buprenorphine compared to 61.9% of individuals who received buprenorphine naloxone tested negative for fentanyl, a statistically significant difference (Nunes, E., 2024).

While most insurance plans covered sublingual buprenorphine, a minority covered extended-release buprenorphine and some required prior authorization from 2108 to 2021 reducing its use (Andraka-Christou, 2023).

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b) Extend-release injectables (week, month)

A small study of persons released from jail on extended-release naltrexone expressed general satisfaction with its effects and control of cravings. Most tested its blocking effect by taking heroin. Similar satisfaction was shared by those who retained methadone or buprenorphine treatment, despite noted inconvenience associated with methadone maintenance (Velasquez, M. 2019). Another study found individuals recently released from prison found that extended-release buprenorphine lessened the likelihood of illicit opioid use, but most individuals, it found, preferred sublingual buprenorphine even though it did not perform as well (Lee, J. 2021). By contrast, within the justice system, a study found that most employees, including judges and probation officers, strongly prefer extended-release naltrexone over methadone and buprenorphine (Andraka-Christou, B. 2019).

An examination of studies on long-acting buprenorphine, including studies involving justice-involved individuals, found individuals prescribed long-acting injectable buprenorphine were overwhelmingly positive. The studies reported it was associated with reduced cravings, reduced recidivism, longer retention, a better outlook for employment and social relationships, opioid abstinence as well as fewer withdrawal symptoms, positive health-related quality of life, minimal depression and/or higher employment than they did before taking buprenorphine (Haight, B. 2019; Heil, J. (2024), Ling, W. 2018.; Ling, W. 2020; Martin, E. 2020). At six months, a comparison of persons prescribed extended-release buprenorphine who had the injections compared to those prescribed it but declined and took sublingual daily buprenorphine found retention for the former was 70.3% compared to 36.5%. They also had higher percent negative urine screens, 67.2% v 36.3% (Heil, J. 2024). Brixadi,TM the most recent injectable buprenorphine medication, has been found by the FDA to be as safe as oral buprenorphine and may be superior to sublingual buprenorphine/naloxone (Park, B. 2022).

The issue of how extended-release naltrexone or buprenorphine compare remains unresolved. One of the few random assignment comparison studies found them to be

equally effective when taken, with buprenorphine yielding greater treatment retention but that it was also associated with more overdose deaths (Lee, J. 2018).

A review of OUD medications that excluded methadone compared relevant studies on two brands of injectable buprenorphine, buprenorphine implants, and injectable naltrexone. It found no relevant studies comparing outcomes on reducing mortality. Discontinuation rates were similar for injectable buprenorphine, implants and injectable naltrexone, although more individuals on injectable naltrexone discontinued before induction. Both injectable and implant buprenorphine outperformed placebos with substantially less attrition. Abstinence, measured as opioid negative urines, was similar for all compared to sublingual daily buprenorphine, however, the implants were more likely to remain abstinent using other measures. Injectable buprenorphine subjects were found to be more likely to be abstinent compared to persons receiving placebos. Opioid cravings associated with injected and implanted buprenorphine were not different than found for daily buprenorphine use, but one study found cravings reduced with injection compared with placebos and another found cravings reduced more with injected naltrexone than buprenorphine (Institute for Clinical and Economic Review, 2018).

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c) Implants

The research regarding the use of implanted naltrexone and buprenorphine finds this delivery system is as effective and generally better than the oral formulations of these medications (Institute for Clinical and Economic Review, 2018). A randomly assigned experiment involving persons with HIV and OUD found that those provided naltrexone implants did better than those provided daily naltrexone pills managing their HIV at week 48. There were also two overdose deaths in the pill group and none in the implant group (Krupitsky, E. 2019). Institute for Clinical and Economic Review. (2018, October 25). Extended-release opioid agonists and antagonist medications for addiction treatment (MAT) in patients with OUD: Effectiveness and value. Evidence report.

[ICER_MAT_Evidence_Report_102518-1.pdf](https://icer.org/wp-content/uploads/2020/10/ICER_MAT_Evidence_Report_102518-1.pdf)

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d) Take home doses compared to dosing in a specialty clinic or doctor's office

Studies that examined allowing patients to receive their medication at home instead of a doctor's office or special clinic, including OTPs, have mixed findings depending on the population and how the take home medication is implemented. One study found that patients who typically receive their medications from a doctor's office were more likely to retain treatment and adhere to their medication by using a pharmacy delivery service to bring their medications to their home (Kolb, E. 2021). Another study found patients'

satisfaction increased if they could take home methadone from medical offices, not OTPs (McCarthy, D. 2021).

A Rhode Island study found that allowing individuals to receive buprenorphine directly from their local pharmacies rather than doctor offices or OTPs were more likely to continue treatment (Green, t. 2023). A study that compared individuals involved in treatment through telemedicine with those receiving it through clinicians during the pandemic found that treatment and medication retention were similar whether patients received various levels of telemedicine or treatment by clinicians (Hailu, R. 2022).

A study focused on adolescents and young adults found that this age group was significantly more likely to retain treatment and provide negative urine screens if provided take home buprenorphine rather than going into an office (Marsch, 2016). However, another study found while take home doses can help increase opioid abstinence, it may lower treatment retention (Elarabi, H. 2021). A large Canadian study found that increasing take home methadone and buprenorphine doses has no impact on risk of opioid overdose, treatment discontinuation, and treatment interruption for those on buprenorphine, but had significant impact for those on methadone reducing all three negative outcomes (Gomes, T. 2022). Among homeless populations, providing buprenorphine at a doctor's office has been found to be associated with improved medication retention and opioid abstinence (Fine, D. 2021).

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<https://doi.org/10.1176/appi.ajp.2021.20101548>.

5 What is the evidence regarding factors associated with retention rates for the medications?

This section presents studies about the retention rates amongst OUD medications. All the studies agree that OUD medications increase treatment retention over placebos. While studies that find most are similar in suppression of opioid use (if provided adequate dosage), generally methadone has been found to be associated with longer treatment retention (Mattick, R. 2014).

Studies have found that retention rates are impacted by external factors beyond the characteristics of the individual medications or how they are administered. Specific subpopulations of people and their life circumstances have been found to be associated with each medication's retention. For example, a Los Angeles naltrexone study found individuals who were older and tested for HIV were more likely to receive two or more doses while those who were admitted to the emergency room in the past year and those with a mental health diagnosis were less likely to receive two or more doses (Cousins, S. 2015). A large Australian study found indigenous patients, younger persons, those with history of psychosis, and those with four or more criminal convictions were associated with increased risk of leaving agonist treatment (Bharat, C. 2021). A cohort study of 1,378 patients receiving buprenorphine who used a telehealth platform found retention was 56.4% at 180 days and 48.3% at 365 days. Rates were not impacted by geographic location, rurality, race or gender, but age appeared to be a factor. Patients over the age of 30 had significantly greater odds of treatment retention (Williams, 2022).

A cross-sectional study compared several thousand individuals with substance use disorder, some recently released from jail and others not recently jailed across rural American. 42.2% of rural persons who had SUDs were recently released from jail. Those recently released were less likely to access treatment and more likely to experience overdoses than those not recently released from jail (Hoover, D. 2023).

Creating a predictive model based on three multicenter randomized clinical trials for at least 12 months involving 3,000 participants found that who did not test positive for opioids during the first three weeks of treatment with methadone, buprenorphine or naltrexone were only at 13% risk of relapse compared to 85% who tested positive or missed tests within the first three weeks of treatment (Luo, S., 2023). A retrospective study of 30,737 individuals who initiated buprenorphine found 15 percent discontinued treatment, almost half within the first several months. Those that continued treatment were more likely 45 years or older, had chronic pain, had insurance, and engaged in outpatient visits. Those who discontinued also were more likely to use stimulants, made emergency room visits, and lived in the southern sections of the country (Faysal, J., 2024).

A randomized clinical study found providing nurse management for OUD in primary care practices increased buprenorphine or naltrexone treatment by 8.2 patient years per 10,000 primary care patients compared to usual care clinics (Wartko, P., 2023).

A cross-sectional study found that cost sharing had little effect on retention on buprenorphine. While costs can be a burden, it does not explain discontinuation (Chua, K. 2024).

A qualitative study of White Americans with a history of stopping OUD medication treatment found individuals stopped treatment as a result of stigma associated with

methadone and buprenorphine, but not naltrexone. They also stopped the agonist medications for fear of becoming dependent upon them or their healthcare providers. Others reported they stopped when they relapsed, were terminated by health providers, or were arrested (Randall-Kosich, O. 2019).

For incarcerated populations, studies have specifically found beginning medication while persons are incarcerated increases retention after release, even compared to individuals who are introduced to the medication immediately upon release (Chan, B. 2021; Kinlock, 2007, Moore, K., 2019). This has been found both for buprenorphine provided before release (Friedmann, P. 2018; Gordan, M. 2017; Lee, J. 2021; Zaller, N., 2013) and naltrexone (Lincoln, 2018).

Additionally, this section presents evidence of different methods to increase retention including contingency management and telemedicine.

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a) Methadone

More studies than not have found that individuals who receive methadone are more likely to continue to take the medication compared to individuals who receive buprenorphine (Burns, L. 2015; Garcia-Portilla, M. 2014; Hser, Y. 2014; Korthuis, P. 2021) including a Cochrane Review of 31 studies (Mattick, R. 2014).

Methadone maintenance has been found to be effective to patients who tested positive for fentanyl at intake. Three-quarters achieved remission within the year's study, 99% who remained in treatment for a year achieved remission. Methadone maintenance was found to be safe despite repeated exposure to fentanyl while taking methadone (Stone, A. 2020).

A blind, randomized study found that adding a pharmacological conditioned open label placebo pill to methadone treatment for 90 days enhanced treatment retention over those receiving methadone without the added pill that patients assumed enhanced the methadone dosage, 77.9% retention vs 61.1% retention. The former also reported they slept better. No other differences were found (Wish, E., 2023). The study that looked at persons receiving methadone before and after the Covid-19 pandemic with liberalized take home doses of methadone found no difference in retention rates and opioid use increased among the later (Williams, A. (2023).

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b) Buprenorphine

A multi-state Medicaid database looked at persons prescribed buprenorphine for OUD. Over a quarter discontinued buprenorphine within the first month of treatment and most discontinued before 180 days. Risk factors for discontinuation included receiving a lower dose, being male, younger, Black or Hispanic, have a capitated insurance plan, comorbid SUD, including AUD, or any inpatient care in the six months before being prescribed buprenorphine (Samples, H. 2018). Another large Medicaid study compared non-telemedicine initiation and telemedicine initiation of buprenorphine in two states. It found the latter was associated with better odds of 90-day retention in both states, Kentucky at 1.13 and Ohio at 1.19 in a regression analysis adjusting for patient demographic and comorbidity characteristics. Telemedicine initiation was not associated with opioid-related nonfatal overdose (Hammerslag, L., 2023).

Dosage has also been found to be a factor, with doses of 16mg/dose or greater associated with greater retention rates compared to lesser doses (Eren, K. 2022). However, a review finds doses of at least 32mg/dose best reduce withdrawal symptoms, cravings, opioid reward, and illicit use while increasing treatment retention (Grande, L., 2023). Individuals who were between 25-34 years of age had the greatest number retained in treatment -for at least 180 days in a longitudinal study of buprenorphine prescriptions. Individuals between 15 -24 years of age had the lowest number. Overall, 29.3% used buprenorphine for at least 180 days (Olson, M. 2020). Providing buprenorphine to incarcerated persons is associated with increased retention post-release compared to people who are first induced after release (Gordan, M. 2017; Lee, J. 2021). Individuals also using methamphetamines have been found to be twice as likely to not complete buprenorphine/naloxone treatment than those who do not use methamphetamines (Tsui, J. 2020). A study comparing persons released from jail on buprenorphine who were then eligible to continue to receive it at a public city hospital with those first prescribed it in the community found the former those released from jail had higher and longer retention rates (Lee,J., 2012). A New York City jail set of interviews with 22 individuals receiving buprenorphine in jail determined that 14 intended to continued treatment once released, seven planned to use street buprenorphine as needed, and one had no plans to continue buprenorphine upon release and return to heroin. All indicated that continuing buprenorphine after release was problematic due to unstable housing, parole requirements and barriers to access (Vail, W. 2021)..

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c) Naltrexone

Patients are more likely to continue to take extended-release injected naltrexone compared to oral naltrexone (Crits-Christoph, P. 2016). The administration of naltrexone during inpatient and residential care is associated with individuals continuing treatment post discharge (Leslie, D. 2015). Providing naltrexone to incarcerated individuals during their incarceration provides higher rates of retention and lower rates of mortality compared to those who receive naltrexone beginning right after they were released (Friedman, P. 2018; Lincoln, T. 2018).

A Los Angeles study of persons in residential treatment for OUD found that older individuals who tested positive for HIV received more injections than those who had been admitted to emergency rooms and had a mental health diagnosis, injected drugs in the prior year received fewer injections. Although the average received overall was 2.4 injections, there was no difference in number of injections between those who used heroin and those who did not or their level of cravings (Cousins, S.2015).

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d) Strategies to extend retention, including telehealth apps

The research presented below provides evidence of various methods that may help increase OUD medication retention. None of the research has claimed to find the gold standard for retention. One study found increased retention for persons with concurrent health conditions was associated with providing additional medical treatment services alongside the OUD medication. Specifically, programs that provided antiviral therapy in conjunction with OUD medication were associated with improved retention (Lancaster, K. 2021).

A study of more than 12,000 patients prescribed agonist medication found concurrent prescriptions for benzodiazepines were associated with longer treatment retention, although they were also associated with increased risk for drug-related mortality (Macleod, J. 2019). Contingency management that provides rewards to promote a desired effect in conjunction with OUD medication has been found to be associated with increased retention for all three OUD medications as well as abstinence in a meta-analysis and systematic review (Bolivar, H. 2021). However, two systematic reviews and 39 primary studies found contingency management was associated with increased antagonist (naltrexone) medication retention, but not agonist medication retention. The same reviews found that interventions using medical, psychiatric, social services, or information technology did not significantly impact retention when compared to the medications alone (Chan, B. 2021). Another study found buprenorphine maintenance with “incentivized therapeutic drug monitoring to enable contingent access to increasing take-home medication supplies increased abstinence from opioids compared with buprenorphine maintenance treatment-as-usual,” but it did not appear to increase treatment retention (Elarabi, H. 2021).

A multisite investigation found at least two professional outpatient visits within 34 days of treatment was associated with patients retaining treatment for six months compared to those that did not have this professional contact or services. However, the level of retention for the former was 47% (Williams, A. 2022).

Within the past few years, the use of telemedicine has increased. For example, the use of telehealth buprenorphine treatment has increased from 2.9% in 2012 to 7.96% in 2019 (Lin, 2021). But there have been no definitive findings that telemedicine is as or more effective as in-person treatment. While some studies have found that telemedicine may modestly increase attendance at counseling appointments, retention and a short-term increase in opioid abstinence (DeFulio, A. 2021; Schuman-Olivier, Z. 2018), another found that using telehealth was no better than standard in-person treatment in improving treatment

retention (Tsui, J. 2021). Another study found incorporation of telehealth technology with MAT is associated with higher patient satisfaction, reduction in health care costs and increase in both access to and use of buprenorphine, but comparable rates of retention (Guillen, A. 2021). An observational cohort study of more than 3,300 looked at telehealth-based buprenorphine treatment that included urine drug tests. It found those that those using a telehealth-based app for OUD treatment with buprenorphine completed a urine test within 30 days and that opioid, cocaine and benzodiazepine use declined, buprenorphine adherence increased. Researchers concluded the study showed that urine testing with a telehealth app provided a feasible alternative to in-person treatment (Williams, 2023).

The beneficial use of telemedicine is further complicated when examining how different populations of people experience it in their treatment. Young adults respond favorably to technology involved in their treatment and have been found to maintain high retention (Peck, K. 2020). While individuals living in rural environments may benefit from telemedicine because it saves them time spent on driving, their medication retention has been found, nonetheless, to decrease over time (Weintraub, E. 2021). The attitudes of health care providers further impacts the use of telemedicine. The research has found, for example, that U.S veterans typically do not use telehealth if they receive treatment from VA medical centers because the VA does not make it available to them (Lin, L. 2021). A study suggests that most health care providers do not recommend telemedicine because they believe it is not as beneficial and safe as in person treatment (Mark, T. 2021). A randomized controlled trial compared a telehealth model with standard methadone treatment and found the former reduce drug use, increased treatment retention (Cooperman, N. 2023). A qualitative study found patients were satisfied with telehealth treatment because speeded up access to treatment, was less stigmatizing (Sousa, J. (2022).

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6 What is the evidence regarding the effectiveness of concurrent psychosocial and 12 Step treatment with OUD medication?

Whether adding psychosocial treatment to OUD medication improves outcomes over the medication alone depends on the medication and the specific treatment. A state Medicaid study found that behavioral health therapy was associated with a low risk of treatment discontinuation for persons on methadone, naltrexone, or buprenorphine, although adolescents, young adults, and pregnant women were found to continue to have a higher risk of discontinuation (Zhang, P. 2022). A meta-analysis found cognitive behavioral therapy and pharmacotherapy were found to be associated with more significant positive treatment outcomes than clinical care, but they had no unique benefit when compared to other specific treatments and pharmacotherapy, including motivational enhancement therapy, contingency management, and 12 step facilitation (Ray, L. 2020).

Specifically, regarding methadone maintenance, a systemic review found that psychosocial treatments combined with pharmacological detoxification treatments were effective in increasing rates of levels of treatment attendance, improving rates of treatment completion, reducing opioid use, and facilitating longer-term abstinence, but psychosocial treatments did not add additional benefits for outcomes including treatment retention and opioid use during treatment (Dugosh, 2016). Other methadone maintenance studies, including one in China (Hser, Y. 2013) have found contingency management participants had significantly more weeks of treatment attendance, longer durations of continued abstinence, lower risk of treatment drop out, and submitted a significantly greater percentage of urines that were opioid-free than those who only received methadone alone (Hser, Y. 2011; Gerra, G. 2011). But the same comparisons found no differences in most outcomes when cognitive behavioral treatment was substituted for contingency management (Moore, B. 2013). Another study that included justice-involved populations found contingency management was associated with increased retention for antagonist but not agonist medications (Chan, B. 2021).

Regarding buprenorphine, a study found 16 weeks of contingency management, cognitive behavioral treatment or the two combined did not improve upon the medication alone in reducing opiate use (Ling, 2013). A randomized clinical trial study also found that adding cognitive behavioral therapy to physician management in providing buprenorphine did not significantly improve outcomes (Fiellin, D. 2013). However, a systemic review that looked at pharmacotherapy for OUD, as well as alcohol and other substance use disorders, found combined cognitive behavioral therapy and pharmacotherapy was associated with increased benefits compared with usual care and pharmacotherapy. All the evidence-based treatment modalities did equally well, suggesting that best practices in addiction treatment should include pharmacotherapy plus cognitive behavioral therapy or another evidence-based therapy, rather than usual clinical management or nonspecific counseling services (Ray, L. 2020). Adding counseling and psychotherapy within the first eight weeks of buprenorphine treatment was found to significantly be associated with an increase in treatment retention (Eren, K. 2022).

All the OUD medications have been found to be compatible within the context of 12-step based treatment and the combination is associated with favorable outcomes (Klein, A. 2019).

A large Medicaid study found that among persons who had prescriptions for buprenorphine for at least seven days, among those who received psychosocial and behavioral therapy, those who received both low or high intensity therapy were more likely to continue buprenorphine treatment than those who received no therapy. The study also found that those who received

the therapy, either low or high intensity, were more likely to have received medical treatment for a prior overdose prior to buprenorphine initiation. It should be noted that 73.8% of the 61,976 patients in the study received therapy (Samples, H. 2020).

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7 What is the evidence regarding opioid withdrawal management?

This section presents studies that examine the research on opioid withdrawal management, including the use of the FDA approved medications for opioid withdrawal management, methadone, buprenorphine, and lofexidine (Lucemyra), as well as the widely off-label use of clonidine.

A survey of more than 500 prisons in 21 states with high opioid overdose rates across the US found most, 81%, screened for OUD at admission and 43% had protocols for withdrawal management. Medication for withdrawal management was provided in 41% of the prisons with 61% providing buprenorphine, 28% methadone, and 5% lofexidine. Half (51%) also provided other medications like clonidine or gabapentin. The single largest barrier reported was lack of money to pay for treatment and medication (Scott, C. 2021). A companion jail survey found 79% of responding jails indicated some aspects of ten OUD best practices within their jails, ranging from 71% using clinical assessments to 96% providing overdose prevention. However, there was considerable variability, ranging from 38% of best practices regarding reentry services to 88% regarding medically managed withdrawal. Researchers concluded training, technical assistance, and funding are needed to improve clinical capacity of jails to administer MOUD and to ensure continuity after release (Scott, C. 2022).

With the increase of fentanyl use, a study has found persons can experience severe withdrawal symptoms after taking fentanyl and then taking other opioids or opiates. A survey of persons with OUD found most reported that taking buprenorphine after fentanyl use was associated with severe withdrawal symptoms. Only a minority (38.4%) reported buprenorphine alleviated withdrawal symptoms. Fewer reported subsequent methadone use was associated with severe withdrawal symptoms, with more (44.3%) reported methadone alleviated withdrawal symptoms (Varshneya, N. 2021).

An open label pilot evaluation of rapid induction of extended-release buprenorphine for individuals with OUD taking fentanyl found after six hours of abstinence and then receiving a single 4 mg dose of transmucosal buprenorphine followed by a 300 mg injection an hour later that they experienced either mild or no active withdrawal symptoms and no serious side effects (Mariani, J. 2023). A nonrandomized trial evaluated seven-day injectable extended-release buprenorphine for patients undergoing minimal to mild opioid withdrawal found between 33 and 43% reported no cravings, between 78 and 85% reported no use of opioids, and 52% found the extended-release buprenorphine was completely effective. Only 2% experienced precipitated withdrawal within an hour. After the study period, 73% of the participants continued buprenorphine treatment (D'Onofrio, G. 2024).

An open label randomized study investigated the use of a nasal spray to treat opioid induced respiratory depression, shallow and slow breathing that is commonly associated with an opioid overdose compared naloxone and nalmefene. It found both to be effective with nalmefene working quicker and both resulting in only mild or moderate adverse events (Ellison, M. 2024).

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a) Forcing methadone and buprenorphine withdrawal

Forcing persons off methadone when they enter prison or jail has been found to increase subsequent aversion to medication-assisted treatment after release (Maradiaga, 2016). In contrast individuals allowed to continue methadone while incarcerated were more than twice as likely to continue the medication once released (Rich, J. 2015). A study of ambulances equipped with buprenorphine found that those given buprenorphine when suffering from an overdose had fewer withdrawal symptoms and were more likely to enter into treatment within 30 days than those serviced by ambulances without buprenorphine. However, there was no difference in incidences of treatment for overdoses (Carroll, G. 2022).

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b) Tapering Individuals Off Opioids

Although tapering persons off opioids with agonist medications is the preferred method for safer, less adverse symptomatic withdrawal management, including subsequent overdoses (Kennedy, M. 2022), nonetheless, research has found that among patients prescribed stable, long-term, higher-dose opioid therapy, tapering events were significantly associated with increased risk of overdose and mental health crisis (Agnoli, A. 2022).

Similarly, a study has found that tapering persons off buprenorphine was associated with the likelihood of high unsuccessful outcomes, i.e., opioid use based on urine tests. Two-week buprenorphine tapering provided only 6.6% successful outcomes. Those receiving four weeks of buprenorphine tapering and eight-week post-medication follow up attained at 49.2% successful outcome. But after eight weeks, the success rate dropped to 8.6%. Researchers concluded that the likelihood of an unsuccessful outcome if tapered off buprenorphine even after 12 weeks is high even for patients also receiving standard medical management (Weiss, R. 2011). A literature review of peer reviewed journal studies concluded that forced tapering and withdrawal during incarceration “can have dire consequences” upon release, increasing the risk of overdose and death upon release to the community (Cates, 2023).

A study of a small pilot program to wean persons off opioid pain medication for chronic, noncancer pain patients found that an outpatient program that included a standardized curriculum, group Cognitive Behavioral Therapy emphasizing pain coping skills and mood regulation, complementary care modalities delivered in a group setting (biofeedback, mindfulness, acupuncture, and gentle motion), and individualized medication management providing the option of buprenorphine, either as an alternative or as a transitional medication, found 90% of participants succeeded and remained off opioid pain medication up to 24 months after the program. But it should be noted, the high success rate included persons who remained on buprenorphine (Silva, M. 2021).

A systematic review of 23 randomized controlled trials found the research suggests that buprenorphine is more effective for detoxification treatments than methadone but there is “some uncertainty” and requires more research (Meador, 2010).

A study comparing the effectiveness of rapid extended-release naltrexone initiation (one day of buprenorphine at minimum dose, one opioid free day, and ascending low doses of naltrexone and adjunctive medications for opioid withdrawal) to standard five-day buprenorphine taper found withdrawal symptoms were not significantly different, adverse events were infrequent but higher with those receiving naltrexone (6.7% v. 1.6%). Those assigned rapid extended-release initiation were much more likely to initiate extended-release naltrexone than those offered it after withdrawing from opioid on buprenorphine (Shulman, M., 2024).

Rather than withdrawing patients from opioids, another study has found that high-dose buprenorphine induction in emergency departments can be done safely and is well tolerated with patients with untreated OUD (Herring, A. 2021). Another study found that rapid micro-induction of buprenorphine can successfully induce patients into buprenorphine treatment and avoid withdrawal symptoms (Klaire, S. 2018). Patients withdrawing from opioids after six to 24 hours were immediately provided a single 4 mg dose of transmucosal of buprenorphine and an hour later a 300 mg extended-release buprenorphine injection. There was a steady decline in symptoms after the injection. But two of the 26 patients experience precipitated opioid withdrawal after the injection (Hassman, H., 2023).

A literature review of 41 research articles found agreement that cannabidiol, a nonintoxicating portion of the cannabis plant, has therapeutic benefits for opioid withdrawal and is well tolerated (Kudrich, C. 2022).

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c) Mitigation medications: lofexidine, clonidine and tapering

Lofexidine (Lucemyra™) and clonidine are two non-opioid medications often used in opioid withdrawal management to mitigate many of the physical symptoms of withdrawal. (Lofexidine was approved by the FDA in 2018. Clonidine has been approved by the FDA for hypertension and attention deficit hyperactivity disorder in children, but not withdrawal management.) Research finds lofexidine to be the superior choice because it is associated with less adverse events than clonidine (Pergoloizzi, J. 2018). However, buprenorphine and methadone tapering have generally been found to be superior to either lofexidine or

clonidine. Individuals that receive buprenorphine or methadone during opioid withdrawal treatment are significantly more likely to complete community-based opioid withdrawal treatment and are less likely to experience adverse events than individuals who receive lofexidine or clonidine (Gowing, L. 2016; Meader, N. 2010).

A review of positive studies of mirtazapine to treat opioid withdrawal symptoms found it to be more effective than Lofexidine due to its ability to alleviate the most distressing symptoms of withdrawal (Lalani, E., 2023).

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8 What is the evidence regarding transitioning patients from methadone to buprenorphine?

This section looks at the research on how individuals can be transitioned from methadone to buprenorphine in ways that are safe and cost effective for treatment programs.

a) Transitioning from methadone to buprenorphine

A systemic review of the literature has found varied ways to transition patients from methadone to buprenorphine depending upon the treatment environment, but such transitions have been found to be expensive and increase diversion (Ghosh, S. 2019). A single experiment found micro dosing with buprenorphine successfully transitioned two patients from methadone to buprenorphine with minimal withdrawal symptoms (Terasaki, D. 2019).

- Ghosh, S.M., Klaire, S., Tanguay, R., Manek, M., & Azar, P. A Review of Novel Methods to Support the Transition from Methadone and Other Full Agonist Opioids to Buprenorphine/Naloxone Sublingual In Both Community and Acute Care Settings. *Canadian Journal of Addiction*, 10(4), 41-50 (2019). Doi: 10.1097/CXA.0000000000000072.
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9 What is the evidence regarding medications for alcohol use disorder?

Globally, alcohol use is one of the leading causes of death, significantly impacting individuals 49 years or younger. Alcohol use increases the risk that individuals will experience mortality from diseases, road accidents, and self-harm (GBD, 2018). Disulfiram, acamprosate, and naltrexone have all been approved by the FDA to treat alcohol use disorder. The research finds, however, there are important aspects of each medication that differentiate their efficacy. This section also includes studies of benzodiazepines used in alcohol withdrawal management. Overall, a scientific review finds all the medications to be associated with abstinence initiation (Witkiewitz, K. 2019). A systemic review and meta-analysis looked at all of the pharmacological treatments for AUD. It found that none of the reviewed medications (nalmefene, baclofen, naltrexone, acamprosate, topiramate) outperformed a placebo for short and long-term alcohol use reduction, although nalmefene appeared superior for some outcomes involving reduced drinking, not abstinence, but caused more adverse events (Kotake, K., 2024). Another study comparing various medications, behavioral health therapies and placebos found that providing placebo with counseling and naltrexone with medical management, intensive counseling, or both yield positive outcomes related to abstinence. Between naltrexone and acamprosate, the study findings suggest that naltrexone is a better medication to consider for alcohol dependence treatment. Also after a year of treatment, participants who received naltrexone had the least risk for heavy drinking (Anton, R. 2006).

- Anton, R.F., O'Malley, S.S., Ciraulo, D.A., Cisler, R.A., Couper, D., Donovan, D.M., Gastfriend, D.R., Hosking, J.D., Johnson, B.A., LoCastro, J.S., Longabaugh, R., Mason, B.J., Mattson, M.E., Miller, W.R., Pettinati, H.M., Randall, C.L., Swift, R., Weiss, R.D., Williams, and L.D., Zweben. (2006). Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence The COMBINE Study: A Randomized Controlled Trial. *JAMA*. 295(17). Doi:10.1001/jama.295.17.2003.
- GBD 2016 Alcohol Collaborators. (2018). Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*. 392(10152). Doi: [https://doi.org/10.1016/S0140-736\(18\)31310-2](https://doi.org/10.1016/S0140-736(18)31310-2)
- Kotake, K., Hosokawa, T., Tanaka, M., So, R., Banno, M., Kataoka, Y., Shiroshita, A., Hashimoto, Y. (2024). Efficacy and safety of alcohol reduction pharmacotherapy according to treatment duration in patients with alcohol dependence or alcohol use disorder: A systematic review and network meta-analysis. *Addiction*, 119(5), 815-832. <https://doi.org/10.1111/add.16421>.
- Witkiewitz, K., Litten, R.Z., & Leggio, L. (2019). Advances in the science and treatment of alcohol use disorder. *Science Advances*. 5(9). Doi:10.1126/sciadv.aax4043.

a) Disulfiram

A study finds that whereas acamprosate and naltrexone can be used to treat moderate or severe alcohol use disorder, disulfiram should not be employed until drinking is under control due to its adverse effects (Mason, B. 2021)

- Mason, B.J., Heyser, C.J. (2021). Alcohol Use Disorder: The Role of Medication in Recovery. *Alcohol Research Current Reviews*. 41(1). <https://doi.org/10.35946/arcrc>

b) Acamprosate

According to a study, acamprosate is suited for individuals who have moderate to severe alcohol use disorder, wish to cut down or quit drinking, and have not responded well to nonpharmacological treatments (Mason, B. 2021). However, one study noted that acamprosate is associated with higher risk of hospitalization which can be reduced if used in conjunction with naltrexone (Heikkinen, M. 2021).

- Heikkinen, M., Taipale, H., Tanskanen, A., Mittendorfer-Rutz, E., Lahtenvuo, M., Tiihonen, J. (2021). Real-world effectiveness of pharmacological treatments of alcohol use disorders in a Swedish nation-wide cohort of 125,556 patients. *Addiction*. <https://doi.org/10.1111/add.15384>
- Mason, B.J., Heyser, C.J. (2021). Alcohol Use Disorder: The Role of Medication in Recovery. *Alcohol Research Current Reviews*. 41(1). <https://doi.org/10.35946/arcr>

c) Naltrexone and agonist medications for AUD and co-occurring OUD

Of the three AUD medications, a study suggests that naltrexone is the most effective because it can be used by itself or along with acamprosate and greatly reduces the likelihood of hospitalizations caused by alcohol (Heikkinen, M. 2021). A systemic review and meta-analysis found naltrexone to be the superior medication for AUD with 50 mg doses associated with lowest relapse rate (McPhetters, M. 2023). Extended-release naltrexone has been found to be more effective in increasing length of sobriety than oral naltrexone (Crits-Christoph, P. 2015; Leighty, A. 2019). It has also been found more effective than psychosocial treatment alone in terms of AUD treatment retention (Crits-Christoph, P. 2015). Naltrexone has been found to be safe for AUD patients with liver disease (Ayyala, D. 2022).

Long term treatment with extended-release naltrexone for AUD decreases the pleasure of alcohol but does not diminish other pleasurable responses (O'Brien, 2011). While not used to treat alcohol use disorder alone, a study looked at days of active OUD medication prescriptions, with either agonist (i.e., buprenorphine or methadone) or antagonist (i.e., oral or extended-release naltrexone) treatments, compared with days without OUD prescriptions for persons with co-occurring AUD. Agonist treatments (buprenorphine and methadone) were associated with reductions in the odds of any alcohol-related acute event compared with nontreatment days, with a 43% reduction for buprenorphine and a 66% reduction for methadone. The antagonist treatment naltrexone was associated with reductions in alcohol-related acute events compared with nonmedication days, with a 37% reduction for extended-release naltrexone and a 16% reduction for oral naltrexone, suggesting that all OUD medications are associated with fewer admissions for alcohol-related acute events in patients with OUD with co-occurring (Xu, K.2021). Similarly, low doses of buprenorphine have been found to be effective in helping patients reduce alcohol consumptions and cravings (Nava, F. 2008).

A double-blind placebo-controlled trial of the oral naltrexone for sexual and gender minority men with mild to moderate alcohol use disorder in San Francisco found a 50 mg dose and weekly counseling for 12 weeks found the naltrexone group significantly reduced the reported number of binge drinking days and the number of drinks per month compared to the placebo group after 12 weeks (Santos, G. 2022).

- Ayyala, D., Bottyan, T., Tien, C., Pimienta, M., Yoo, J., Stager, K., Gonzalez, J.L., Stolz, A., Dodge, J.L., Terrault, N.A., and Han, H. (2022). Naltrexone for alcohol use disorder: Hepatic safety in patients with and without liver disease. *Hepatology Communications*. 6(12), 3433-3442. Doi:10.1002/hep4.2080.

- Crits-Christoph, P., Lundy, C., Stringer, M. A., Gallop, R., & Gastfriend, D. R. (2015). Extended-release naltrexone for alcohol and opioid problems in Missouri parolees and probationers. *Journal of Substance Abuse Treatment*, 56, 54–60.
- Heikkinen, M., Taipale, H., Tanskanen, A., Mittendorfer-Rutz, E., Lahtenvuo, M., & Tiihonen, J. (2021). Real-world effectiveness of pharmacological treatments of alcohol use disorders in a Swedish nation-wide cohort of 125,556 patients. *Addiction*. <https://doi.org/10.1111/add.15384>
- Leighty, A. E., & Ansara, E.D. (2019). Treatment outcomes of long-acting injectable naltrexone versus oral naltrexone in alcohol use disorder in veterans. *Mental Health Clinician*. 9(6), 392-396. <https://doi.org/10.9740/mhc.2019.11.392>
- McPheeters, M., O'Connor, E.A., Riley, S., Kennedy, S.A., Voisin, C., Kuznacic, K., Coffey, C.P., Edlund, M.D., Bobashev, G., and Jonas, D.E. (2023). Pharmacotherapy for Alcohol Use Disorder A Systematic Review and Meta-Analysis. *JAMA Network*, 330(17), 1653-1665. Doi:10.1001/jama.2023.19761.
- Nava, F., Manzato, E., Leonardi, C., & Lucchini, A. (2008). Opioid maintenance therapy suppresses alcohol intake in heroin addicts with alcohol dependence: Preliminary results of an open randomized study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 32, 1867-1872. <https://doi.org/10.1016/j.pnpbp.2008.08.019>
- O'Brien, C.P., Gastfriend, D.R., Forman, R.F., Schweizer, E., Pettinati, H.M. (2011). Long-term Opioid Blockade and Hedonic Response: Preliminary Data from Two Open-Label Extension Studies with Extended-Release Naltrexone. *American Journal of Addiction*, 20(2), 106-112. Doi: 10.1111/j.1521-0391.2010.00107.x.
- Santos, G.M., Ikeda, J., Coffin, P., Walker, J., Matheson, T., Ali, A., McLaughlin, M., Jain, J., Arenander, J., Vittinghoff, E., Batki, S. (2022). Targeted Oral Naltrexone for Mild to Moderate Alcohol Use Disorder Among Sexual and Gender Minority Men: A Randomized Trial. *American Journal of Psychiatry*. 179(12), 915-926. Doi:10.1176/appi.ajp.20220335.
- Xu, K.Y., Presnall, N., Mintz, C.M., Borodovsky, J.T., Bhat, N.R., Bierut, L.J., & Grucza, R.A. (2021). Association of OUD Treatment with Alcohol-Related Acute Events. *JAMA Network*. 4(2). doi:10.1001/jamanetworkopen.2021.0061

d) Benzodiazepines

This study examined the consequences of lowering benzodiazepine use in alcohol withdrawal management in hospitals across northern California. While the new protocol reduced the use of benzodiazepines and increased the use of adjunctive medications such as clonidine, gabapentin, phenobarbital, thiamine, and valproic acid and reduced the use of intensive care units, it was associated with increased mortality which researchers attributed to some patients' difficulty adjusting to changed medications (Smith, J. 2022). An examination of 13,000 opioid overdose deaths between 2001 and 2007 found in the year before death, over half who died had filled prescriptions for opioids or benzodiazepines, and many for both (Olfson, M. 2017)

- Olfson, M., Wall, M., Wang, S., Crystal, S., & Blanco, C. (2017). Service use preceding opioid-related fatality. *The American Journal of Psychiatry*, 175(6), 538–544. <https://doi.org/10.1176/appi.ajp.2017.17070808>
- Smith, J.T., Sage, M., Szeto, H., Myers, L.C., Lu, Y., Martinez, A., Kipnis, P., & Liu, V.X. (2022). Outcomes After Implementation of a Benzodiazepine-Sparing Alcohol Withdrawal Order Set in an Integrated Health Care System. *Journal of the American Medical Association*. 5(2). doi: 10.1001/jamanetworkopen.2022.0158

10 What is the evidence regarding medications for methamphetamines?

A review of studies finds a consensus amongst the research that medications for OUD are not effective in treatment for individuals who use methamphetamines (Ballester, J. 2016).

However, newly tested medications may be more useful. A study found including mirtazapine with substance use counseling reduced methamphetamine use and HIV risk behaviors among cisgender men and transgender women who have sex with men. The benefits extended after treatment despite suboptimal medication adherence. (Coffin, P. 2019). Another study of an experiment found that naltrexone plus oral extended-release bupropion (an antidepressant) in adults with moderate or severe methamphetamine use disorder over 12 weeks found a positive treatment effect of 13.6% measured by negative methamphetamine tests compared to 2.5% for the control placebo group (Trivedi, M. 2021).

- Ballester, J., Valentine, G. & Sofuoglu, M. (2016). Pharmacological treatments for methamphetamine addiction: current status and future directions. *Expert Review of Clinical Pharmacology*. 10(3), 305-314. doi:10.1080/17512433.2017.1268916
- Coffin, P.O., Santos, G.M., Hern, J., Vittinghoff E., Walker J.E., Matheson, T.,...Batki, S.L. 2019. Effects of Mirtazapine for Methamphetamine Use Disorder Among Cisgender Men and Transgender Women Who Have Sex with Men: A Placebo-Controlled Randomized Clinical Trial. *JAMA Psychiatry*, doi: <https://doi.org/10.1001/jamapsychiatry.2019.3655>
- Trivedi, M.H., Walker, R., Ling, W., Cruz, A. D., Sharma, G., Carmody, T., Ghitza, U.E., Wahle, A., Kim, M., Shores-Wilson, K., Sparenborg, S., Coffin, P., Schmitz, J., Wiest, K., Bart, G., Sonne, S.C., Wakhlu, S., Rush, A.J., Nunes, E.V., Shoptaw, S. (2021). Bupropion and Naltrexone in Methamphetamine Use Disorder. *The New England Journal of Medicine*. 384. 140-153. doi: 10.1056/NEJMoa2020214

Appendix A: Summarizes of All Cited Studies

Agnoli, A., Xing, G., Rancredi, D.J., Magnan, E., Jerant, A., & Fenton, J.J. (2021). Association of Dose Tapering With Overdose or Mental Health Crisis Among Patients Prescribed Long-term Opioids. *Journal of American Medical Association*. 326(5), 411-419. doi: 10.1001/jama.2021.11013.

This retrospective cohort study examined the associations between opioid dose tapering and rates of overdose and mental health crises among patients prescribed stable, long-term, and high dose opioids. Deidentified medical records, pharmacy claims, and enrollment data from 2009 to 2019 of 113,618 adults in the US prescribed more than 50 morphine milligram equivalents (MMEs) of opioids were reviewed. Participants prescribed with buprenorphine were excluded from this study. Participant's data were observed over a 12-month period, where researchers examined emergency department visits and inpatient hospital admissions for alcohol intoxication, drug withdrawal, and mental health crisis for depression, anxiety, or suicide attempts.

- Opioid dose tapering was associated with an incidence rate of 9.3 overdose events per 100 persons compared to 5.5 overdose events per 100 persons during non-dose tapering periods.
- Tapering was associated with an incidence rate of 7.6 mental health crises events per 100 persons compared to 3.3 events per 100 persons non tapering.
- **Research Conclusions:** Research findings suggest that patients prescribed high doses of opioid medication have a significant higher risk of experiencing an overdose and mental health crisis during tapering periods.

Ahmadi, J., Jahromi, M.S., & Ehsaei, Z. (2018). The effectiveness of different singly administered high doses of buprenorphine in reducing suicidal ideation in acutely depressed people with co-morbid opiate dependence: a randomized, double-blind clinical trial. *Trials*, 19(1), 462. doi:10.1186/s13063-018-2843-9.

This study investigated how large doses of buprenorphine effect suicidal ideation of individuals diagnosed with opioid dependence and major depression. The sample included 51 suicidal men who were diagnosed with opioid dependence and major depressive disorder in an inpatient hospital over 3 days with a two week follow up. The patients were randomized into three groups to receive 32mg, 64 mg, or 96mg of buprenorphine. Each medication group had 17 participants. The medication was administered while the patients were in moderate opiate withdrawal.

- Each medication group saw a reduction in the number of days that there were suicidal thoughts. However, there was not a significant difference in suicidal thoughts when all three groups were compared.
- During the 2-week follow up none of the participants experienced suicidal ideation.
- Four patients (one from the 32mg, one from the 64mg, and two from the 96mg groups) experienced hypotension, nausea, or vomiting. Among the rest of the 47 participants there were no other significant adverse effect related to the medication.

- **Research Conclusions:** High doses of buprenorphine treatment appear to be a fast-acting treatment for suicidal ideation in those that are suffering from opioid dependence and major depression.

Alderks, C. E. (2017, August 22). Trends in the use of methadone, buprenorphine, and extended-release naltrexone at substance abuse treatment facilities: 2003–2015 (update). The CBHSQ Report. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration.

https://www.samhsa.gov/data/sites/default/files/report_3192/ShortReport-3192.html.

This report updates the trends in the use of methadone and buprenorphine and adds to these trends by including the use of extended-release, injectable naltrexone in the treatment of opioid use disorders in substance abuse treatment facilities. This report includes data from opioid treatment programs (OTPs) as well as facilities that did not have OTPs (hereafter referred to as “non-OTP facilities”). It does not include data from private physicians who are not affiliated with a substance abuse treatment program or facility.

- The increase in the number of clients receiving methadone treatment coupled with the stability of the proportion of clients receiving this treatment indicates that the overall availability of methadone treatment has increased over time.
- Likewise, the numbers of clients receiving buprenorphine at substance abuse treatment facilities on the survey reference date increased. At OTPs, the number of clients increased from 727 clients in 2004, the first year N-SSATS collected buprenorphine client counts, to 21,236 clients in 2015; at non-OTPs, the number increased from 1,670 clients in 2004 to 54,488 clients in 2015.
- **Research Conclusions:** These buprenorphine numbers include only those clients who received their buprenorphine through a DATA 2000 waived physician affiliated with a facility. It does not include any clients who received buprenorphine through an independent DATA 2000 waived physician. In 2013, 359 clients in facilities with OTPs and 3,422 clients in facilities without OTPs received extended-release, injectable naltrexone services. In 2015, a total of 712 clients in facilities with OTPs and 6,323 clients in facilities without OTPs received these services. Again, these numbers include only those clients who received their naltrexone services through a treatment facility, not through an independent medical professional.

Ali, M. M. (2021), Suicidal behavior, OUD, and behavioral health treatment: Prevalence and correlates among adults in the United States 2015-2018

This retrospective study examined the risk of suicidal behavior among individuals with opioid use disorder and if behavioral health treatment helps lower the risk of suicidal behavior. Data were obtained from the 2015-2018 National Survey of Drug Use and Health, which provided details about suicidal behavior.

Individuals with opioid use disorder had a higher rate of suicidal behavior than those without opioid use disorder (22% vs 4%).

- 43% of individuals with opioid use disorder reported that they had not received substance use disorder treatment nor mental health treatment.

- The odds of suicidal behavior for individuals with opioid use disorder was 49% lower if they received substance use disorder treatment, 5% lower with mental health treatment, and 28% lower when receiving both substance use disorder and mental health treatment.
- **Research Conclusions:** Individuals with opioid use disorder have an increased risk of suicidal behaviors compared to those without opioid use disorder. Substance use treatment appears to be a superior intervention compared to mental health treatment and mental health treatment with substance abuse treatment. There is not a clear understanding as to why substance use and mental health treatment combined does not improve upon outcomes from substance use treatment only.

Anbalagan, S., Anderson, V., Favara, M.T., Stark, D., Carola, D., Solarin, K., Adeniyi-Jones, S., Kraft, W.K., and Aghai, Z.H. (2024). Buprenorphine vs. morphine: impact on neonatal opioid withdrawal syndrome (NOWS) outcomes in a single center retrospective study. Journal of Perinatology. <https://doi.org/10.1038/s41372-024-02046-7>.

This retrospective study compared the outcomes of infants with neonatal opioid withdrawal syndrome (NOWS) treated with buprenorphine or morphine. The study sample consisted of 649 infants born between January 1st 2011 through July 30th, 2022 at a gestational age of 35 weeks or above who were admitted to a level 3 NICU in Philadelphia for pharmacotherapy and medical management for NOWS. The study sample of infants were mostly White (58%), male at the time of birth (51%), on average were 38 weeks old, and were born by vaginal delivery (65.5%). The birth mother of study infants had a median maternal age 30 years, and most mothers were enrolled in a methadone maintenance program (78%). A total of 232 infants were treated with buprenorphine and 417 infants were treated with morphine.

- The length of treatment was significantly higher amongst infants treated with morphine (25 days) compared to infants treated with buprenorphine (13 days).
- The length of stay in the hospital was significantly higher amongst infants treated with morphine (31 days) compared to infants treated with buprenorphine (18.5 days).
- 25.3% of infants treated with morphine and 21.1% of infants treated with buprenorphine need phenobarbital as a secondary medication.
- 3.6% of infants treated with morphine and 5.6% of infants treated with buprenorphine needed clonidine as a secondary medication.
- **Research Conclusions:** The findings of this retrospective study suggest that providing buprenorphine to infants with NOWS lead to shorter hospital stays and length of treatment compared to providing morphine treatment.

Andraka-Christou, B., Gabriel, M., Madeira, J., & Silverman, R.D. (2019). Court personnel attitudes towards medication-assisted treatment: A state-wide survey. Journal of Substance Abuse and Treatment. 104, 72-82. doi: 10.1016/j.jsat.2019.06.011.

This study explored the thoughts and feelings that justice system professionals have towards MAT. Surveys were distributed to 231 Indiana judges, probation officers, law enforcement personnel, attorneys, program directors, counselors, and case managers who were registered for a MAT educational summit in 2018.

- Participants had significantly more positive attitudes towards extended-release naltrexone than methadone and oral buprenorphine. Methadone was the least liked medication.
- Prosecutors and law enforcement personnel were significantly more likely to have negative attitudes towards oral buprenorphine and methadone.
- Participants who had previous exposure to MAT training were more likely to have more positive attitudes for all MAT medications.
- Participants with less education were significantly more likely to have negative attitudes towards extended-release naltrexone.
- Gender, age, rurality, and personal/family recovery history was not associated with a difference in medication attitudes.
- **Research Conclusions:** Findings from the survey show that justice system professionals have a preference of extended-release naltrexone over other medications. The survey was unable to provide evidence for the reason why extended-release naltrexone was preferred, the researchers could only make inferences about the reason. Previous experience with MAT and education level were associated with positive attitudes towards MAT, suggesting that more awareness and educational interventions are needed to properly inform justice system professionals, especially prosecutors and law enforcement.

Andraka-Christou, B., Simon, K.I., Bradford, W.D., Nguyen, T. (2023). Buprenorphine Treatment for Opioid Use Disorder: Comparison Of Insurance Restrictions, 2017-21. Health Affairs, 42(5). <https://doi.org/10.1377/hlthaff.2022.01513>.

This study examined insurance-imposed utilization restrictions for buprenorphine to treat opioid use disorder for each year from 2017 to 2021. Study authors examined the insurance coverage, prior authorization requirements, and potential access barriers of Medicaid, Medicare Advantage, and commercial insurance.

- Most insurance plans covered sublingual buprenorphine and the need of prior authorization decreased from 2018 to 2021.
- 46% of commercial plans and 19% of Medicare Advantage plans covered extended releases buprenorphine. Medicaid plans often covered extended-release buprenorphine, however 37% of plans often required prior authorization.
- **Research Conclusions:** Study findings suggest that sublingual is the easiest form of buprenorphine that individual's can obtain especially due to prior authorization not always being required. There appears to be difficulty in obtaining extended-release buprenorphine for most insurance plans with prior authorization being an additional barrier to the treatment.

Anton, R.F., O'Malley, S.S., Ciraulo, D.A., Cisler, R.A., Couper, D., Donovan, D.M., Gastfriend, D.R., Hosking, J.D., Johnson, B.A., LoCastro, J.S., Longabaugh, R., Mason, B.J., Mattson, M.E., Miller, W.R., Pettinati, H.M., Randall, C.L., Swift, R., Weiss, R.D., Williams, and L.D., Zweben. (2006). Combined Pharmacotherapies and

Behavioral Interventions for Alcohol Dependence The COMBINE Study: A Randomized Controlled Trial. JAMA. 295(17). Doi:10.1001/jama.295.17.2003.

This randomized controlled trial evaluated the efficacy of combining medication and behavioral health therapies to treat alcohol dependence and whether a placebo with counseling could be beneficial to treatment. After completing a baseline assessment and attaining four-days of abstinence, 1,383 alcohol dependent participants (42 women and 955 men) were randomly assigned to one of nine groups for 16 weeks of outpatient treatment. Eight of the assigned groups included 1,226 participants who received medical management treatment which consisted of 9-session interventions that focused on medication adherence and abstinence. Four of these assigned groups (n= 619) received intensive counseling that were conducted by alcohol treatment specialists while the remaining four did not receive intensive counseling. These eight treatment groups either received naltrexone (100 mg), acamprosate (3g), naltrexone and acamprosate, or placebos with naltrexone or acamprosate or placebo only. The ninth group of 157 participants received intensive counseling only with no medication. Participants were observed for one year after treatment. To be eligible for the study participants had to have an alcohol dependence diagnosis, have 4-21 days of abstinence, had either 14 drinks (women) or 21 drinks (men) per week with at least 2 heavy drinking days during a 30-day period within 90 days of study enrollment. Participants were excluded from the study if they had a history of other substance use other than nicotine or cannabis, psychiatric disorders that require medication, and unstable medical conditions. Participants had an average age of 44 years, had at least 12 years of education (77%), single (58%), and White (77%).

- The study found no significant differences in treatment retention between study groups.
- 70 adverse events occurred during the study, with two events possibly related to study medication (1 naltrexone and 1 acamprosate).
- The most common adverse event was hospitalization for detoxification (n=38).
- During treatment, participants who received naltrexone with medical management (80.6%), medical management and placebos (79.2%), and naltrexone with intensive counseling and medical management (77.1%) had highest percent days of abstinence.
- One year after treatment, participants treated with placebo and medical management (61.4%) had a lower percentage of days abstinence than those treated with naltrexone and medical management (66.2%) and those treated with intensive counseling with naltrexone (67.3%), and without naltrexone (66.6%).
- Participants increased the likelihood of having at least one heavy drinking day one year after treatment, however participants who received naltrexone had the least amount of risk of heavy drinking.
- Acamprosate showed no significant effect on drinking compared to the placebo and naltrexone.
- Research Conclusions: The study appears to show that providing placebo with counseling and naltrexone with medical management, intensive counseling, or both yield positive outcomes related to abstinence for drinking. Between naltrexone and acamprosate, the study findings suggest that naltrexone is a better medication to consider for alcohol dependence treatment.

Ayyala, D., Bottyan, T., Tien, C., Pimienta, M., Yoo, J., Stager, K., Gonzalez, J.L., Stolz, A., Dodge, J.L., Terrault, N.A., and Han, H. (2022). Naltrexone for alcohol use disorder: Hepatic safety in patients with and without liver disease. *Hepatology Communications*. 6(12), 3433-3442. Doi:10.1002/hep4.2080.

This retrospective cohort study evaluated the safety of naltrexone to treat alcohol use disorder patients with liver disease. A total of 160 patients, who were 18 years or older and had prescriptions for naltrexone to treat alcohol use disorder in inpatient and outpatient settings were identified for the study. Patients were grouped into two groups, without liver disease (n=60) and with liver disease (n=100). Patients with chronic liver diseases were excluded from the study. Majority of the sample were men (80%), Hispanic (64%), prescribed with a daily naltrexone 50mg dose (88%), insured by Medicaid (89%, and had a median age of 49 years.

- At 10 months, eight patients died, with a median of deaths occurring five months after the initial naltrexone prescription. The deaths were found to not have been related to naltrexone treatment.
- After receiving a naltrexone prescription, 30 patients had at least one alcohol related hospitalization. Hospitalizations were highest among patients with liver disease and short-term naltrexone prescriptions.
- Patients who were prescribed 25mg of naltrexone (42.9%) were more likely to have an alcohol related hospitalization compared to patients prescribed 50mg of naltrexone (25.5%).
- **Research Conclusions:** The findings of this retrospective study show that naltrexone is a safe medication for patients with liver disease and alcohol use disorder. Short term naltrexone prescription, liver disease, low dosage naltrexone were predictors of alcohol related hospitalizations.

Bala, N., Naib, G., Singh, M., Kaur, M., Singh, A., Kaur, S. (2023). A Follow up Study Among Patients on Opioid Substitution Therapy (OST) in Terms of Relapse Rate, Factors Affecting Relapse Rate and HCV Incidence. *Annals of International Medical and Dental Research*, 9(3), 243-248. Doi: 10.53339/aimdr.2023.9.3.29.

This study examined the relapse rate, risk factors, and the incidence of hepatitis C of individuals receiving opioid substitution therapy. The study took place in India where 200 individuals were randomly assigned to receive buprenorphine substitution therapy (n=100) or methadone maintenance treatment (n=100) between May 1st 2021 through April 30th 2022. Individuals were eligible for the study if they were on buprenorphine or methadone treatment for at least 3 months prior to the study and were 18 years of age or older, however individuals were excluded if they had comorbid drug addictions or psychiatric or medical ailments. Individuals were followed every 3 months for one year where they filled out a 14-item questionnaire which gathered data on how often certain events could have or did lead to a relapse in the previous weeks.

- The relapse rate among patients who received buprenorphine treatment was 42% and the treatment dropout rate was 17%. Individuals treated with methadone had a relapse rate of 35% and a treatment dropout rate of 15%.
- The two most common factors that led to relapses at 3 and 9 months were “I was with others having a good time and we felt like getting high together” and “I saw someone else use or saw drugs and felt I had to use.”

- The two most common factors for relapse at 6 months were “I was offered drugs” and “I saw someone else use or saw drugs and felt I had to use.”
- The incident of hepatitis C amongst the buprenorphine group was 72% and 78% for the methadone group.
- **Research Conclusions:** Study findings show that amongst study individuals receiving methadone and buprenorphine treatment had a high incidence rate of hepatitis C. Individuals who received methadone had a lower relapse and treatment dropout rate than individuals receiving buprenorphine. Findings appear to suggest that the most common reason that individuals relapsed were because they saw someone else using and wanted to use as well. This study was conducted in India, so study findings may not be representative to individuals in the United States.

Ballester, J., Valentine, G. & Sofuoglu, M. (2016). Pharmacological treatments for methamphetamine addiction: current status and future directions. *Expert Review of Clinical Pharmacology*. 10(3), 305-314. doi:10.1080/17512433.2017.1268916.

This article reported a comprehensive review of clinical trials that tested medications for methamphetamine use disorder. The reviewers looked at published research and searched PubMed and Google Scholar as well as ClinicalTrials.gov to identify recent completed trials. Found the studies to date suffer from small sample sizes, high dropout rates and multiple comorbidities.

- Found that the results on the effects of medication for methamphetamine use disorder were “largely negative”
- Found new treatment targets, including methamphetamine-induced disruptions in cognition and in the neuroimmune system merit trials with agents that selectively moderate these processes.

Bazazi, A. R., Yokell, M., Fu, J. J., Rich, J. D., & Zaller, N. D. (2011). Illicit use of buprenorphine/naloxone among injecting and noninjecting opioid users. *Journal of Addiction Medicine*, 5(3), 175–180. <https://doi.org/10.1097/ADM.0b013e3182034e31>.

This study examined the use, procurement, and motivations for the use of diverted buprenorphine/naloxone among injecting and noninjecting opioid users in an urban area. A survey was self-administered among 51 injecting opioid users and 49 noninjecting opioid users in Providence, RI. Participants were recruited from a fixed-site syringe exchange program and a community outreach site between August and November 2009.

- A majority (76%) of participants reported having obtained buprenorphine/naloxone illicitly, with 41% having done so in the previous month. More injection drug users (IDUs) than non-IDUs reported the use of diverted buprenorphine/naloxone (86% vs. 65%).
- The majority of participants who had used buprenorphine/naloxone reported doing so to treat opioid withdrawal symptoms (74%) or to stop using other opioids (66%) or because they could not afford drug treatment (64%). More IDUs than non-IDUs reported using diverted buprenorphine/naloxone for these reasons.
- Significantly more non-IDUs than IDUs reported ever using buprenorphine/naloxone to “get high” (69% vs. 32%).

- The majority of respondents, both IDUs and non-IDUs, were interested in receiving treatment for opioid dependence, with greater reported interest in buprenorphine/naloxone than in methadone.
- Common reasons given for not being currently enrolled in a buprenorphine/naloxone program included cost and unavailability of prescribing physicians.
- **Research Conclusions:** The use of diverted buprenorphine/naloxone was common in our sample. However, many opioid users, particularly IDUs, were using diverted buprenorphine/naloxone for reasons consistent with its therapeutic purpose, such as alleviating opioid withdrawal symptoms and reducing the use of other opioids.

Bharat, C., Larney, S., Barbieri, S., Dobbins, T., Jones, N.R., Hickman, M., Gisev, N., Ali, R., & Degenhardt, L. (2021). The effect of person, treatment, and prescriber characteristics on retention in opioid agonist treatment: a 15-year retrospective cohort study. *Addiction*. doi: 10.1111/add.15514.

- This retrospective longitudinal study observed retention in buprenorphine and methadone treatment in relation to the characteristics of the patient, treatment, and prescriber. Participants included 22,577 patients who were entering opioid agonist treatment for the first time in New Wales Australia from August 1, 2001, to December 31, 2015. Most patients in the study were male (69%), non-Indigenous (77%), and a median age of 29 years old.
- The risk of leaving treatment when taking buprenorphine compared to methadone was higher among those who started treatment from 2001-2003 but was lower among those who started treatment from 2013-2015.
- The risk of leaving treatment was reduced among patients whose prescriber had a longer history of prescribing medication.
- Indigenous patients, younger age, history of psychosis, and four or more criminal convictions were associated with an increased risk of leaving treatment.
- **Research Conclusions:** Study findings suggest that opioid agonist treatment retention is affected by the prescriber, treatment, and patient characteristics. While the explanation of why the shift from methadone to buprenorphine helping retain patients is not clear, there should be a greater focus to retain young people, indigenous people, and people in the criminal justice.

Binswanger, I.A., Sern, M.F., Deyo, R.A., Heagerty, P.J., Cheadler, A., Elmore, J.G., and Koepsell, T.D. (2007). Release from Prison- A High Risk of Death for Former Inmates. *The New England Journal of Medicine*, 356(2), 157-165. Doi: 10.1056/NEJMsa064115.

This retrospective cohort study investigated the risk of death of inmates upon their release from Washington State prisons to find out the major causes of death, whether the first two weeks of release from prison elevated the risk of death, and to compare inmate mortality rates amongst Washington State residents. The study identified 30,237 individuals who

were released from the Washington State Department of Corrections between July 1999 through December 2003. Individuals released from jails were excluded from the study. Majority of the sample were non-Hispanic White (62%), male (87%), average age of 33.4 years, an average of 22.9 months of incarceration. It should be noted that 91% of individuals who identified as Hispanic also reported being White.

- Of the 443 individuals who died after their release from prison, 253 individuals died within one year after their release.
- The risk of death among former incarcerated individuals was 3.5 times higher than the general population of Washington state.
- Compared to general population of Washington state, the risk of all cause death within the first two weeks for individuals released from prison was 12.7 times higher and 129 times higher specifically for drug overdose deaths.
- The leading cause of death amongst former incarcerated individuals was drug overdose (103 deaths). Overdoses were the most common cause of death within two weeks after release (n=27). Deaths from overdose were most common amongst individuals younger than 45 years of age.
- Cocaine was most common drug to have caused overdose amongst formerly incarcerated individuals (n=50), followed by psychostimulants (n=19), heroin (n=18), methadone (n=18). 27 deaths involved multiple drugs.
- **Research Conclusions:** The study finds that released from prison, individuals are at much higher risk for death, especially drug overdose deaths than the general population.

Bolivar, H.A., Klemperer, E.M., Coleman, S.R., DeSarno, M., Skelly, J.M., & Higgins, S.T. (2021). Contingency Management for Patients Receiving Medication for Opioid Use Disorder, A Systematic Review and Meta-analysis. Journal of American Medical Association. doi:10.1001/jamapsychiatry.2021.1969.

This systematic review and meta-analysis examined the use of contingency management in addressing clinical challenges among patients receiving medication for opioid use disorder. 74 studies published from 1984-2019 were reviewed. The findings presented in this review concern the outcomes of contingency management used to treat six clinical problems: stimulant use, polysubstance use, illicit opioid use, cigarette smoking, therapy attendance, and medication adherence.

- 18 of 22 studies found contingency management used to treat stimulant use significantly increased abstinence. Methadone was used in 21 of the 22 studies.
- Contingency management was found to have increased abstinence from polysubstance use in 16 out 23 studies. Methadone was used in 13 studies followed by buprenorphine (n=6), naltrexone (n=2), combined methadone and buprenorphine (n=2), and levacetylmethadol (n=1).
- 7 of 11 studies found contingency management used to treat illicit opioid use significantly increased abstinence. Methadone was used in nine studies while buprenorphine and naltrexone were used in one study each.
- Therapy attendance (7 out 11 studies) and medication adherence (6 out of 9 studies) saw an increase through contingency management. Methadone was prescribed in all therapy attendance studies. Naltrexone was primarily used in the medication adherence studies.

- **Research Conclusions:** This systematic review and meta-analysis found that contingency management was useful in increasing abstinence among various drugs and improved treatment adherence and attendance among opioid use disorder patients. Methadone was the most used medication used in conjugation with contingency management.

Borodovsky, J. T., Levy, S., Fishman, M., & Marsch, L. (2018). Buprenorphine treatment for adolescents and young adults with opioid use disorders: A narrative review. *Journal of Addiction Medicine*, 12(3), 170–183.

<https://doi.org/10.1097/ADM.0000000000000388>.

This narrative review examines scientific literature to discuss findings of random controlled and observational studies that evaluated the use of buprenorphine to treat adolescents. Three randomized control studies and nine observational studies were reviewed.

- In the randomized control studies, adolescents who received buprenorphine for long periods of time demonstrated better opioid abstinence outcomes than adolescents that received buprenorphine for a shorter time period.
- In each of the random controlled treatments, adolescents who received buprenorphine for long periods of time were more likely to remain in treatment than those who received buprenorphine for a short period of time.
- Adolescents who were able to take self-administered buprenorphine at home 2–3 times per week exhibited more negative urine screen (42.2% vs. 8.6%) and higher retention rates (46.7% vs. 17.3%) than adolescents who had to go to a clinic daily for buprenorphine.
- Like the randomized control studies, the observational studies that were reviewed supported the long-term use buprenorphine leads to better outcomes of opioid abstinence.
- **Research Conclusions:** Buprenorphine should be used as a first line treatment for adolescents along with other long-term management strategies.

Bunting, A.M., Oser, C.B., Staton, M., & Knudsen, H.K. (2021). Pre-incarceration polysubstance use involving opioids: A unique risk factor of postrelease return to substance use. *Journal of Substance Abuse Treatment*. 127. doi:

<https://doi.org/10.1016/j.jsat.2021.108354>.

This study investigated the relationship between pre incarceration polysubstance opioid use as a risk factor for continued substance use after release. Data were obtained from 501 justice involved individuals who were enrolled in a therapeutic community treatment program while incarcerated. Participants answered a self-reporting survey that captured the type of drugs use prior to incarceration, occurrence of a relapse, and drugs used during relapse after incarceration.

- Individuals who primarily used alcohol and nonmedical buprenorphine prior to incarceration had an increased risk of relapse post incarceration.
- The individuals who primarily used alcohol and nonmedical buprenorphine often used marijuana and nonmedical opioids prior to incarceration.

- The daily amount of alcohol and nonmedical buprenorphine used were unique among individuals who used marijuana and nonmedical opioids.
- **Research Conclusions:** Findings suggest that individuals who use alcohol or nonmedical buprenorphine with marijuana and nonmedical opioids prior to being incarcerated are at a higher risk of relapsing upon release. The daily amount of alcohol and nonmedical buprenorphine used appears to not have an influence either way on a person's risk of relapse.

Burns, L., Gisev, N., Larney, S., Dobbins, T., Gibson, A., Kimber, J., Larance, B., Mattick, R. P., Butler, T., & Degenhardt, L. (2015). A longitudinal comparison of retention in buprenorphine and methadone treatment for opioid dependence in New South Wales, Australia. *Addiction*, 110(4), 646–655. <https://doi.org/10.1111/add.12834>

This Australian study looked at 7,183 individual first time on buprenorphine compared with 8,417 first time on methadone between 2001 and 2010.

- Those starting buprenorphine switched medications more frequently and had more subsequent treatment episodes. Buprenorphine retention was also poorer. On average, only 44% spent 3+ months in treatment compared with 70% of those commencing methadone. Buprenorphine retention was also poorer. However, Buprenorphine retention for first-time entrants improved over time, whereas methadone retention did not.
- The risk of leaving a first treatment episode was greater on any given day for those receiving buprenorphine, dependent on the year treatment was initiated.
- **Research Conclusions:** There was no interaction between any demographic variables and medication received, suggesting no clear evidence of any particular group for whom each medication might be better suited in terms of improving retention. Despite increased retention rates for buprenorphine in study, individuals starting on methadone treatment showed higher retention rates.

Burns, M., Tang, L., Chang, C.H., Kim, J.Y., Ahrens, K., Allen, L., Cunningham, P., Gordon, A.J., Jarlenski, M.P., Lanier, P., Mauk, R., McDuffie, M.J., Mohamoud, S., Talbert, J., Zivin, K., & Donohue, J. (2022). Duration of Medication Treatment for Opioid-Use Disorder and Risk of Overdose among Medicaid Enrollees in Eleven States: A Retrospective Cohort Study. *Addiction*. <https://doi.org/10.1111/add.15959>.

This retrospective cohort study evaluated the outcomes between medication for opioid use disorder continuation in relation to discontinuation and opioid overdoses among Medicaid individuals. The study included 293,180 Medicaid enrollees between the ages of 18-64 with a diagnosis of opioid use disorder and had their first claim for a medication for opioid use disorder between 2016-2017. The Medicaid enrollees were included in the study if they lived in Delaware, Kentucky, Maryland, Maine, Michigan, North Carolina, Ohio, Pennsylvania, Virginia, West Virginia, and Wisconsin.

- 51% of Medicaid enrollees had an overdose and 67% discontinued medication for opioid use disorder prior to the overdose.

- Medicaid enrollees who continued medication for opioid use disorder were associated with a lower risk of overdoses compared to those who continued for 60, 120, 180, 240, and 300 days.
- For every 60 days an individual stayed on medication, their risk of overdosing decreased by 10%.
- **Research Conclusions:** Study findings suggest that continuing medication for opioid use disorder for a long period of time can significantly reduce the risk of an opioid related overdose after an individual's first claim of medication.

Buttram, M.E., Kurtz, S.P., Margolin, Z.R., & Severtson, S.G. (2021). Increasing Rates of Buprenorphine Diversion in the United States, 2002 to 2019. *Pharmacoepidemiology and Drug Safety*. <https://doi.org/10.1002/pds.5334>.

This study reported a national level examination of the rates of buprenorphine diversion from 2002 to 2019. Case report data were obtained from quarterly surveys about prescription drug diversion completed by law enforcement and agencies involved in drug diversion investigations. 9,670 cases of diverted buprenorphine were reported in the United States during the study period. Quarterly rates of buprenorphine diversion per 100,000 persons and 100,000 prescriptions were used for calculations of the results.

- Increases in diversion rates from 2002 through 2006 were not statistically significant but from 2008 to 2019 diversion rates increased by .0067 cases per 100,000 persons.
- Buprenorphine diversion rates by prescriptions dispensed gradually increased by .28 case per 100,000 prescriptions each year since 2010 through 2019.
- The Northeast region of the United States was the only region that did not experience an increase in buprenorphine diversion rates after 2006. Researchers were unable to explain this occurrence.
- **Research Conclusions:** Study findings show that the diversion of buprenorphine has been gradually increasing in the United States over the years particularly around the early 2010's with the only exception being the northeast portion of the United States. Additional research is needed to better explain buprenorphine diversion rates.

Carlson, R.G, 2020, Unintentional drug overdose: Is more frequent use of non-prescribed buprenorphine associated with lower risk of overdose?

Researchers investigated a hypothesis that people with opioid use disorder who have used non prescribed buprenorphine frequently in the past six months are less likely to experience an unintentional drug overdose. The study was of 356 adults in Dayton, Ohio with moderate or severe opioid use disorder who used non prescribed buprenorphine at least once in the past six months. Participants were recruited by answering a recruitment flier posted in the community, social media, and local newspaper. Overall, 50.3% of the participants were male, mean age 39.2 years old, 89% were non-white Hispanic, 23% were married or lived with a partner, 78% had a high school degree/GED or higher education, 54.8% considered themselves being homeless in the past six months. Participants completed a baseline structured interview and a six month follow up interview for data collection. Participants used non-prescribed buprenorphine 26.9 (14.6%) days on average. About 90% of participants

reported using buprenorphine for self-treatment of opioid use withdrawal symptoms.⁹⁸ (27.5%) participants experienced at least one drug overdose in the past six months. 221 (62.3%) participants experienced at least one overdose more than six months ago. Over 95% of overdoses were related to the use of heroin/non-prescribed fentanyl or non-prescribed pharmaceutical opioid. Heroin/non-prescribed fentanyl was used 56.4% of the days in the past six months by participants. 65% of participants who used heroin/non-prescribed fentanyl reported injection as the most frequent route of administration.

- Participants who used non-prescribed buprenorphine more than 5.4% of days had 33% lower odds of an overdose.
- The odds of an overdose were two times greater for participants with prior overdose experience.
- Participants who reported injection as the most common route of heroin/non-prescribed fentanyl were 2.5 times more likely to experience an overdose compared to those who used a non-injection route. Methamphetamine use, incarceration, and crack/cocaine use were also associated with greater odds of an overdose.
- **Research Conclusions:** Research findings have confirmed the hypothesis that people who use non-prescribed buprenorphine frequently have a lower risk of an overdose. An increased risk unintentional overdosing may be attributed to injection drug use, incarceration, methamphetamine, and crack and cocaine use.

Carson, E.A. (2021). Mortality in Local Jails, 2000-2019- Statistical Tables. Bureau of Justice Statistics Statistical Tables. Washington, D.C.: US Department of Justice, Bureau of Justice Statistics. <https://bjs.ojp.gov/content/pub/pdf/mlj0019st.pdf>.

This report by the Bureau of Justice, provides statistical information on the deaths in jails from 2000 to 2019. The report provides data on the cause of death, location of death, characteristics of those who deceased, and the mortality rate of deaths in local jails by state.

- In 2019, suicide (n=355) was the leading single cause of death in jails, however illnesses as a group had the most deaths (n=516), with heart disease as the most common illness (n=198). Drug and alcohol intoxication accounted for 15% of deaths in 2019 which was a 4% increase from 2000.
- In 2019, majority of incarcerated individuals who died were 55 years or older, been incarcerated for 30 days or less, and were identified as being non-Hispanic white.
- 42% of non-convicted individuals held in jails during 2000-2019 died of either suicide (n=5,084) or drug or alcohol intoxication.
- The median time from jail admission to death was 17 days from 2000-2019.
- About 50% of jail deaths from 2000-2019 occurred in a medical unit either inside or outside of the jail.
- **Research Conclusions:** This findings of morality in local jails reveals that mortality in jails has risen from 2000-2019 with illnesses and suicide being the two most common causes of death.

Cates, L., Brown, A.R. (2023). Medications for opioid use disorder during incarceration and post-release outcomes. Health and Justices 11(1). <https://doi.org/10.1186/s40352-023-00209-w>.

This literature review investigated the post release outcomes associated with the use of medications for opioid use disorder in correctional settings in the United States. The literature review included 22 peer reviewed studies that included participants who were incarcerated in the United States, examined post release outcomes associated with medication for opioid use disorder while incarcerated, and published prior to September 20, 2022. Eleven of the reviewed studies were randomized controlled designs, while the remaining 11 studies were nonexperimental design. The mean sample size of the studies was 777 participants, nine studies examined methadone only, three studies examined buprenorphine only, six studies examined extended-release naltrexone only, one study examined levo-alpha acetylmethadol, and three studies examined multiple medications. Most studies took place in the northeastern and mid-Atlantic regions of the United States. Jails were the most frequent study location (n=13), while five took place in prisons only, and four took place in both jails and prisons.

- Providing medications for OUD to incarcerated populations is associated with increased engagement in treatment post release.
- It is also associated with decreased opioid use, injected drug use, and overdoses after release.
- Forced tapering and withdrawal during incarceration can increase the risk of overdose and death upon release.
- Methadone was associated with decreased criminal involvement while buprenorphine studies found either reduced or no change in criminal involvement and naltrexone was not associated with reduced criminal involvement unless there were at least two injections post release.
- **Research Conclusions:** Initiating or continuing opioid medication during incarceration reduces the risk for opioid use and overdose upon release and increases community treatment engagement.

Chambers, L.C., Hallowell, B.D., Zullo, A.R., Paiva, T.J., Berk, J., Gaither, R., Hampson, A.J., Beaudoin, F., Wightman, R.S. (2023). Buprenorphine Dose and Time to Discontinuation Among Patients with Opioid Use Disorder in the Era of Fentanyl. JAMA Network Open. 6(9). Doi: 10.1001/jamanetworkopen.2023.34540.

This retrospective cohort study examined the association between buprenorphine dose and the time to treatment discontinuation 180 days after initiation during a period of high fentanyl availability. The study examined data from 6,499 individuals who had data in the Rhode Island Prescription Drug Monitoring Program data set for initiating sublingual buprenorphine treatment for opioid use disorder between October 1, 2016, and September 30, 2020. Most individuals in the study were between 25-44 years of age (57%), male (61%), had private insurance (47%), initially prescribed with a daily 16mg dose of buprenorphine (50%), and lived less than five miles away from their pharmacy (72%). The Rhode Island Prescription Drug Monitoring Program included data from retail pharmacies, but it did not capture data on buprenorphine prescriptions from certain health care settings such as hospitals or opioid treatment programs or correctional situations.

- 180 days after initiation, 465 of individuals were censored due to a dose change. Individuals who were prescribed 16mg were most likely to be censored compared to individuals who were prescribed 24mg.
- 59% of individuals initially prescribed 16 mg of buprenorphine discontinued buprenorphine treatment within 180 days compared to 53% of individuals prescribed 24mg.
- **Research Conclusions:** The study findings appear to show that individuals who have a dose of 24 mg of buprenorphine are more likely to retain treatment than individuals prescribed 16 mg of buprenorphine during a time of high fentanyl availability. The data presented in this study primarily came from retail pharmacies and most study individuals lived less than five miles of their pharmacies, so this study sample may not be reflective of the population.

Chan, B., Gean, E., Arkhipova-Jenkins, I., Gilbert, J., Hilgart, J., Fiordalisi, C., Kimberly, H., Brandt, I., Stoeger, E., Paynter, R., Korthuis, P., & Guis, J.M. (2021). Retention Strategies for Medications for OUD in Adults: A Rapid Evidence Review. Journal of Addiction Medicine. 15(1), 74-84. doi: 10.1097/ADM.0000000000000739

This evidence review examined interventions that help to improve retention for medications for opioid use disorder. Two systemic reviews and 39 primary studies (randomized trials of care settings, service, logistical support, contingency management, health information technology, extended-release formulations, and interventions) from February 2009 through August 2019 were reviewed. All the studies assessed retention for at least three months.

- Initiating medications for opioid use disorder among soon to be released incarcerated individuals improved medication retention upon release.
- Antagonist medications but not agonist medications significantly improved retention when contingency management was used.
- Interventions using medical, psychiatric, social services, or informational technology did not significantly impact retention when compared to MAT alone.
- Studies comparing extended-release buprenorphine to daily buprenorphine produced similar results in retention between the two groups. However, studies comparing extended-release naltrexone to daily buprenorphine/naltrexone were inconsistent about which drug was helpful in increasing retention.
- **Research Conclusions:** This review summarized recent studies on different interventions that could be used to help increase medication for opioid use disorder retention. Among the reviewed studies, there were consistent findings that retention increased among individuals in the criminal justice system being provided medication or opioid use disorder and individuals using antagonist medications while participating in a contingency management program.

Chatterjee, A., Weitz, M., Savinkina, A., Macmadu, A., Madushani, M.A., Potee, R.A., Ryan, D., Murphy, S.M., Walley, A.Y., Linas, B.P. (2023). Estimated Costs and

Outcomes Associated With Use and Nonuse of Medications for Opioid Use Disorder During Incarceration and at Release in Massachusetts. JAMA Network Open, 6(4). Doi:10.1001/jamanetworkopen.2023.7036.

This study used a simulation model to assess the effects of a policy change that would require all Massachusetts jails and prisons to screen for opioid disorders and offer all FDA medications for opioid use disorder have on overdose mortality and costs. Study authors used the Researching Effective Strategies to Prevent Opioid Death (RESPOND) simulation model to project outcomes, costs, and cost effectiveness. The model simulated 30,000 incarcerated individuals in Massachusetts in three treatment scenarios eight years prior to any intervention (2013-2020) and then five years of intervention time (2021-2025). The first treatment scenario involved no medication for opioid use disorder during incarceration. Treatment scenario two involved extended-release naltrexone that was only offered upon release. The third scenario involved extended-release naltrexone, methadone, and buprenorphine offered at intake to jail.

- Without any medications for opioid use disorder in a correctional setting, there were 40,927 medication initiations over the course of 5 years, extended naltrexone at release from jail or prison resulted in an additional 10,466 treatment initiation and providing all medications for opioid use disorder added 11,923 treatment initiations.
- Compared to not receiving medication during incarceration, receiving medication for opioid use disorder at a correctional setting increased the likelihood of treatment retention. Six months after release 41% of individuals who were given all medications for opioid use disorder continued to receive medication compared to 21% of individuals who received extended-release naltrexone at release.
- Compared to no medication for opioid use disorder offered during incarceration, each of the remaining scenarios resulted in fewer deaths with all medications for opioid use disorder decreasing deaths by 6.6% compared to a 3.2% for extended-release naltrexone.
- Compared to not offering any medication, all medications for opioid use disorder increased costs by \$852 per person whereas extended-release naltrexone increased costs by \$2,723 per person.
- **Research Conclusions:** Study findings suggest that offering medication for opioid use disorder in a correctional setting can decrease the odds of overdose and increase the likelihood of treatment in the community. While medication for opioid use disorder increases costs per person for correctional settings, the findings suggest that offering extended-release naltrexone upon release is expensive and providing access to all FDA medications for opioid use disorder at the start of incarceration is a more cost-effective use of resources.

Chua, K.P., Conti, R.M., Lagisetty, P., Bohnert, A.S.B., Nuliyalu, U., Nguyen, T.D. (2024). Association Between Cost-Sharing and Buprenorphine Prescription Abandonment. Journal of General Internal Medicine. <https://doi.org/10.1007/s116-024-08819-2>.

This cross-sectional study investigated the association between the patients portion of treatment costs or more commonly known as cost sharing, and buprenorphine prescription abandonment. Study authors examined 2022 buprenorphine claims data of commercially insured patients and Medicare patients. A total of 2,346,994 commercially insured and

1,242,596 Medicare patients claims data were analyzed. Abandonment of a buprenorphine prescription was considered 14 days of not picking up a prescription at a pharmacy.

- The average cost sharing per 30 days was \$28.10 for commercially insured patients which was associated with 1.5% of patients abandoning buprenorphine prescriptions.
- The study found that 66% of commercially insured patients paid \$20 or less for buprenorphine.
- The average cost sharing per 30 days was \$8.40 for Medicare patients which led to a 1.2% abandonment of buprenorphine prescriptions.
- The study found that 92% of Medicare patients paid \$20 or less for buprenorphine.
- Buprenorphine abandonment was highest amongst patients who were new to taking buprenorphine compared to patients who had more than 90 days of buprenorphine use.
- **Research Conclusions:** The findings of this study show that cost sharing has a minimal effect upon patients abandoning their buprenorphine prescriptions. While cost sharing can be burden for patients, it is not the sole reason as to why patients abandon their buprenorphine prescription, so providers need to examine as a small component of a larger strategy to increase buprenorphine dispensing.

Chung, K., Wu, H., Hsu, C., Lu, Y., & Li, D. (2019). Factors impeding switching from methadone to buprenorphine in heroin users receiving methadone maintenance therapy: A naturalistic cohort study. *Journal of Substance Abuse Treatment*, 105, 51–56. <https://doi.org/10.1016/j.jsat.2019.07.017>.

This study investigated the predictive factors that make individuals unable to switch from methadone treatment to buprenorphine/naloxone treatment. This was a 5-year retrospective study that included a sample of 168 individuals (138 men and 30 women) with opioid dependence at MMT clinic sites in Taiwan. Individuals that had psychiatric comorbidity and other substance use disorders except nicotine were excluded from the study.

- 70 of the 168 participants (41.7%) failed switching from methadone to buprenorphine/naloxone.
- A high average dose of methadone (HR=1.02; P=0.01), higher maximal maintenance dose of MMT (HR=1.02; P<0.001), a higher dose of buprenorphine and a low attendance rate during the three months before switching (HR=0.09; P=0.002) were all factors that were associated with failed switching.
- **Research Conclusions:** Clinicians should talk with their patients about tapering the doses of methadone and improving their attendance if they want to switch from methadone to buprenorphine. Additional studies are needed to verify if the findings generalize other populations.

Cicero, T. J., Ellis, M. S., Surratt, H. L., & Kurtz, S. P. (2014). Factors contributing to the rise of buprenorphine misuse: 2008–2013. *Drug and Alcohol Dependence*, 142, 98–104. <https://doi.org/10.1016/j.drugalcdep.2014.06.005>.

This study examined the motivations underlying the use of buprenorphine outside of therapeutic channels and the factors that might account for the reported rapid increase in buprenorphine misuse in recent years. This study used: (1) a mixed methods approach

consisting of a structured, self-administered survey (N=10,568) and reflexive, qualitative interviews (N=208) among patients entering substance abuse treatment programs for opioid dependence across the country, centered on opioid misuse patterns and related behaviors; and (2) interviews with 30 law enforcement agencies nationwide about primary diverted drugs in their jurisdictions.

- The misuse of buprenorphine has increased substantially in the last 5 years, particularly amongst past month heroin users. It serves a variety of functions for the opioid-abusing population: to get high, manage withdrawal sickness, as a substitute for more preferred drugs, to treat pain, to manage psychiatric issues, and as a self-directed effort to wean off opioids.
- **Research Conclusions:** It appears that buprenorphine is rarely preferred for its inherent euphorogenic properties, but rather serves as a substitute for other drugs, particularly heroin, or as a drug used, preferable to Methadone, to self-medicate withdrawal sickness or wean off opioids.

Coffin, P.O., Santos, G.M., Hern, J., Vittinghoff E., Walker J.E., Matheson, T.,...& Batki, S.L. 2019. Effects of Mirtazapine for Methamphetamine Use Disorder Among Cisgender Men and Transgender Women Who Have Sex with Men: A Placebo-Controlled Randomized Clinical Trial. JAMA Psychiatry, doi:<https://doi.org/10.1001/jamapsychiatry.2019.3655>.

This double blind randomized clinical trial study conducted at an outpatient research clinic in San Francisco from August 2013 to September 2017 examined the efficacy of mirtazapine in the treatment of methamphetamine use disorder and the reduction of HIV risk behaviors. The participants of the study were community recruited adults who were sexually active, cisgender men, transgender men, or transgender women who had sex with men, had methamphetamine use disorder and were actively using methamphetamine. 120 participants were enrolled (5 transgender women and 115 cisgender men). The participants were randomly given mirtazapine or a placebo for 24 weeks with a 12 week follow up.

- 66% of the treatment visits were completed by the participants.
- The rate of methamphetamine positive urine screens significantly declined amongst the participants taking mirtazapine throughout the length of the study compared to the placebo group.
- During the first 12 weeks medication adherence was 38.5% in the mirtazapine group vs 39.5% in the placebo group. During weeks 13 to 24 the adherence of the mirtazapine group decreased to 29.1% compared to 38.5% in the placebo group.
- Changes in sexual behavior was not significantly different during the first 12 weeks of the study. However, during the last 12 weeks of the study, the mirtazapine group reported fewer sexual partners and fewer episodes of sex without condoms.
- **Research Conclusions:** Despite mirtazapine not yielding effective adherence rates, it did however show a reduction in methamphetamine use and to influenced lowering risky HIV behaviors.

Connery, H.S., & Weiss, R.D. (2020). Discontinuing Buprenorphine Treatment of Opioid Use Disorder: What Do We (Not) Know? American Journal of Psychiatry. 177(2), 104-106, doi:10.1176/appi.ajp.2019.19121245.

This retrospective longitudinal study examined the relationship between the length of buprenorphine treatment and the health outcomes that occur when buprenorphine treatment has been discontinued. The participants of this study included 9,000 adult Medicaid patients with opioid use disorder who filled their buprenorphine prescription consecutively for at least 6 months before discontinuing. The health outcomes of the patients were recorded during a 6 month follow up period after buprenorphine treatment was discontinued. The health outcomes that were observed were all cause emergency department visits and hospitalizations, receipt of an opioid analgesic prescription, and the occurrences of a medically treated drug overdose event that was opioid or non-opioid related. To compare outcomes, the patients were assigned different cohorts, based on how long they were on buprenorphine (6-9 months, 9-12 months, 12-15 months, or 15-18 months).

- 15-18-month cohort was significantly less likely to be seen in an emergency department, to be hospitalized, or receive a prescription for an opioid analgesic compared to the 6-9-month cohort.
- All groups had high rates of emergency department visits following discontinuation of buprenorphine (>40%)
- 5.6% of the sample experienced nonfatal drug overdoses.
- Fatal overdoses were unable to be detected in this study due to a timing discrepancy between termination of Medicaid enrollment and study eligibility.
- **Research Conclusions:** Patients with opioid use disorder who take buprenorphine for a longer period have a better health outcome during discontinuation than those who had a shorter treatment.

Connock, M. 2007. Methadone and buprenorphine for the management of opioid dependence: A systematic review and economic evaluation.

This study assesses the clinical and cost effectiveness of buprenorphine maintenance therapy (BMT) and methadone maintenance therapy (MMT) for the management of opioid-dependent individuals. The assessment used major electronic databases through August 2005 plus an updated search for randomized controlled trials (RCTs).

- Both flexible-dose MMT and BMT were found more clinically effective and more cost-effective than no drug therapy in dependent opiate users. A flexible dosing strategy with MMT was found to be somewhat more effective in maintaining individuals in treatment than flexible-dose BMT and therefore associated with a slightly higher health gain and lower costs.
- **Research Conclusions:** The possible risk of higher mortality of MMT and individual opioid dependent users' preferences and efficacy of medications in particular patient subgroups such as within the criminal justice system, calls for further research in directly comparing the two medications.

Cooperman, N.A., Lu, S., Hanley, A.W., Puvananayagam, T., Dooley-Budsock, P., Kline, A., & Garland, E.L. (2023). Recovery Enhancement vs Usual Care in Individuals

With Opioid Use Disorder and Pain A Randomized Clinical Trial. JAMA Psychiatry. Doi:10.1001/jamapsychiatry.2023.5138.

This randomized controlled trial compared a telehealth treatment model called Mindfulness Oriented Recovery Enhancement (MORE) with standard methadone treatment among individuals with opioid use disorder and pain. From August 2020 through June 2022, 154 participants were randomly assigned to receive standard methadone treatment (n=67) or MORE (n=67) across five clinics in New Jersey. Participants who were assigned to methadone treatment only received medication and counseling. Individuals assigned to MORE received the same methadone treatment as the standard methadone treatment only group plus eight weekly two hour telehealth group session that provide training in mindfulness, reappraisal, and savings. Most participants were female (57% and had a mean age of 48.5 years.

- 44 participants (57.1%) who received methadone treatment only and 39 participants (50.6%) who received MORE returned to drug use. The study found this to be a significant difference.
- 17 participants (22.1%) who received methadone treatment only and 20 participants (13%) who received MORE dropped out of methadone treatment. The study found this to be a significant difference.
- At the 16 week follow up, 95% of MORE participants adhered to methadone treatment compared to 83.6% of methadone treatment only participants.
- Participants who received MORE had reduced depression scores, pain scores, and anxiety scores through 16 weeks compared to participants who received methadone treatment only.
- **Research Conclusions:** The findings of this study appear to suggest that the telehealth program model MORE lessened drug use, depression, pain and increases treatment retention and adherence better than methadone treatment alone. In general, the study findings may suggest that providing individuals with an additional program model with medication treatment may yield the best treatment results.

Cousins, S.J., Radfar, S.R., Crevecœur-MacPhail, D., Ang, A., Darfler, K., & Rawson, R.A. (2015). Predictors of Continued Use of Extended-Release Naltrexone (XR-NTX) for Opioid-Dependence: An Analysis of Heroin and Non-Heroin Opioid Users in Los Angeles County. Journal of Substance Abuse Treatment, doi:10.1016/j.jsat.2015.12.004.

171 participants at residential substance use disorder treatment centers in Los Angeles participated in a study to identify characteristics that are mostly associated with adherence to extended release naltrexone and to determine if there is a difference between heroin and non-heroin opioid use adherence to extended release naltrexone. Of the 171 participants, 54% were male, 66% were non-Hispanic white, and 68% had a heroin use disorder. The data that were collected was compared to opioid use population data of Los Angeles County.

- Of the 171 participants that received extended release naltrexone, the average dose received over the course of the study was 2.4.
- Individuals who are older and tested for HIV were characteristics of receiving two or more doses of naltrexone. While being admitted into the emergency room and have a

mental health diagnosis, non-heroin users who injected drugs in the past 12 months were less likely to receive 2 or more doses.

- Urge to use opioids decreased within the first 30 days of initial doses of extended release naltrexone among heroin and non-heroin users.
- There was no significant difference between heroin and non-heroin user's adherence to naltrexone and their urge to use opioids.
- **Research Conclusions:** Findings suggest that extended release naltrexone may contribute to decreases in urges to use among both heroin and non-heroin opioid users.

Coviello, D.M. 2012. A multisite pilot study of extended-release injectable naltrexone treatment for previously opioid-dependent parolees and probationers.

This study assesses whether offenders who are mandated to community-based outpatient treatment have better completion rates compared to those who volunteer to enter treatment. The participants were enrolled in an intensive outpatient program involving counseling but no MAT. The 160 research participants were a heterogeneous group of substance abusers who were under various levels of criminal justice supervision (CJS) in the community. The 160 research participants, under various levels of criminal justice supervision, were enrolled in an intensive outpatient program and recruited between July 2007 and October 2010. All offenders received weekly therapy sessions using a cognitive problem-solving framework, and 45% completed the 6-month treatment program.

- Those mandated to the program showed less motivation to enter but were over ten times more likely to complete treatment compared to those who were not court ordered.
- **Research Conclusions:** Findings reveal that stipulated treatment for offenders may be an effective way to increase treatment compliance.

Crits-Christoph, P., Lundy, C., Stringer, M. A., Gallop, R., & Gastfriend, D. R. (2015). Extended release naltrexone for alcohol and opioid problems in Missouri parolees and probationers. *Journal of Substance Abuse Treatment*, 56, 54–60. <https://doi.org/10.1016/j.jsat.2015.03.003>.

This study compares the naturalistic outcomes of parolees and probationers with alcohol and/or opioid problems who were treated with injectable naltrexone (XR-NTX) to those treated with other medication-assisted therapies or psychosocial treatment only. The study consisted of using intake and discharge data collected as part of the Substance Abuse and Mental Health Services Administration's (SAMHSA's) Treatment Episode Data Set (TEDS) assessments, controlling for group differences using propensity scores that were based on a range of intake variables.

The groups were followed during the 2013 fiscal year.

Those receiving XR-NTX (136) had longer durations of care compared to oral naltrexone (163) and psychosocial treatment only (866), 97 days vs. 69 days vs. 63 days.

- Those receiving XR-NTX were more likely to achieve abstinence at discharge from supervision compared to oral naltrexone, buprenorphine/naloxone, and psychosocial treatment only.
- No differences were found in employment or arrests in this relatively short time frame.

- **Research Conclusions:** The real-world effectiveness of XR-NTX in such a criminal justice population encourages its use.

Daubresse, M., Saloner, B., Pollack, H. A., & Alexander, G. C. (2017). Non-buprenorphine opioid utilization among patients using buprenorphine. *Addiction*, 112(6), 1045–1053. <https://doi.org/10.1111/add.13762>.

This study looked at prescriptions for buprenorphine and Suboxone, a combination of buprenorphine and naloxone, an anti-overdose medication. This study examined pharmacy claims for more than 38,000 new buprenorphine users who filled prescriptions between 2006 and 2013 in 11 states. It looked at non-buprenorphine opioid prescriptions before, during, and after each patient's first course of buprenorphine treatment, which typically lasted 1–6 months. It did not look at the use of heroin and non-prescribed opioids.

- Most of the study subjects discontinued using buprenorphine within 3 months.
- 43% of patients who received buprenorphine also filled an opioid prescription during their buprenorphine treatment.
- 67% filled an opioid prescription during the 12 months following buprenorphine treatment. Most patients continued to receive similar amounts of opioids before and after buprenorphine treatment.
- **Research Conclusions:** Most patients continue to receive similar amounts of opioids before and after buprenorphine treatment. The findings suggest that doctors are not checking patient prescription records and are prescribing painkillers to the very people who should not be getting them.

DeFulio, A., Rzeszutek, M.J., Furgeson, J., Ryan, S., & Rezanian, S. (2021). A smartphone-smartcard platform for contingency management in an inner-city substance use disorder outpatient program. *Journal of Substance Abuse Treatment*. 120. <https://doi.org/10.1016/j.jsat.2020.108188>.

This study evaluated the clinical outcomes associated with a smart phone application and smart card for opioid use disorder patients at a clinic in Cincinnati, Ohio. The smart phone application provided appointment reminders and GPS tracking of successful attendance, 36 in app self service CBT modules, video-selfie monitoring for alcohol abstinence, logs of in person urinalysis conducted at the clinic, and delivered \$100 per month for healthy behaviors that could be instantly transferred to a smart debit card that blocks risky purchases such as bars and liquor stores. 86 patients with opioid use disorder were selected to use the application and smart debit card for nine weeks. These patients were predominately white (85%), male (54%), average age of 39 years, Medicaid insured (85%), and were prescribed buprenorphine (94%). A control group who received services at the same time from a similar clinic in Cincinnati was used for comparison.

- Use of the smartphone app was associated with an 9% increase in counseling appointment attendance between the second and fourth months of the study.
- Patients using the smartphone app were twice as likely to provide consistent negative urine screens than the control group.
- 66% of the CBT modules were completed by the smartphone application group of patients.

- **Research Conclusions:** Study findings show that the use of a smart phone application with financial incentives can help increase treatment attendance, provides accessible treatment through CBT modules, and encourage substance use abstinence.

Degenhardt, L., Clark, B., Macpherson, G., Leppan, O., Nielsen, S., Zahara, E., Larance, B., Kimber, J., Martino-Burke, D., Hickman, M., Farrell, M. (2023). Buprenorphine versus methadone for the treatment of opioid dependence: a systematic review and meta-analysis of randomized and observational studies. The Lancet, 10(6), 386-402. [https://doi.org/10.1016/S2215-0366\(23\)00095-0](https://doi.org/10.1016/S2215-0366(23)00095-0).

This systematic review and meta-analysis aimed to compare buprenorphine and methadone in the treatment of opioid dependence. The outcomes of interest were retention in treatment at 1, 3, 6, 12, and 24 months, treatment adherence, and opioid use. The study identified 32 RCT and 69 observational studies that compared buprenorphine to methadone and an additional 51 RCT's and 124 observational studies that reported on buprenorphine treatment retention. Of the reviewed studies most, participants were male (66.1%) and had an average age of 37.1 years.

- After the one month follow up, methadone was found to have better odds of retaining participants than buprenorphine in most studies.
- There was no evidence that suggested that treatment adherence differed between buprenorphine and methadone treatment.
- RCT studies that measured extra medical opioid use by urinalysis found that those who were treated with buprenorphine were less likely use extra medical opioids than those treated with methadone. Differences to test extra medical opioid use by other methods did not yield any significant results.
- Among secondary outcomes examined, there were reduced cocaine use, cravings, anxiety, cardiac dysfunction, and an increase in treatment satisfaction among participants treated with buprenorphine compared to methadone. Study authors noted that secondary outcome findings were based upon five studies that were not consistent across study type and the measures used to record outcomes.
- **Research Conclusions:** Findings from the systematic review and meta-analysis suggest that after one month treatment retention is better amongst individuals treated with methadone compared to buprenorphine, however there is not much a difference between the two medications for treatment adherence.

Domzaridou, E., Carr, M.J., Webb, R.T., Ashcroft, D.M. (2023). Non-fatal overdose risk associated with prescribing opioid agonists concurrently with other medication: Cohort study conducted using linked primary care, secondary care and mortality records. Addiction. <https://doi.org/10.1111/add.16306>.

This retrospective cohort study investigated whether benzodiazepines, gabapentinoids, antipsychotics, antidepressants, Z-drugs, or opioids increase the risk of non-fatal overdose when they are prescribed with opioid agonist treatment. The study included patients between 18-64 years of age with prescriptions for methadone or buprenorphine from January 1, 1998, through December 31, 2017, who received treatment from primary care in the United Kingdom. The study identified 20,898 patients to include in the study of which 72.5% had prescriptions for methadone and 27.5% had prescriptions for buprenorphine.

Most methadone patients were male (69.3%), 25-34 years of age (39.4%), median treatment duration 632 days, and were prescribed benzodiazepines (29.3%). Most buprenorphine patients were male (72.2%), 25-34 years of age (36.9%), median treatment duration 284 days, and were prescribed opioids for pain (29.5%).

- 4,512 nonfatal overdoses occurred during the study of which 2,687 (60%) had an overdose during their first opioid agonist treatment episode.
- Benzodiazepines, gabapentinoids, and z- drugs were found to provide the highest risk of an overdose during co prescription with opioid agonist treatment, but antidepressants did not increase the risk of overdose.
- **Research Conclusions:** Study findings show that patients who were co-prescribed benzodiazepines, antipsychotics, gabapentinoids, and z-drugs with opioid agonist treatment were at an elevated risk of overdose. Readers should take note that the study did not provide the duration of treatment that patients were co-prescribed to support these outcomes.

Dong, H., Stringfellow, E.J., Russell, W.A., Jalali, M.S. (2022). Racial and Ethnic Disparities in Buprenorphine Treatment Duration in the US. JAMA Psychiatry. doi:10.1001/2022.3673

This study examined the ethnic and racial disparities in the availability and duration of buprenorphine treatment for people with opioid use disorder. Researchers obtained prescription data from health technology company IQVIA from 2006 to 2020 to assess the disparities between ethnic and racial groups.

- 84.1% of white patients had access to buprenorphine, however only 8.1% of black patients, and 6.3% of Hispanic patients had access.
- The average length of treatment for White patients was 53 days, while Black patients was 44 days and Hispanic patients was 40 days.
- Study researchers were unable to identify possible reasons for the disparities.
- **Research Conclusions:** The study findings show that nonwhite patients do not receive the same amount of access to buprenorphine treatment and are not retained in treatment the same amount of time as white patients. While these disparities exist, researchers are unable to pinpoint specific causes of the disparities.

D’Onofrio, G., Herring, A.A., Perrone, J., Hawk, K., Samuels, E.A., Cowan, E., Anderson, E., McCormack, R., Huntley, K., Owens, P., Martel, S., Schactman, M., Lofwall, M.R., Walsh, S.L., Dziura, and Fiellin, D.A. (2024). Extended-Release 7-Day Injectable Buprenorphine for Patients With Minimal to Mild Opioid withdrawal. JAMA Network Open. 7(7). Doi:10.1001/jamanetworkopen.2024.20702.

This nonrandomized trial evaluated the acceptability, tolerability, and safety of seven-day injectable extended-release buprenorphine to treat patients with untreated opioid use disorder who are undergoing minimal to mild opioid withdrawal. The study was conducted in four urban teaching hospitals in the Northeast, Mid-Atlantic, and Pacific regions of the United States. Study eligibility required participants to be 18 years of older, have moderate to severe opioid use disorder, have a positive urine screen for opioids, undergo minimal to mild withdrawal, and be able to speak English. Participants were excluded from the study if their urine screen was positive for methadone, were pregnant, needed opioids for pain management, had a recent overdose, or were enrolled in opioid use disorder treatment and

had received medication in the past seven days. The study screened 635 participants for study eligibility and found that 533 participants were ineligible due to not having used opioid in the past 40 days (n=460), thus leaving the study sample size at 100 participants. Most of the study sample were male (72%), White (51%), had public insurance (79%), and tested positive for fentanyl at study enrollment (70%). Participants received a 24mg dose of 7 day-extended-release buprenorphine and remained in the emergency department for four hours after the injection for observations and were referred to community-based treatment for additional treatment.

- 7% of participants experienced moderate or greater withdrawal within four hours of injection and 2% experienced precipitated withdrawal within one hour.
- Between 33% and 43% of participants reported zero cravings on any given day during the seven days. Between 78% and 85% of participants reported no use of opioids on any given day during the seven days.
- 17% of participants reported at least one symptom at the injection site. Of these participants 11 participants reported tenderness and 7 reported pain at the injection site.
- 52% of participants felt that extended-release buprenorphine was completely effective. Majority of participants believed the importance of extended-release buprenorphine included improved privacy (62%), less visits to pharmacies (75%), does not require daily medication (67%), and improves ease of traveling (70%).
- 7 days after extended-release buprenorphine injection, there were no reports of opioid overdose.
- 73% of participants received opioid use disorder treatment after the study period ended.
- Five serious adverse events were reported that required hospitalization, of which two were associated with medication.
- Research Conclusions: The findings of the study give support that that extended-release buprenorphine is safe, well tolerated, and has high satisfaction among treating individuals with withdrawal. Additionally, the use of extended-release buprenorphine led to majority of patients continuing buprenorphine treatment in the community. The findings of this study may not be generalizable to all individuals with opioid use disorder who are looking for withdrawal treatment due to this study only examining individuals who had minimal to mild withdrawal treatment.

Dugosh, K., Abraham, A., Seymour, B., McLoyd, K., Chalk, M. & Festinger, D. (2016). A systematic review on the use of psychosocial interventions in conjunction with medications for the treatment of opioid addiction. *Journal of Addiction Medicine*, 10(2), 93–103. <https://doi.org/10.1097/ADM.0000000000000193>.

This review discusses 14 studies that evaluated the effectiveness of providing psychosocial treatment in combination with methadone maintenance treatment (MMT).

- Nine of the 14 studies reported significant effects of the psychosocial treatment on treatment attendance and drug use.
- Five studies demonstrated greater treatment attendance and two studies demonstrated lower treatment dropout rates.

- Five studies demonstrated decreased opioid use among MMT clients receiving psychosocial treatment.
- Seven studies revealed significant effects of psychosocial interventions on secondary outcomes including HIV risk, psychosocial functioning, adherence to psychiatric medications, alcohol use, and fear of detoxification.
- **Research Conclusions:** Results of the studies generally support the use of psychosocial interventions (such as contingency management and cognitive behavioral therapy) in combination with MMT. The incremental efficacy of adding psychosocial interventions to medically assisted treatment, however, varied for different outcomes, across studies, and within psychosocial intervention types. This can likely be attributed to the fact that the comparison groups were not consistent across studies.

Dunlop, A.J., Roberts, White, B., Roberts, J., Cretikos, M., Attalla, D., Ling, R., Searles, A., Mackson, J., Doyle, M.F., McEntyre, E., Attica, J., Oldmeadow, C., Howard, M.V., Murrell, T., Haber, P.S., & Lintzeris, N. (2021). Treatment of opioid dependence with depot buprenorphine (CAM2038) in custodial settings. *Addiction*. <https://doi.org/10.1111/add.15627>.

This open label trial examined the safety and effectiveness of a new buprenorphine formulation called CAM2038 in a custodial setting. Participants for this study were adults 18 years or older with moderate to severe opioid use disorder who were serving a sentence of 6 months or more across seven correctional centers in metropolitan and rural areas of North South Wales, Australia. For 16 weeks, a group of participants (n=67) who were not obtaining opioid agonist treatment (OAT) upon their incarceration were given two buprenorphine formulations, CAM2038 q1w (given weekly) and q4w (once monthly). A comparison group of participants (n=62) was created of whom were already stable on methadone upon incarceration. Demographically both group of participants were similar, except the buprenorphine group of participants were more likely to be HCV positive and less likely to report previous OAT.

- Treatment retention for depot buprenorphine was 92% vs 98.4% for methadone.
- 65 out of 67 participants receiving depot buprenorphine reported at least one adverse with 88% of them reporting it as mild. The most common adverse events were injection site pain, constipation, injection site welling, headaches.
- 45 out of 62 participants receiving methadone reported at least one adverse event with 75% of them being mild.
- At baseline 17% of participants had a history of diverting methadone or sublingual buprenorphine while incarcerated. During the study, no participant reported any attempts of diverting or removing their injection of buprenorphine or methadone.
- Depot buprenorphine cost \$112 per patient per month. While oral methadone cost \$339 and sublingual buprenorphine cost \$1,299.
- The depot buprenorphine group saw a significant decline in injection drug use and non-prescribed opioid use from baseline to the end of the study.

- **Research Conclusions:** Research findings suggest that depot buprenorphine is a comparable form of treatment to methadone and does not provide an increased risk to diversion for incarcerated individuals. Furthermore, depot buprenorphine is more cost-effective form of treatment than methadone and sublingual buprenorphine.

Earley, P., Zummo, J., Memisoglu, A., Silverman, B., & Gastfriend, D. (2017). Open-label Study of Injectable Extended-release Naltrexone (XR-NTX) in Healthcare Professionals With Opioid Dependence. *Journal of Addiction Medicine*. 11(3),224-230, doi:10.1097/ADM.0000000000000302

During a time period of 24 months, a group of 38 opioid dependent health care professionals in outpatient treatment across 8 US cities were observed to track the long term safety, treatment adherence, abstinence, changes in opioid craving, and quality of life while being treated with extended release naltrexone. The health care professionals involved in this study consisted of 30 nurses, 4 doctors, 1 pharmacist, 1 substance misuse treatment counselor, and 2 unspecified health care workers. 31 of the 38 participants were women, 37 of the participants were white, and the average age of the group was 42.4 years old. At baseline 19 of the participants had voluntarily stopped working, 12 were still practicing with no restrictions, 4 were practicing with some restrictions, and 3 had their license revoked. Over the course of the study the participants were given one injection of extended release naltrexone once a month combined with extensive outpatient treatment that consisted of individual and group drug counseling, encouragement to attend self-help meetings, and regular monitoring of drug use.

- Of the 38 participants in the study only 15 (39.5%) remained in the study for 24 months. 7 dropped out due to adverse events, 7 were unable to be found during follow up, 5 withdrew their consent, 1 participant relocated, 1 participant was withdrawn by the investigator, and 5 withdrew due to other reasons. The median time of discontinuation was 6 months
- 37 of the 38 participants experienced at least 1 adverse event over the 24-month study. The most common adverse events were nausea (42.1%), injection site pain (36.8%), anxiety (28.9%), and headaches (26.3%)
- 92.1% of the participants attended counseling and 94.5% attended support meetings over the course of the study. By the end of the study 66.7% of the participants attended a counseling and 80% attended a support meeting.
- Opioid cravings were reduced over the course of the study by 45.2%
- Of the 22 participants who were unemployed at the baseline, 10 participants reported improved employment status by the study's end. 16 of the participants that were employed, only 2 reported worse employment status at the end of the study.
- **Research Conclusions:** The results of the study were consistent with prior research studies about extended release naltrexone in efficacy and safety and adds to the evidence for long term safety and positive treatment outcomes for extended release naltrexone in opioid dependent individuals for durations up to 24 months.

Eibl, J.K. 2019. Evaluating the impact of prescribed versus nonprescribed benzodiazepine use in methadone maintenance therapy: Results from a population based retrospective cohort study.

The study included patients from 52 opioid use disorder outpatient clinics who were initiating methadone maintenance treatment (MMT) and who were also taking prescribed benzodiazepines, nonprescribed benzodiazepines, or no benzodiazepines. Participants were followed from treatment initiation to treatment discontinuation, death, or 1-year follow-up. Urine drug screening (UDS) data and prescribing information from single-payer health records were examined. The study's primary outcome measure was methadone treatment retention at the 1-year follow-up visit. A total of 3,692 participants initiating methadone-assisted treatment for the first time made up the study. Seventy-six percent had no benzodiazepine prescription and <30% screening positive for benzodiazepine, 13% had a benzodiazepine prescription but had negative UDS, 6% did not have a benzodiazepine prescription but had positive UDS, and 6% had a benzodiazepine prescription and had positive UDS.

- Patients using nonprescribed benzodiazepine who had positive UDS were found to be more likely to discontinue MMT compared with participants not using benzodiazepine or those using benzodiazepine as prescribed.
- **Research Conclusions:** The use of the prescribed benzodiazepine may not affect retention of MMT.

Elarabi, H.F., Shawky, M., Mustafa, N., Radwan, D., Elaraheed, A., Ali, A.Y., Osman, M., Kashmar, A., Kathiri, H.A., Gawad, T., Kodera, A., Jneibi, M.A., Adem, A., Lee, A.J., & Marsden, J. (2021). Effectiveness of incentivized adherence and abstinence monitoring in buprenorphine maintenance: a pragmatic, randomized controlled trial. *Addiction*. <https://doi.org/10.1111/add.15394>.

This randomized controlled study compared the clinical effectiveness of buprenorphine maintenance with incentivized medication adherence and abstinence monitoring versus typical buprenorphine maintenance. Participants were opioid use disorder adults and were voluntarily seeking treatment at an inpatient and outpatient addiction treatment center in Abu Dhabi, United Arab Emirates. Participants were admitted to the clinic's inpatient service for 4 weeks for medically supervised withdrawal, buprenorphine induction, and dose stabilization. After 4 weeks in inpatient, participants were then transitioned to outpatient services where they were randomly assigned to a group that received buprenorphine maintenance with incentivized medication adherence and abstinence monitoring (n=70) or typical buprenorphine maintenance (n=71). The incentivized group went to the clinic daily for 5 days to receive their medication. If participants attended all of their clinic appointments and provided negative urine screens for opioids, they were then given a seven day take home supply. The take home supply was gradually increased (14-, 21-, and 28-day supply) if participants took their medication and continued to provide negative urine screens. The treatment as usual group was required to attend the clinic for five days and was given a seven day take home supply if members attended all appointments and provided negative urine screens. If participants took their medication and provided negative urine screens, a 14 day take home supply was given. For both groups if a participant was nonadherent or produced a positive urine screen they were returned to a previous take home supply amount.

- In the first week of buprenorphine maintenance at the outpatient clinic, 16 participants left treatment (six in the incentivized group and ten in the treatment as usual group).

Throughout the length of the study, 30 participants in the incentivized group and 38 participants from the treatment as usual group discontinued the study.

- 55 participants from the incentivized treatment group received no more than 14 take home supplies. Seven participants received a 21-day supply, and one participant received a 28 supply.
- 51 participants in the treatment as usual group received no more than 14 take home supplies. 20 participants did not receive more than seven take home supplies.
- The percentage of negative urine drug screens for the incentivized group was 90.5% versus 71.8% in the treatment as usual group.
- The participants of this study were almost exclusively male, with only two female participants. Researchers noted that they had no control over the referral process.
- **Research Conclusions:** Buprenorphine maintenance with incentivized and treatment as usual approaches gave participants the ability to have an increased at home supply of medication with less frequent trips to the clinic. Incentivized approach appears to be better in promoting abstinence from opioids compared to a treatment as usual approach, but both approaches have problems with increasing treatment retention. The lack of gender diversity among the participants should be remembered when considering the study findings.

Ellison, M., Hutton, E, Webster, L., Skolnick, P. (2024). Reversal of Opioid-Induced Respiratory Depression in Healthy Volunteers: Comparison of Intranasal Nalmefene and Intranasal Naloxone. The Journal of Clinical Pharmacology.
<https://doi.org/10.1002/jcph.2421>.

This open label randomized study investigated the use of a nasal spray to treat opioid induced respiratory depression, shallow and slow breathing that is commonly associated with an opioid overdose. A total of 69 healthy male and female participants were randomized to receive naloxone or nalmefene to reverse opioid induced respiratory depression. For participants to be eligible for the study, participants had to be between 18-55 years of age, weigh more than 50kg, have a BMI between 18-32 kg/m², and be non-opioid dependent but have been exposed to opioid at least once prior to study screening. Participants were ineligible for the study if they had a history of severe seasonal or nonseasonal allergies or had nasal passage abnormalities. The study sample were primarily male (69.6%), white (82.6%), and had an average of 29.1 years. Participants were administered a hypercapnic gas mixture through a mask after which participants were given either naloxone or nalmefene for 15 mins.

- Both naloxone and nalmefene reduced opioid induced respiratory depression 2.5 to 20 min after administration. Nalmefene reduced opioid respiratory depression faster than naloxone.
- 86.7% of participants treated with naloxone reported experiencing adverse events that occurred during treatment while 91.8% of participants treatment reported experiencing adverse events that occurred during treatment. For both medications, none of the adverse events were reported as being serious and were described as mild or moderate.

- 13% of the study sample discontinued the study due to adverse events experienced during treatment.
- **Research Conclusions:** This open label randomized study found that both naloxone and nalmefene are both effective in reducing shallow and slow breathing caused by an opioid overdose, however the treatment effects of nalmefene occur faster than naloxone. Study participants experienced a high frequency of adverse events; however, none were reported as serious.

Eren, K., Schuster, J., Herschell, A., Loveland, D., Neimark, G., Mihalyo, M., Hurford, M., Houck, P., Ryan, N. (2022). Association of Counseling and Psychotherapy on Retention in Medication for Addiction Treatment Within a Large Medicaid Population. Journal of Addiction Medicine, 3(16), <https://doi.org/10.1097/ADM.0000000000000914>.

This cohort study examined the impact that counseling and psychotherapy have on retention for individuals with opioid use disorder, as well as buprenorphine dosage impact on retention. 4,987 Medicaid patients from 41 counties in Pennsylvania who had a full year without medication for opioid use disorder following initiation of treatment with buprenorphine/naloxone in 2016 to 2017 and remained eligible for Medicaid 80% of their time in the following two years.

- Adding counseling and psychotherapy within the first eight weeks of treatment was significantly associated with an increase in treatment retention.
- The study found that 16mg/d or greater dose of buprenorphine was significantly associated with greater retention compared to smaller doses.
- **Research Conclusions:** The findings of this study suggest that providing counseling or psychotherapy within the first two months of opioid use disorder treatment can increase treatment retention. Additionally, buprenorphine doses of 16mg/d or greater can greatly improve treatment retention as well.

Evans, E.A., Pivovarova, E., Stopka, T.J., Santelices, C., Ferguson, W.J., & Friedmann, P.D. (2022). Uncommon and preventable: Perceptions of diversion of medication for opioid use disorder in jail. Journal of Substance Abuse Treatment. <https://doi.org/10.1016/j.jsat.2022.108746>.

This qualitative study explored the perceptions and opinions that jail staff had about buprenorphine diversion after the implementation of a buprenorphine program in their jails and the strategies that they use to detect and prevent diversion. Study authors conducted one on one interviews with 61 staff members from seven Massachusetts jails that provided buprenorphine, usually as a crushed-up tablet. Two of the jails were in an urban area, four were in the suburbs, and one was in a rural area. Staff members that completed the sample were clinical staff (i.e nurses), correctional officers, and senior administrators (program administrators and superintendents). Most of the participants were women (60.7%), mean age of 45 years old, White (80.3%), had a Master's degree (45.9%), and worked at their current position for 4-9 years (32.7%).

- Majority of jail staff thought buprenorphine would be problematic, however attempts to smuggle buprenorphine into jail decreased or stopped after the implementation of

buprenorphine in jail. Buprenorphine treatment disrupted the illicit buprenorphine market in jails and reduced violence related to access to the medication.

- Inmates being forced to give up their medication was the most common form of diversion that occurred, however the instances of coercion decreased when buprenorphine became more accessible to inmates.
- Recommendations for successful MOUD treatment in jail included acknowledging how MOUD is a legitimate form of treatment and is not illicit contraband, educate staff and patients about diversion detection and prevention, encourage staff to refine existing diversion prevention protocols and to co-create new ones, define different types of diversion, and assess how and why they happen, and create a therapeutic treatment environment.
- **Research Conclusions:** Study findings show that prior thoughts about buprenorphine treatment in jails turned out to be incorrect. Buprenorphine was not being diverted often and if it was, an individual was often forced to give it up to another inmate.

Faysal, J.A., Alam, N.E., Young, G.J., Lo-Ciganic, W.H., Goodin, A.J., Huang, J.L., Wilson, D.L., Park, T.W., and Hasan, M. (2024). An explainable machine learning framework for predicting the risk of buprenorphine treatment discontinuation for opioid use disorder among commercially insured individuals. Computers in Biology and Medicine, 177. <https://doi.org/10.1016/j.combiomed.2024.108493>.

This retrospective study developed a machine learning framework to predict the discontinuation of buprenorphine care within 12 months following treatment initiation. The study used commercial claims of insured adults between the ages of 18-64 years, initiated buprenorphine between July 2018 and December 2020, and had no buprenorphine prescriptions six months prior to study enrollment. The study sample included 30,373 individuals of which most were male and had a mean age of 40.9 years. For this study, treatment discontinuation was 30 days or more without a buprenorphine prescription within one year of treatment initiation. The machine learning model focused on two stages of treatment: treatment initiation and one to three months after treatment initiation.

- 14.9% of individuals discontinued treatment. Of the individuals who discontinued treatment, 46% of individuals stopped treatment within the first three months.
- The model found that age (45 years and above), chronic pain, use of opioid analgesic, HMO or other (non-HMO and non-EPO) type insurance plan type, and outpatient visits were variable that were negatively correlated with buprenorphine discontinuation.
- The model found that initial days of buprenorphine supply, living in the southern section of the United States, inpatient visits, emergency department visits, and the use of stimulants were variables that were positively correlated with buprenorphine discontinuation.
- **Research Conclusions:** The research suggests that continuation of buprenorphine could be determined by examining specific factors arrived at through a study of this study sample. Most influential risk factors for discontinuation included early-stage medication adherence, age, and initial days of supply.

Ferrant, O., Papin, F., Clin, B., Lacroix, C., Sausseureau, E., Remoue, J., & Goulle, J. (2011) Fatal poisoning due to snorting buprenorphine and alcohol consumption. *Forensic Science International*. 204, 8-11. <https://doi.org/10.1016/j.forsciint.2010.05.015>

This case study describes the lethal risks of buprenorphine when it is used intravenously and combined with either benzodiazepines, alcohol, or other central nervous system depressants. Three cases of fatal buprenorphine related poisoning after snorting with no suspected traumatic injury from a third party were examined. Each of these cases had their autopsies performed at the Forensic Medicine Unit of Caen University Hospital in France. Case 1 involved a 17-year-old male who snorted Subutex with no history of a drug addiction. Case 2 involved a 27-year-old male who snorted Subutex with did no history of a drug addiction. Case 3 involved a 35-year-old male who inhaled Subutex with a history of chronic alcoholism and addiction to cocaine and cannabis.

- Case 1 snorted Subutex, consumed alcohol, and used cannabis the evening before his death. Blood alcohol concentration was 1.82 g/L and blood buprenorphine concentration was 15.4 ng/ml. The forensic report for case 1 suggested that the death was caused by an accidental fatal poisoning due to the central nervous system respiratory depressant effects of the combination of buprenorphine and ethanol by snorting buprenorphine.
- Case 2 inhaled Subutex and consumed beer and whisky the evening before his death. Case 2 had a blood alcohol concentration of 1.06 g/L and a blood buprenorphine level of 6.1 ng/ml. Forensic reports concluded that death was caused by the combined effects of snorted buprenorphine and alcohol which caused central nervous system respiratory depression.
- Case 3 consumed alcohol, smoked cannabis, and inhaled a white powder the night before he died. Case 3 had a blood buprenorphine concentration 7.1 ng/ml and a blood alcohol concentration of 1.61 g/L. Forensic reports found the cause of death to have been related to the side effects of snorting buprenorphine and drinking alcohol, which caused central nervous system depression.
- **Research Conclusions:** Each of these three cases ended with fatal respiratory depression despite the differing amounts of buprenorphine snorted, drug use, and similarly moderate amount of alcohol consumed. These findings suggest that nasally administered buprenorphine with moderate alcohol consumption is a fatal combination among people with or without a drug addiction.

Fiellin, D. A., Barry, D. T., Sullivan, L. E., Cutter, C. J., Moore, B. A., O'Connor, P. G., & Schottenfeld, R. S. (2013). A randomized trial of cognitive behavioral therapy in primary care-based buprenorphine. *The American Journal of Medicine*, 126(1), 74.e11–74.e17. <https://doi.org/10.1016/j.amjmed.2012.07.005>.

This 24-week randomized clinical trial of 141 opioid-dependent patients in a primary care clinic compared patients managed by a physician providing buprenorphine to those managed by a physician providing buprenorphine plus cognitive behavioral therapy (CBT). The outcome measure was self-reported frequency of illicit opioid use and the maximum number of consecutive weeks of abstinence from illicit opioids.

- The two treatments had similar effectiveness, reducing mean self-reported frequency of opioid use from 5.3 days per week at baseline to 0.4 days per week for the second half of maintenance.
- There was no difference with respect to cocaine use or study completion.
- **Research Conclusions:** Among patients receiving buprenorphine/naloxone in primary care for opioid dependence, the effectiveness of physician management did not differ significantly from that of physician management plus CBT.

Finan, P., Mun C.J., Epstein, D.H., Kowalczyk, W.J., Phillips, K.A., Agage, D.,...& Preston, K.L. (2020) Multimodal assessment of sleep in men and women during treatment for opioid use disorder. *Drug and Alcohol Dependence*, 207, doi: <https://doi.org/10.1016/j.drugalcdep.2019.107698>.

The National Institute of Drug Abuse Intramural Research Program in Baltimore Maryland monitored patients with opioid use disorder treated on either methadone or buprenorphine to investigate the differences in sleep continuity, comparing 55 patients (26 methadone and 29 buprenorphine) who lived in the city of Baltimore. In the methadone group, there were 16 men and 10 women. In the buprenorphine group there were 25 men and 4 women. The participants data was collected using a daily sleep diary for 17 weeks and a home sleep electroencephalography for 1 week for those actively participating in treatment.

- There were no significant differences in sleep continuity and quality obtained from the sleep dairy and EEG between patients who took methadone vs buprenorphine
- Men tended to have a lower sleep quality than women based upon EEG results of the stages of sleep.
- Patients who took buprenorphine had more shallow stage sleep than patients who took methadone.
- **Research Conclusions:** Patients who were treated with either methadone or buprenorphine did not significantly differ in the quality of their sleep when self-recorded in a sleep diary and recorded on an EEG machine. However, sex seems to be a predictor of sleep quality.

Fine, D.R., Lewis, E., Weinstock, K., Wright, J., Gaeta, J.M., & Baggett, T.P. (2021). Office-Based Addiction Treatment Retention and Mortality Among People Experiencing Homelessness. *Journal of the American Medical Association*. 4(3). doi: [10.1001/jamanetworkopen.2021.0477](https://doi.org/10.1001/jamanetworkopen.2021.0477).

This retrospective cohort study conducted by the Boston Health Care for the Homeless Program evaluated treatment retention and mortality in their program among individuals experiencing homelessness with opioid use disorder. The study included 1,467 participants who were 18 years and above with at least one treatment encounter at Boston Health Care for the Homeless Program between January 1 and December 31, 2018. Most participants were men (71.3%), non-Hispanic white (49.8%), mean age of 42.2 years old, had a diagnosis of another drug use disorder (81.9%), and had public insurance (86.3%).

- 193 participants died during the study, with drug overdose accounting for 51.8% of deaths. Opioids were present in 100% of the overdose deaths.

- 957 participants (65.2%) initiated buprenorphine therapy during the study. Buprenorphine retention decreased from 41.5% at 1 month to 17.6% at 6 months, and 10.2% at 12 months.
- Treatment retention at Boston Health Care of Homeless was 45.2% at 1 month then decreased to 17.6% at 6 months, and 11.3% at 12 months.
- Hispanic ethnicity was associated with increased treatment retention at 1 month. Researchers believe that community partnerships along with bicultural and bilingual staff at Boston Healthcare for the Homeless program helped increase retention among Hispanics.
- Continuous opioid abstinence was 28.3% during the first month, then declined to 6.1% at 6 months, and 2.9% at 12 months.
- **Research Conclusions:** Study findings show that among homeless individuals with opioid use disorder, mortality rates were high, with a high number of deaths caused drug overdose. Treatment retention, buprenorphine use, and opioid abstinence drastically decreased over time from the first month.

Finigan, M., Perkins, T., Zold-Kilbourn, P., Parks, J. & Stringer, M. (2011). Preliminary evaluation of extended-release naltrexone in Michigan and Missouri drug courts, *Journal of Substance Abuse Treatment*, 41 (3): 288-93. Doi:10.1016/j.sat.2011.04.003.

This pilot, retrospective case series analysis compared 32 defendants given extended-release naltrexone while in two drug court treatment programs matched with 32 who did not receive the medication.

- Treatment with extended-release naltrexone was associated with 57% reduction in missed drug court sessions.
- It was also associated with 35% reduction in monthly ratio of positive drug and alcohol tests to total tests.
- 8% of those receiving extended-release naltrexone were rearrested compared to 26% who did the receive the medication.
- **Research Conclusion:** Treatment with extended-release naltrexone appeared to be feasible and was associated with a consistently large treatment effect across multiple outcomes relevant to the drug court setting.

Flam-Ross, J.M., Marsh, E., Weitz, M., Savinkina, A., Schackman, B.R., Wang, J., Madushani, R.A., Morgna, J.R., Barocas, J.A., Walley, A.Y., Chrysanthopoulou, S.A., Linas, B.L., Assoumou, S.A. 2023. Economic Evaluation of Extended-Release Buprenorphine for Persons with Opioid Use Disorder. *JAMA Network Open*, 6(9). Doi:10.1001/jamanetworkopen.2023.29583.

This economic evaluation evaluated the cost effectiveness of extended-release buprenorphine compared to transmucosal buprenorphine. The evaluation used a model to simulate the lifetime of a closed cohort of 100,000 individuals with opioid use disorder

treated with buprenorphine in Massachusetts. The model simulated three scenarios: 1) individuals did not have access to medication for opioid use disorder or medically managed withdrawal; 2) individuals were treated with transmucosal buprenorphine, however if individuals did not retain treatment, they were transitioned between no treatment, extended release buprenorphine, methadone, naltrexone, and detoxification; and 3) individuals were treated with extended release buprenorphine, if individuals did not retain treatment, they were transitioned between no medication, transmucosal buprenorphine, methadone, naltrexone, and detoxification.

- Compared to no medication treatment, treatment with transmucosal buprenorphine and extended-release buprenorphine increased life expectancy by seven years.
- When extended-release buprenorphine was compared to transmucosal buprenorphine, it had a .05-year lower life expectancy and a higher lifetime cost per person (\$308,700 vs \$304,700).
- The total pharmaceutical cost of treatment with extended-release buprenorphine was lower than transmucosal buprenorphine (\$293,040 vs \$293,730).
- **Research Conclusions:** This economic simulation of Massachusetts individuals with opioid use disorder exposed to no medication, transmucosal buprenorphine, and extended-release buprenorphine suggests that transmucosal buprenorphine is associated with lower costs and higher life expectancy than extended buprenorphine and no medication. However, when examining total pharmaceutical costs, extended-release buprenorphine fared better than transmucosal buprenorphine.

Food and Drug Administration. (2022). FDA warns about risks of dental problems associated with buprenorphine medicines dissolved in the mouth to treat opioid use disorder and pain. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-risks-dental-problems-associated-buprenorphine-medicines-dissolved-mouth-treat?msclkid=af1b0708d06211ec80a2fd20005f51c2>.

This article by the food and drug administration (FDA) issues a warning to prescribers and patients about the potential dental problems that may occur from dissolving buprenorphine in the mouth. Buprenorphine tablets and films that can be dissolved underneath the tongue or placed against the inside of the cheek have been identified by the FDA to cause dental problems. Buprenorphine delivered as a skin patch or injection have not raised any concerns.

- The most common dental problems that may occur are tooth decay, cavities, dental abscesses/infections, tooth erosions, and total tooth loss.
- To lessen dental problems after buprenorphine has completely dissolved, patients should take a large sip of water, swish it around the mouth and swallow, wait an hour before brushing teeth. Additionally, regular dental checkups are advised.
- Prescribers should advise patients to see a dentist soon after starting and during buprenorphine treatment.
- **Research Conclusions:** The FDA has found that patients who are prescribed sublingual buprenorphine are likely to experience dental problems. To lessen the likelihood of dental problems patients should thoroughly rinse out their mouths after buprenorphine administration and routinely see their dentist.

Friedmann, P. D., Wilson, D., Hoskinson, R., Jr., Poshkus, M. M., & Clarke, J. G. (2018). Initiation of extended release naltrexone (XR-NTX) for opioid use disorder prior to release from prison. *Journal of Substance Abuse Treatment*, 85, 45–48. <https://doi.org/10.1016/j.jsat.2017.04.010>.

This small, 15-person study compared adult prison inmates who received their first injection of naltrexone, Vivitrol, prior to release (9), followed by 5 months of injections post-release compared to individuals who did not receive their first injection until after release (6).

- The pre-release injection group had higher retention in treatment post-release.
- Of the pre-release injection group, 100% received the first injection in prison, while only 67% received their first injection in the comparison group. In the pre-release injection group, 78% went on to receive more than the initial injection, while only 17% did in the comparison group.
- Only 22% of the pre-release injection group had all six injections while none of the comparison group did.
- The pre-release injection group had greater abstinence and a higher proportion of self-reported opioid-free days in the first month post-release (83% vs. 46%) and fewer positive urine drug tests in the 6 months post-release (22% vs. 33%).
- **Research Conclusions:** The initiation of Vivitrol begun pre-release might be an effective approach to reduce relapse, but these findings require confirmation in a larger trial.

Garcia-Portilla, M. P., Bobes-Bascaran, M. T., Bascaran, M. T., Saiz, P. A., & Bobes, J. (2014). Long term outcomes of pharmacological treatments for opioid dependence: Does methadone still lead the pack? *British Journal of Clinical Pharmacology*, 77(2), 272–284. <https://doi.org/10.1111/bcp.12031>.

This review compared multiple methadone and buprenorphine studies.

- Uncontrolled methadone studies with large patient samples with follow ups from 6 months to 30 years found high retention rates from 70% to 84% at 1 year, but others found rate of only 30% at two years for methadone. All found significant reduction in use of drugs and overdoses among those who retained methadone. Many also noted crime reduction.
- There are fewer buprenorphine studies and they show shorter durations and smaller patient numbers, but found 60% to 90% retention for a year, and greater significant reduction in opioid and cocaine use than methadone.
- Methadone is useful in increasing retention in treatment, physical and mental health levels and functioning and quality of life, and in decreasing the use of illicit drugs and HIV risk behaviors. Higher doses are necessary to eliminate heroin use. Although the mortality rate increases during the first 2 weeks of treatment, there is a progressive reduction afterwards.
- **Research Conclusions:** Comparative studies with methadone have generally reported a slight advantage for methadone, although some recent studies have found the

opposite. Due to its relatively widespread availability, there are risks of accidental overdose, misuse and abuse.

GBD 2016 Alcohol Collaborators. (2018). Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet. 392(10152). Doi: [https://doi.org/10.1016/S0140-736\(18\)31310-2](https://doi.org/10.1016/S0140-736(18)31310-2).

This study conducted a systematic review and metanalysis to estimate global alcohol use and deaths that are attributable to alcohol use from 1990 to 2016 amongst individuals 15 years or older. Study authors used 694 data sources to capture the amount of alcohol consumed by using the Global Health Data Exchange and reviewed 592 retrospective studies on the risk of alcohol use. Using this information, study authors were able to make estimates of the prevalence of current drinking, abstinence, distribution of alcohol consumption among current drinkers, and alcohol attributable deaths.

- Globally in 2016, alcohol use was the seventh leading risk factor for death and was the leading risk factor for death amongst individuals between 15-49 years old.
- Among individuals 15-49 years old the leading causes of death attributable to alcohol use were tuberculosis, road injuries, and self-harm.
- Among individuals 50 years or older alcohol consumption was attributable to a cause of cancer.
- Alcohol consumption was significantly more likely to be the cause of health problems in men than in women.
- The rate of alcohol consumption that minimized health risks was zero drinks per week.
- **Research Conclusions:** Globally alcohol use is one of the leading causes of death that significantly impacts individuals 49 years or younger. Alcohol use increases the risk that individuals will experience mortality from diseases, road accidents, and self-harm. The study estimated that drinking zero drinks per week is the most effective way to decrease the likelihood of harm caused by alcohol use.

Gerra G, Saenz E, Busse A, ... & Somaini, C. D. (2011). Supervised daily consumption, contingent take-home incentive and non-contingent take-home in methadone maintenance. Prog Neuropsychopharmacol Biol Psychiatry; 35 2:483–489.

This study compared supervised daily methadone, take home methadone that is used as an incentive, and non-incentive-based take home methadone doses among heroin addicted patients. The study was conducted across three addiction service centers in Italy and included 300 patients. The patients were heroin dependent for at least four-year, average age of 28 years old, and had abused alcohol or some other illicit drug. Study participants were nonrandomly assigned to three groups of 100 participants to test the difference in methadone maintenance outcomes and observed for 12 months.

- 45% and 50% of participants dropped out of the study from the groups who received daily supervised methadone and non-incentivized take home methadone doses, respectively. 26% of the participants who received incentivized take home methadone doses dropped out of the study.

- Participants who received non incentivized take home doses had the highest risk of committing a crime compared to the other two groups.
- Compared to the supervised methadone group, the non-incentivized take home dose group were six times more likely to sell their medication.
- **Research Conclusions:** Study findings show that non incentivized take home doses of methadone can increase diversion, lead to more criminal activity, and lower retention, whereas incentivized take home doses does the opposite.

Ghosh, S.M., Klaire, S., Tanguay, R., Manek, M., & Azar, P. A. (2019). Review of Novel Methods To Support The Transition From Methadone and Other Full Agonist Opioids To Buprenorphine/Naloxone Sublingual In Both Community and Acute Care Settings. Canadian Journal of Addiction, 10(4), 41-50. Doi: 10.1097/CXA.0000000000000072.

This systematic review presented evidence from research articles that discuss methods to transition individuals from methadone or prescribed or illicit opioid agonists to sublingual buprenorphine/naloxone. Additionally, this review discusses protocols to use in the community and acute care settings for buprenorphine induction. The review consisted of randomized controlled trials, review articles, case series, and case reports.

The traditional method of transferring a patient from methadone to buprenorphine involves a gradual reduction of methadone doses until a patient starts to feel mild to moderate withdrawal between doses, taper daily methadone to 30mg or less before switching, and initiate buprenorphine treatment when the patient has a clinical opioid withdrawal scale score greater than 12, which should take about 24-72 hours. First day of dosing with buprenorphine should be less than 4mg, second day dose should be less than 8mg, afterwards rapid dose stabilization should be performed after.

- The Bernese method is a slow as possible introduction to buprenorphine. This method consists of dividing 2mg tablets of buprenorphine into eighths or quarters and titrating until a sufficient level has been reached followed by the discontinuation of the previous opioid medication. Concerns with this method include difficulty in dividing doses and individuals may experience mild withdrawal symptoms.
- Buprenorphine transdermal patch method consists of staggering two buprenorphine patches over a 3-day period to limit the risk of withdrawal. A urine screen is conducted 1-2 days after the second patch, if the screen is positive for buprenorphine, the previous opioid medication must stop, and buprenorphine induction should begin. This method is ideally used in an outpatient setting and is very expensive due to the high cost of the patches. There is a risk of diversion with the buprenorphine patches.
- Rapid Micro induction dosing involves administering buprenorphine every 3-4 hours without requiring a period of withdrawal. This method is best used in inpatient settings.
- Fentanyl patch method begins with a dose of fentanyl based upon a patient's current methadone use. Once a fentanyl patch is applied all other opioid medications must be discontinued. This method is best used during inpatient and is expensive due to the cost of the fentanyl patches. This method carries a risk of diversion of fentanyl patches if the patient is not observed carefully.

- **Research Conclusions:** The methods in this review are all effective ways in which to transfer a patient from methadone to buprenorphine. Despite the effectiveness of these methods, some of them are effective in certain treatment environments, are expensive, and increase the likelihood of diversion.

Gomes, T., Campbell, T.J., Kitchen, S.A., Garg, R., Bozinoff, N., Men, S., Tadrus, M., Munro, C., Antoniou, T., Werb, D., & Wyman, J. (2022). Association Between Increased Dispensing of Opioid Agonist Therapy Take-Home Doses and Opioid Overdose and Treatment Interruption and Discontinuation. *Journal of the American Medical Association*. 327(9), 846-855, doi:10.1001/jama.2022.1271.

This retrospective study investigated whether an increase in take home doses from opioid agonist therapy during COVID-19 was associated with an increase in treatment retention and overdoses. A cohort of 21,297 individuals receiving opioid agonist therapy in Ontario, Canada between March 22, 2020, and April 21, 2020, were observed for 180 days. The study sample were primarily between ages of 38 to 42 and were male. 16,862 individuals received methadone and 4,435 received buprenorphine/naloxone.

- Among individuals receiving methadone, an increase in take home doses were significantly associated with a lower risk of opioid overdose, treatment discontinuation, and treatment interruption compared to those who did not have an increase in their take home doses.
- There were no significant differences in opioid overdoses, treatment discontinuation, and treatment interruption among individuals who received did and did not receive an increase in their take home buprenorphine.
- **Research Conclusions:** Research findings show that increasing take home doses of opioid agonist therapy can significantly lower rates of treatment interruption, treatment discontinuation, and opioid overdose among clients who are prescribed methadone. Buprenorphine is effective as well but increasing the take home supply does not provide any additional treatment benefits.

Gordon, M. S., Kinlock, T. W., Schwartz, R. P., O'Grady, K. E., Fitzgerald, T. T., & Vocci, F. J. (2017). A randomized clinical trial of buprenorphine for prisoners: Findings at 12-months post-release. *Drug and Alcohol Dependence*, 172, 34–42. <https://doi.org/10.1016/j.drugalcdep.2016.11.037>.

This study examines whether starting buprenorphine treatment prior to prison and after release from prison is associated with better drug treatment outcomes and whether males and females responded differently to the combination of in-prison treatment and post-release service setting. The study was conducted between 2008 and 2012 at two Baltimore prisons (N=211) and tested as a 2 x 2 x 2 design (InPrison Treatment: Condition: Buprenorphine Treatment vs. Counseling Only) x 2 (Post-Release Service Setting Condition: Opioid Treatment Program vs. Community Health Center) x 2 (Gender). It looked at results over 12 months post-release.

- The in-prison buprenorphine treatment condition effect led to a higher mean number of days of community buprenorphine treatment compared to the post-release induction on buprenorphine.

- There were no statistically significant effects for the in-prison treatment condition in terms of: days of heroin use, crime, and positive urine screening test results for opioids and cocaine.
- There were no statistically significant hypothesized gender effects.
- **Research Conclusions:** Although initiating buprenorphine treatment in prison compared to after release was associated with more days receiving buprenorphine treatment in the designated community treatment program during the 12-month post-release assessment, it was not associated with superior outcomes in terms of heroin and cocaine use and criminal behavior.

Gowing , L., Farrell, M., Ali, R., & White, J.M. (2016). Alpha2-adrenergic agonists for the management of opioid withdrawal. Cochrane Database of Systematic Reviews, Issue 5. Art. No.: CD002024. DOI: 10.1002/14651858.CD002024.pub5.

This systematic review looked at 26 randomized controlled trials to assess the use of the alpha2-adrenergic agonists (e.g., clonidine and lofexidine) in reducing withdrawal symptoms and severity, and assess adverse effects, duration of treatment, and completion of treatment. The studies in the review compared alpha2-adrenergic agonists to placebo, reducing doses of methadone over 10 days, or symptomatic medications.

- The signs and symptoms of withdrawal appeared earlier when managed with an alpha2-adrenergic agonist when compared to a tapered methadone intervention and they resolved more quickly. Conversely, peak withdrawal symptoms were found to occur at the end of the taper with methadone.
- Severe, intolerable withdrawal symptoms that led participants to discontinue treatment was somewhat more likely to occur in those treated with an alpha2-adrenergic agonist than those treated with reducing doses of methadone.
- Neither alpha2-adrenergic agonists nor tapered methadone completely curbed the withdrawal symptoms of aches and pains, sleep disturbances, loss of energy, chills, or anxiety.
- Among people who discontinued treatment, those taking alpha2-adrenergic agonists discontinued earlier in their course of treatment than those taking reducing doses of methadone.
- The mean duration of treatment until full resolution of withdrawal was significantly longer for individuals treated with reducing doses of methadone compared to those treated with alpha2-adrenergic agonists.
- The most common adverse effects of alpha2-adrenergic agonists were dry mouth, sedation, drowsiness, and dizziness (clonidine); low blood pressure, insomnia, asthenia (i.e., lethargy), and dizziness (lofexidine). Significantly more people treated with an adrenergic agonist experienced adverse effects than those treated with reducing doses of methadone.
- **Research Conclusions:** The completion rates of withdrawal treatment are similar for alpha2-adrenergic agonists and methadone. Duration of treatment was longer and there

were fewer adverse effects with methadone when compared to alpha2-adrenergic agonists. Symptom severity is worse early in treatment for alpha2-adrenergic agonists whereas it peaks near the end of the taper for individuals taking reducing doses of methadone.

Grande, L., Cundiff, D., Greenwald, M., Murray, M., Wright, T.E., Martin, S.A. (2023). Evidence on Buprenorphine Dose Limits: A Review. Journal of Addiction Medicine. doi: 10.1097/ADM.0000000000001189.

This review describes patient centered goals and clinical criteria for determining dose adequacy of buprenorphine, review of the history of buprenorphine dose regulation in the United States, the pharmacological principles and research results regarding buprenorphine dose dependency, and diversion concerns.

- Adequate dose of buprenorphine should aim to eliminate negative reinforcement by suppressing opioid withdrawal symptoms and cravings, eliminate positive reinforcement by blocking euphoric and drug seeking effects, and block respiratory depressions and overdose harm.
- Providing buprenorphine dose up to at least 32mg/d include reductions in withdrawal symptoms, cravings, opioid reward, and illicit use while increasing treatment retention.
- Pregnant individuals who are initially stable on buprenorphine have an increased risk of experiencing withdrawal symptoms during pregnancy. Withdrawal among pregnant individuals increases the risk of miscarriages, intrauterine growth restriction, and preterm birth. To avoid withdrawal symptoms, higher doses of buprenorphine that may exceed 32mg/d may be necessary.
- The most common form of diversion is self-treatment of opioid use disorder because legal access to medication is unavailable.
- Risk of overdose death is reduced among individuals who use nonprescribed buprenorphine are more likely to enter formal treatment when it becomes available.
- **Research Conclusions:** Study findings suggest that providing 32mg/d dose of buprenorphine yields the most favorable treatment results, however pregnant individuals may need higher doses to reduce the risk of withdrawal symptoms and complications related to giving birth. Additionally, the study found that the most common form of diversion is self-treatment due to treatment services being unavailable. Individuals who self-treat with diverted buprenorphine are likely to enter treatment when it becomes available.

Green, T., Clarke, J., Brinkley-Rubinstein, L., Marshall, B., Alexander-Scott, N., Boss, R., & Rich, J. D. (2018). Postincarceration fatal overdoses after implementing medications for addiction treatment in a statewide correctional system. JAMA Psychiatry, 75(4), 405–407. <https://doi.org/10.1001/jamapsychiatry.2017.4614>

This research studies the inmates entering Rhode Island Department of Corrections who were receiving medications for addiction treatment after the program for screening and treatment was launched in 2016. The study compares the proportion of people who died from accidental overdose who were incarcerated in 2017 with those incarcerated in 2016.

- Results show that 26 of 179 individuals (14.5%) who died of an overdose in the first 6 months of 2016 were recently incarcerated compared with 9 of 157 (5.7%) in the same period in 2017, a 60.5% reduction in mortality.
- **Research Conclusions:** Despite the lack of data on whether deaths involved persons released on MAT, the study concludes that linking inmates to treatment is a promising strategy to address high rates of overdose.

Green, T., Serafinski, R., Clark, S.A., Rich., Bratberg. (2023). Physician-Delegated Unobserved Induction with Buprenorphine in Pharmacies. The New England Journal of Medicine. 388, 185-186. doi: 10.1056/NEJMc2208055.

This pilot study investigated whether the use of addiction care programs in pharmacies could assist with lowering the use of illicit opioids and lower the likelihood of an overdose. Researcher partnered with six pharmacies that were located inside or near community behavioral health centers in high drug overdoses areas in Rhode Island to implement their program. At all six selected pharmacies, 100 participants were observed as they sought buprenorphine or naltrexone. Participants were able to walk into the pharmacy to received medication on the same day or call in to make an appointment to receive medication their requested time/date. Participants met with pharmacist for about an hour to get medical and drug history and to assess withdrawal, afterwards participants met with a nurse or doctor. Of the 100 participants who visited the pharmacy for their first visit, 42 participants did not continue to visit the pharmacy due to unknown reasons. The remaining 58 participants were divided into two treatment groups. One group visited the pharmacy on a weekly basis, while the second group were enrolled into a typical outpatient addiction treatment program.

- Participants were 72% more likely to continue treatment for a month at the pharmacy compared to an outpatient treatment program.
- The risk of an overdoses or an emergency department visit were the similar between participants receiving treatment from pharmacies and the outpatient treatment programs.
- Participants preferred receiving treatment at the pharmacy because it felt familiar, was not viewed as embarrassing, children could be brought to appointments, and no one was dismissed if a saliva test showed traces of other drugs.
- **Research Conclusions:** Study findings suggest that receiving opioid medication from a pharmacy is more likely to have patients to retain medication and makes them feel better about treatment and easier to attend despite life circumstances compared to a typical outpatient treatment center. Even though most participants of this study retained treatment at pharmacies compared to outpatient treatment centers, neither treatment setting was preventive than the other in reducing the likelihood of overdoses.

Guillen, A.G., Reddy, M., Saadat, S., & Chakravarthy, B. (2021). Utilization of Telehealth Solutions for Patients with Opioid Use Disorder Using Buprenorphine: A Scoping Review. Telemedicine Journal. doi: 10.1089/tmj.2021.0308.

This scoping review examined the evidence related to telehealth interventions being used to treat opioid use disorder with buprenorphine and its effect on patient outcomes. Peer reviewed and gray literature articles published between 2008 and 2021 related to telehealth

used in buprenorphine treatment were reviewed. The literature search yielded 69 articles for review.

- Telehealth technology with medication assisted treatment for opioid use disorder was associated with a higher patient satisfaction, lower costs of health, and comparable rates of retention, and higher access and usage of buprenorphine.
- The COVID-19 pandemic is credited as a leading cause to the increased capabilities of telehealth technologies and the relaxed federal guidelines to allow for the technological expansion.
- **Research Conclusions:** The findings of this review show that the treatment outcomes associated with telehealth appear to be beneficial for patients. COVID-19 has sped up the creation and use of telemedicine technologies.

Gryczynski, J. Lee, J., Dusek, K., McDonald R., Sharma, A. Malone, M. Monico, L., Cheng, A., DeVeaugh-Geiss, A., Chilcoat, H. (2021). Use of non-prescribed buprenorphine in the criminal justice system: Perspectives of individuals recently released from incarceration, Journal of Substance Abuse Treatment, 127, 108349.

- Researchers conducted face-to-face interviews with 150 formerly recently incarcerated adults in Baltimore and New York with OUD.
- 63% reported illicit/non-prescribed opioid use during incarceration; 39% reported non-prescribed buprenorphine use.
- Non-prescribed buprenorphine was described as the “most widely available” opioid in prisons or jails in both states with 81% declaring it was “very” or “somewhat” easy to obtain.
- The average price of illicit buprenorphine was ten times higher than what it cost in the community.
- Participants reported they used illicit buprenorphine to get “high or mood alteration” while incarcerated but for “therapeutic motives (self-treatment)” in the community.
- Use of illicit buprenorphine in prison and jail was associated with being young and longer incarceration history; in the community it was associated with being single, prior buprenorphine treatment experience, and housing situation and being associated with a Maryland recruitment site for the study
- **Research Conclusion:** These findings suggest that different dynamics and demand characteristics underlie the use of non-prescribed buprenorphine in community and incarceration contexts.

Haight, B. R., Learned, S. M., Laffont, C. M., Fudala, P. J., Zhao, Y., Garofalo, A. S., Greenwald, M. K., Nadipelli, V. R., Ling, W., & Heidbreder, C. (2019). Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: A

multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet, 393(10173), 778–790. [https://doi.org/10.1016/S0140-6736\(18\)32259-1](https://doi.org/10.1016/S0140-6736(18)32259-1).

This randomized, double-blind, placebo-controlled, phase 3 trial was done at 36 treatment centers in the United States. Treatment-seeking adults aged 18–65 years who had moderate or severe opioid use disorder (as defined by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders) entered an open-label run-in phase of up to 2 weeks' treatment with buprenorphine/naloxone sublingual film. Eligible participants were then randomly assigned (4:4:1:1) with an interactive voice/web-response system to receive BUP-XR 300 mg/300 mg (six injections of 300 mg), BUP-XR 300 mg/100 mg (two injections of 300 mg plus four injections of 100 mg), or volume-matched placebo every 28 days, and received weekly individual drug counseling. The primary efficacy endpoint was participants' percentage abstinence from opioid use, defined as the percentage of each participant's negative urine samples and self-reports of illicit opioid use from week 5 to week 24, analyzed in the full analysis set. From Jan 28, 2015, to Nov 12, 2015, potential participants were screened and 201 received BUP-XR 300 mg/300 mg, 203 received BUP-XR 300 mg/100 mg and 100 received placebo.

- Mean participants' percentage abstinence was 41.3% for BUP-XR 300 mg/300 mg and 42.7% for 300 mg/100 mg, compared with only 5.0% (17·0) for placebo for both BUP-XR regimens.
- No compensatory non-opioid drug use was observed during BUP-XR treatment.
- The most common adverse events were headache (17 [8%] participants in the BUP-XR 300 mg/300 mg group vs. 19 [9%] participants in the BUP-XR 300 mg/100 mg group vs. 6 [6%] participants in the placebo group), constipation (16 [8%] vs. 19 [9%] vs. 0), nausea (16 [8%] vs. 18 [9%] vs. 5 [5%]), and injection-site pruritis (19 [9%] vs. 13 [6%] vs. 4 [4%]).
- The BUP-XR safety profile was consistent with other buprenorphine products for treatment of opioid use disorder, except for injection-site reactions, which were reported in more than 5% of all participants who received BUP-XR but were mostly mild and not treatment-limiting.
- **Research Conclusions:** Treatment with BUP-XR was also well tolerated. The availability of this monthly formulation, delivered by health care providers, represents an advance in treatment for opioid use disorder that enhances the benefits of buprenorphine by delivering sustained, optimal exposure, while reducing risks of current buprenorphine products. As with buprenorphine in general, injectable buprenorphine promotes abstinence significantly over treatment without buprenorphine.

Hailu, R., Mehrotra, A., Huskamp, H.A., Busch, A.B., Barnett, M.L. (2023). Telemedicine Use and Quality of Opioid Use Disorder Treatment in the US During the COVID-19 Pandemic. JAMA Network Open, 6(1). doi: 10.1001/jamanetworkopen.2022.52381

This retrospective cohort study compared the quality of treatment for patients who received opioid use disorder treatment from clinicians to patients who received telemedicine during the COVID-19 pandemic. Administrative claims data from the pre-pandemic (March 14, 2019 to March 13, 2020) were compared to data during the pandemic period of (March 14, 2020, to March 13, 2021). The study was limited to clinicians who were most likely to provide office-based treatment. The study sample included 1,768 clinicians who served 11,801

patients, of which 5,990 were treated before the pandemic and 5,811 were treated during the pandemic. The mean age of patients were 53.9 years and there was a 50/50 split between men and women.

- There was no significant change in visit volume for patients visits to clinicians with high and low telemedicine usage before and during the pandemic.
- Comparing low telemedicine use vs high telemedicine use, patients who initiated medication for opioid use disorder within 14 days were equally likely to have at least one subsequent prescription 30 to 90 days.
- There were no significant differences in opioid use disorder related events for patients who saw clinicians with high and low telemedicine usage before and during COVID-19.
- **Research Conclusions:** The results of the study appear to show that treatment and medication retention were similar among patients who received various levels of telemedicine before and during the COVID-19 pandemic. These findings further suggest that telemedicine is safe to use.

Hammerslag, L.R., Mack, A., Chandler, R.K., Fanucchi, L.C., Feaster, D.J., LaRochelle, M.R., Lofwall, M.R., Nau, M., Villani, J., Walsh, S.L., Westgate, P.M., Slavova, S., Talbert, J.C. (2023). Telemedicine Buprenorphine Initiation and Retention in Opioid Use Disorder Treatment for Medicaid Enrollees. JAMA Network Open, 6(10). Doi:10.1001/jamanetworkopen.2023.36914.

This retrospective cohort study examined treatment retention and opioid related nonfatal overdose outcomes between telemedicine and traditional transmucosal buprenorphine opioid use disorder treatment during the COVID 19 pandemic in Kentucky and Ohio. The study examined Kentucky (n=41,266) and Ohio (n=50,648) Medicaid claims and enrollment data from November 1, 2019, through December 31, 2020. Individuals from Kentucky were mostly women (51.5%) with an average age of 37.1 years and Ohio individuals were mostly women (52.2%) with an average age of 37.1 years).

- Telemedicine in Kentucky and Ohio increased in the first two quarters of 2020, however in both states a decline in usage began to occur by Q4 2020.
- Buprenorphine retention for at least 90 days after initiation was 45% in Kentucky and 28.5% in Ohio.
- The odds of high treatment retention were associated with telemedicine, age, sex, and rural status in both states.
- Telemedicine initiation was not associated with opioid related nonfatal overdose in both states.
- Non-Hispanic Black individuals had the lowest odds of telemedicine initiation and were less likely to retain treatment for at least 90 days compared to non-Hispanic White individuals.
- **Research Conclusions:** Study findings show that among Medicaid enrollees in Kentucky and Ohio, telemedicine for buprenorphine had become more widely used at the beginning of the COVID-19 pandemic and had helped with treatment retention and

lowered the risk of nonfatal opioid overdoses, however treatment barriers such as race was a significant factor in access to treatment which may have resulted in the decline of telemedicine use the late quarters of 2020.

Hartung, D.M., McCracken, C.M., Nguyen, T., Kempny, K., & Waddell, E.N. (2023). Fatal and non-fatal opioid overdose risk following release from prison: A retrospective cohort study using linked administrative data. Journal of Substance Use Addiction Treatment. Doi:10.1016/j.josat.2023.208971.

This study estimated the risk of fatal and non-fatal opioid overdoses among adults released from prison. The study sample included adults who were released from Oregon's prison system between January 1, 2014, and December 31, 2017. Medicaid claims data were used to identify emergency department and inpatient admissions. A total of 18,258 individuals were released from prison during the study of which most were male (87%), between the ages of 26-64 years old (83.4%), had a high school degree or GED (61.4%), and needed substance use disorder treatment (67%).

- After release from prison, 579 fatal or non-fatal opioid overdose events occurred, of which 11% were fatal.
- The risk of opioid overdoses within the first two weeks of releases was twice as high as the risk of overdose in other time periods.
- Females, individuals with substance use disorder, and individuals who needed mental health treatment had the highest risk of overdose.
- **Research Conclusions:** The findings of the study show that risk of opioid overdose is high within the first two weeks of release from prison. Additionally, the risk of an overdose is highest among incarcerated individuals who identify as females, diagnosed with substance use disorder, or have mental health treatment needs.

Hartung, D.M., McCracken, C.M., Nguyen, T., Kempny, K., & Waddell, E.N. (2023). Fatal and non-fatal opioid overdose risk following release from prison: A retrospective cohort study using linked administrative data. Journal of Substance Use Addiction Treatment. Doi:10.1016/j.josat.2023.208971.

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Hassman, H., Stafford, S., Shinde, S.N., Heath, A., Boyett, B., Dobbins, R.L. (2023). Open-label, rapid initiation pilot study for extended-release buprenorphine subcutaneous injection. *The American Journal of Drug and Alcohol Abuse*, 49(1), 43-52. <https://doi.org.1080/00952990.2022.2106574>.

This open label pilot study evaluated the safety and tolerability of administering of a single 4mg dose of transmucosal buprenorphine dose followed by an injection of a 300mg extended-release buprenorphine among patients with opioid use disorder. Participants of this study were selected if they were 18 years or older, had a diagnosis of moderate or severe opioid use disorder, were seeking buprenorphine treatment for opioid use disorder, and were deemed appropriate candidates by study staff. Prior to the start of the study, participants were advised to abstain from short acting opioids for at least 6 hours and long-acting opioids for 24 hours before day 1 of the study and abstain from alcohol. Patients that tested positive for opioids or alcohol were dismissed from the study with eligibility to reenter the study within 30 days. At study enrollment patients' withdrawal symptoms and opioid cravings were assessed followed by a single 4mg dose of transmucosal buprenorphine, and an hour later the 300mg extended-release buprenorphine dose was administered. Patients came into the clinic on a weekly basis for 28 days after the extended-release buprenorphine administration to again assess withdrawal and opioid cravings. All participants received counseling following treatment and were permitted to enroll in an extension study for another 5 months of extended-release buprenorphine injections. 26 patients enrolled in the study and received the transmucosal buprenorphine dose, however 24 patients received the extended-release buprenorphine injection. All participants reported opioid use in the previous 30 days with heroin and oxycodone as the most used drug.

- 62% of patients experienced their most severe withdrawal symptoms before the extended-release buprenorphine injection. There was a steady decline in withdrawal symptoms after the first extended-release buprenorphine injection.
- 2 participants experienced precipitated opioid withdrawal following the extended-release buprenorphine injection. Both participants reported polydrug use and had high levels of fentanyl and nor fentanyl in their urine samples.
- 20 participants (83%) reported at least one adverse event with Irritability (n=12) as the most common adverse event.
- This study did not use a control group, so the findings of this study may not be reflective of the real-world population.
- **Research Conclusions:** Study findings appear to show that providing a dose of transmucosal buprenorphine followed by an extended-release buprenorphine dose was well tolerated and lowered opioid withdrawal symptoms. A notable decision to not use a control group makes it difficult to generalize these findings.

Heikkinen, M., Taipale, H., Tanskanen, A., Mittendorfer-Rutz, E., Lahtenvuo, M., & Tiihonen, J. (2021). Real-world effectiveness of pharmacological treatments of alcohol

use disorders in a Swedish nation-wide cohort of 125,556 patients. *Addiction*. <https://doi.org/10.1111/add.15384>.

This Swedish based study investigated the real-world effectiveness of pharmacological treatments (disulfiram, acamprosate, naltrexone, and nalmefene) to treat alcohol use disorder. Data were obtained from 125,556 Swedish residents 16-64 years old who were diagnosed with alcohol use disorder and were registered in a national registry for first time treatment contact due to alcohol use disorder between July 1, 2006 to December 31, 2016. The participants were mainly men (62.5%) with a mean age of 38.1.

- 32,129 (25.6%) of participants used a pharmacological treatment: 19,274 (15.4%) used disulfiram, 11,432 (9.1%) used acamprosate, 10,872 (8.7%) used naltrexone, 693 (.6%) used nalmefene, and 6,398 used two or more of the previously mentioned drugs simultaneously.
- Naltrexone by itself or combined with either acamprosate or disulfiram was associated with a significantly lower risk of hospitalization due to alcohol use when compared to participants that did not use an alcohol use disorder medication.
- Acamprosate was associated with a significantly higher risk of hospitalization when compared to participants who did not take any medication.
- 43,678 (34%) participants used benzodiazepines and related drugs which were associated with an increased risk of hospitalization due to alcohol use disorder.
- 7832 (6.2%) participants died during the study period. There was no significant difference in all-cause mortality with any of the studied medications. Participants who used benzodiazepine and other related drugs was a significant factor in all cause mortalities.
- **Research Conclusions:** The use of naltrexone by itself or combined with acamprosate or disulfiram appears to be an effective treatment for people with alcohol use disorder to avoid hospitalizations related to alcohol use. People with alcohol use disorder should beware benzodiazepine use due to the increased likelihood of hospitalization and death.

Heil, J., Salzman, M., Hunter, K., Baston, K.E., Milburn, C., Schmidt, R., Haroz, R., & Ganetsky, V.S. (2024). Evaluation of an injectable monthly extended-release buprenorphine program in a low-barrier specialty addiction medicine clinic. *Journal of Substance Use and Addiction Treatment*, 156. Doi:10.1016/j.josat.2023.209183.

This retrospective cohort study compared six-month treatment retention and urine drug screens between patients who initiated extended-release buprenorphine and those who were prescribed extended-release buprenorphine but did not initiate it. The study examined 233 patients who attended a low barrier addiction medicine specialty clinic between 12/1/2018 through 12/31/2020. Of the 233 patients enrolled in the study, 148 (63.8%) identified themselves as non-Hispanic White, and 218 (93.6%) had Medicare/Medicaid.

- 50% of patients initiated extended-release buprenorphine. Having a co-occurring substance use disorder and being prescribed extended-release buprenorphine for a reason other than unstable course of remission for opioid use disorder was associated with a greater likelihood of initiating extended-release buprenorphine.

- Six-month retention was higher among patients who initiated extended-release buprenorphine compared to those who did not initiate (70.3% vs 36.5%). Patients with private insurance were more likely to remain in treatment at six months compared to patients with Medicaid or Medicare insurance.
- Patients who initiated extended-release buprenorphine had a higher percentage of negative urine screens for opioids compared to patients who did not initiate extended-release buprenorphine (67.2% vs 36.3%).
- **Research Conclusions:** The results of the study show that patients who initiated extended-release buprenorphine were more likely to retain treatment at six months and have more negative urine screens for opioids compared to patients who did not initiate extended-release buprenorphine. While these results are supportive for the use of extended-release buprenorphine, the study was unable to determine if patients had additional services outside of the addiction clinic in the community, so it is difficult to determine if just extended-release buprenorphine was the cause of the positive study outcomes.

Heimer, R., Black, A.C., Lin, H., Grau, L.E., Fiellin, D.A., Howell, B.A., Hawk, K., D'Onofrio, G., Becker, W.C. (2024). Receipt of opioid use disorder treatments prior to fatal overdoses and comparison to no treatment in Connecticut, 2016-17. Drug and Alcohol Dependence, 254. <https://doi.org/10.1016/j.drugalcdep.2023.111040>.

- This retrospective cohort study investigated the risk of death following exposure to opioid use disorder treatment compared to no treatment at all among individuals living in Connecticut. Study data relied upon state agency data on accidental and undetermined opioid overdose deaths in 2017 and the exposure to opioid use disorder treatment six months prior to death. The study included 965 accidental or undetermined poisoning among residents in Connecticut of which the mean age was 41.2 years, 75.6% male, 90.6% White, and 70.1% had a history of fentanyl use.
- Of the 965 individuals with accidental or undetermined poisonings that involved opioids, 711 individuals did not have a record of receiving treatment for opioid use disorder within six months of their death.
- Individuals who were not exposed to non-medication for opioid use treatment were twice as likely compared to individuals who were exposed to medication for opioid use treatment to have been incarcerated the year prior to their death.
- Exposure to methadone or buprenorphine treatment reduced the risk of death by 38% and 34% respectively.
- **Research Conclusions:** Study findings show that individuals who received medication for opioid use disorder treatment have a reduced risk of experiencing an overdose compared to individuals who did not receive medication for opioid use disorder treatment. Additionally, this study highlights that incarcerated individuals who do not receive medication for opioid use disorder are at a heightened risk for death if not linked to treatment. It should be noted that study authors only included medication for opioid use disorder data the included buprenorphine and methadone, thus the study did not include data about naltrexone.

Herring, A.A., Vosooghi, A.A., Luftig, J., Anderson, E.S., Zhao, X., Dziura, J., Hawk, K.F., McCormack, R.P. Saxone, A., & D'Onofrio, G. (2021). High-Dose Buprenorphine Induction in the Emergency Department for Treatment of Opioid Use Disorder. *Journal of American Medical Association*. 4(7). doi:10.1001/jamanetworkopen.2021.17128.

This retrospective study described the safety and tolerability of patients receiving doses of buprenorphine 12mg or higher. Electronic health records were reviewed of 391 patients who were treated with sublingual buprenorphine in the emergency department at an urban hospital in Oakland California from January 1, 2018, to December 31, 2018. Most patients reviewed in this study were male (68.3%), minorities (43.5% black and 14.6% Hispanic or Latinos), enrolled in California medical assistance (70%), and had never been treated with buprenorphine (53.5%).

- There were 366 inductions of buprenorphine 12mg or more, 138 doses of buprenorphine greater than or equal to 28mg. There were no cases of respiratory depression or sedation reported. Naloxone was not administered to any patients after buprenorphine administration.
- There were five reported cases of precipitated withdrawal, but none of them were related to high dose buprenorphine use.
- There were no life threatening events, serious adverse events, or hospitalizations associated with high dose buprenorphine.
- Researchers noted that a limitation of this study was that it was conducted at a single site and did not have a comparison group.
- **Research Conclusions:** Research findings suggest that high doses of buprenorphine are safe for opioid use disorder patients to use and does not cause an increase in withdrawal or adverse events.

Hickman, M., Steer, C., Tilling, K., Lim, A. G., Marsden, J., Millar, T., Strang, J., Telfer, M., Vickerman, P., & Macleod, J. (2018). The impact of buprenorphine and methadone on mortality: A primary care cohort study in the United Kingdom. *Addiction*, 113(8), 1461–1476. <https://doi.org/10.1111/add.14188>.

This is a cohort study with linkage between clinical records from Clinical Practice Research Datalink and mortality register in UK primary care. A total of 11,033 opioid-dependent patients who received Opioid Substitution Treatment from 1998 to 2014 followed up for 30,410 person-years.

- All-cause mortality (ACM) and drug-related poisoning (DRP) rates were 1.93 and 0.53 per 100 person-years, respectively.
- DRP was elevated during the first 4 weeks of OST (incidence rate ratio [IRR] = 1.93 95% confidence interval [CI] = 0.97–3.82), the first 4 weeks off OST (IRR = 8.15, 95% CI = 5.45–12.19) and the rest of time out of OST (IRR = 2.13, 95% CI = 1.47–3.09) compared with mortality risk from 4 weeks to end of treatment.
- Patients on buprenorphine compared with methadone had lower ACM rates in each treatment period.

- After adjustment, there was evidence of a lower DRP risk for patients on buprenorphine compared with methadone at treatment initiation (IRR = 0.08, 95% CI = 0.01–0.48) and rest of time on treatment (IRR = 0.37, 95% CI = 0.17–0.79).
- Treatment duration (mean and median) was shorter on buprenorphine than methadone (173 and 40 versus 363 and 111, respectively).
- Model estimates suggest that there was a low probability that methadone or buprenorphine reduced the number of DRP in the population: 28% and 21%, respectively.
- **Research Conclusions:** In UK general medical practice, opioid substitution treatment with buprenorphine is associated with a lower risk of all-cause and drug-related poisoning mortality than methadone. In the population, buprenorphine is unlikely to give greater overall protection because of the relatively shorter duration of treatment.

Hoover, D.B., Korthuis, P.T., Waddell, E.N., Foot, C., Conway, C., Crane, H.M., Friedmann, P.D., Go, V.F., Nance, R.M., Pho, M.T., Satcher, M.F., Sibley, A., Westergaard, R.P., Young, A.M., Cook, R. (2023). Recent Incarceration, Substance Use, Overdose, and Service Use Among People Who Use Drugs in Rural Communities. *JAMA Network Open*, 6(11). Doi:10.1001/jamanetworkopen.2023.42222.

This cross-sectional study compared access to substance use treatment, use of medication for opioid use disorder treatment, and the rate of overdose among recently incarcerated individuals who use drugs and individuals who use drugs but had not been recently incarcerated. Study authors administered a community survey in 65 rural counties across Illinois, Wisconsin, North Carolina, Oregon, Kentucky, West Virginia, Ohio, Massachusetts, New Hampshire, and Vermont between January 25, 2018, through March 17, 2020. Overall, 2,935 participants completed the survey of which most were men (56.6%), White (85%), used opioids in the past 30 days (85.4%), used methamphetamine or amphetamine (74.2%), injected drugs daily (56.7%) and an average age of 36 years.

- 42.2% of individuals were incarcerated for at least one day in jail or prison in the past six months. Wisconsin had the highest rate of recent incarceration (53.4%), whereas Ohio had the lowest (16.7%).
- Compared to individuals who had no recent incarceration, individuals who were recently incarcerated were more likely to enroll into substance use disorder treatment, however there was no significant difference between the two groups in their use of taking medications for opioid use disorder in the past 30 days.
- Recently incarcerated individuals were more likely to try and fail to access treatment in the past 6 months compared to individuals who were not recently incarcerated (47.1% vs 34.4%).
- Recently incarcerated individuals were more likely than non-recently incarcerated individuals to have ever received a naloxone kit (59.4% vs 50.2%) but were not likely to currently carry a naloxone kit (38% vs 35.1%) than individuals who were not recently incarcerated.
- Recently incarcerated individuals experienced more overdoses in the past six months than individuals who were not recently incarcerated. (22.3% vs 15.3%)

- **Research Conclusions:** The findings of this cross-sectional study suggests that individuals who use drugs in rural communities and were recently incarcerated are at a higher risk to not be able to access treatment for substance use and experience more overdoses compared to individuals who were not recently incarcerated. These findings appear to suggest that the criminal legal system needs to have more effective plans in place in rural areas to address the treatment for substance use.

Hser YI, Li J, Jiang H, ..Zhao, M. (2011). Effects of a randomized contingency management intervention on opiate abstinence and retention in methadone maintenance treatment in China. *Addiction* 2011; 106 10:1801–1809.

This study investigated if contingency management could improve treatment retention and reduce drug use. 219 participants were randomly assigned to receive standard treatment with incentives (n=160) or just standard care (n=159) over a 12-week period in community-based methadone maintenance clinics Shanghai and Kunming China. The study sample were primarily men (76.2%), mean age of 38, average of 9.4 years of drug use, and 57.8% had injected drugs in the past 30 days.

- In Kunming, the incentivized group had higher retention than the non-incentivized group (75% vs 44%). However, in Shanghai there was no significant difference (90% vs 86%).
- Negative urine screens, sustained abstinence from opioids were significantly higher among the incentivized group than the non-incentivized group.
- **Research Conclusions:** Study findings show that incentivized methadone maintenance can increase retention and lower illicit opioid use.

Hser, Y. I., Saxon, A. J., Huang, D., Hasson, A., Thomas, C., Hillhouse, M., Jacobs, P., Teruya, C., McLaughlin, P., Wiest, K., Cohen, A., & Ling, W. (2014). Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. *Addiction*, 109(1), 79–87. <https://doi.org/10.1111/add.12333>.

This study examines patient and medication characteristics associated with retention and continued opioid use with methadone versus buprenorphine/naloxone treatment. This analysis included 1,267 participants in nine opioid treatment programs between 2006 and 2009 and randomized to receive open label buprenorphine or methadone treatment for 24 weeks.

- Results show that treatment completion rate was 74% for methadone versus 46% for buprenorphine. The rate among methadone participants increased to 80% when the maximum dose reached or exceeded 60 mg/day. With buprenorphine, the completion rate increased linearly with higher doses, reaching 60% with doses of 30–32 mg/day.
- Of those remaining in treatment, positive opioid urine results were significantly lower among buprenorphine relative to methadone participants during the first 9 weeks of treatment.
- Higher medication dose was related to lower opiate use, more so among buprenorphine patients.
- Factors associated with dropout include: 1) buprenorphine; 2) lower medication dose (<16 mg for buprenorphine, <60 mg for methadone); 3) the interaction of dose and

treatment condition (those with higher buprenorphine dose were 1.04 times more likely to drop out than those with lower methadone dose; and 4) being younger, Hispanic, and using substances during treatment.

- **Research Conclusions:** Methadone is associated with better retention in opioid treatment than buprenorphine, as is the use of provision of higher doses of both medications. Provision of buprenorphine is associated with lower continued use of illicit opioids.

Hser, Y., Zhu, Y., Fei, Z., Mooney, L., Evans, E.A., Kelleghan, A., Matthews, A., Yoo, C., & Saxon, A.J. (2021). Long-term Follow-up Assessment of Opioid Use Outcomes among Individuals with Comorbid Mental Disorders and Opioid Use Disorder Treated with Buprenorphine or Methadone in a Randomized Clinical Trial. *Addiction*. <https://doi.org/10.1111/add.15594>.

This randomized control trial investigated how methadone and buprenorphine effect a person's opioid usage among people with comorbid opioid use disorder. 1,269 adults from nine federal opioid treatment clinics were randomized to take buprenorphine or methadone for 24 weeks. After 24 weeks, participants were referred or transferred to community treatment programs or were tapered off the medication. Participants were asked to complete a three-year follow-up assessment, of which 597 participants completed. 50.6% of participants had a mood disorder, 19.1% had a mental health disorder other than a mood disorder, and 30.3% did not have any comorbid mental health diagnosis.

- Compared to methadone, buprenorphine use was associated with a lower likelihood of opioid use among participants with mood disorders, those without a mental health diagnosis and the least number of days using opioids among participants with a mental health diagnosis.
- Methadone was effective in reducing opioid use among participants who did not have a mood disorder.
- Researchers did not have information on the medications that participants received for their mental health treatment in combination to methadone or buprenorphine during the study.
- **Research Conclusions:** Study findings show that buprenorphine is significantly better at reducing opioid use among adults with comorbid opioid use and mental health disorders and those without a mental health disorder. Methadone was primarily effective in reducing opioid use among participants who had a mental health disorder that was not a mood disorder. Researchers did not have adequate information on the other medications that participants received and the additional care for treating these mental health disorders which may have influenced study findings.

Institute for Clinical and Economic Review. (2018, October 25). Extended-release opioid agonists and antagonist medications for addiction treatment (MAT) in patients with opioid use disorder: Effectiveness and value. Evidence report. https://icer.org/wp-content/uploads/2020/10/ICER_MAT_Evidence_Report_102518-1.pdf

This review focused on the efficacy, safety, and effectiveness of extended-release medications (naltrexone vs. buprenorphine) versus transmucosal formulations of buprenorphine/naloxone (implants). Examined studies of patients 16 years or older with opioid use disorder. For the comparison of the interventions of interest versus each other and versus transmucosal formulations of buprenorphine/naloxone, researchers extracted any relevant data, whether in published or unpublished form (e.g., conference abstracts or presentations, FDA review documents).

- The number of opioid-negative urines for extended-release naltrexone did not statistically differ in comparison to sublingual buprenorphine/naloxone. Results from the Probuphine (implant) trials showed statistically significantly greater abstinence than daily buprenorphine/naloxone on various measurements.
- Participants on Sublocade (injectable buprenorphine) treatment were also more likely to be abstinent in comparison to placebo.
- Relapse to opioid use was a measure specific to trials of Vivitrol; a statistically significantly higher rate of relapse was seen with Vivitrol versus buprenorphine/naloxone in the intent-to-treat group because of many unable/unwilling to have first Vivitrol injection.
- Vivitrol was the only intervention with data on diminishing illicit use of opioids which was assessed in one key trial. That trial found that Vivitrol decreased use of heroin and other illicit opioids when compared to buprenorphine/naloxone over the duration of the trial.
- Results showed an overall increase in quality of life in patients receiving Vivitrol compared with placebo. Patient satisfaction with treatment occurred more with Vivitrol than with buprenorphine/naloxone.
- **Research Conclusions:** The findings of our analysis suggest that the interventions of interest result in only marginal changes in quality-adjusted life years (QALYs) relative to generic buprenorphine/naloxone, but universally higher costs, with resulting ratios when calculable, well above commonly cited thresholds of \$50,000 to \$150,000 per QALY gained. QALY is a generic measure of disease burden, including both the quality and quantity of life lived, used to assess the value for money of medical intervention. One QALY equates to one year of perfect health.

Jackson, H., Mandell, K., Johnson, K., Chatterjee, D., & Vanness, D. J. (2015). Cost-effectiveness of injectable extended-release naltrexone compared with methadone maintenance and buprenorphine maintenance treatment for opioid dependence. *Journal of Substance Abuse*, 36(2), 226–231.
<https://doi.org/10.1080/08897077.2015.1010031> maintenance treatment for opioid dependence.

This study estimated the cost-effectiveness of injectable naltrexone (XR-NTX) compared with methadone and buprenorphine maintenance treatments (MMT and BMT) for adult males enrolled in opioid treatment in the United States. A Markov model (used to model randomly changing systems assuming future states depend only on current state, not prior events) with daily time cycles was used to estimate the incremental cost per opioid-free day in a simulated cohort of adult males aged 18–65 over a 6-month period from the state health program perspective. Five states were considered to describe the process of opioid

dependence treatment: (1) maintenance in a treatment program and abstaining from using opioids; (2) maintenance in a treatment program but relapsing to opioid use; (3) attrition from treatment and abstaining from using opioids; (4) attrition from treatment and relapsing to opioid use; or (5) death. Transition probabilities for MMT and BMT were estimated from a Cochrane library meta-analysis of 24 clinical trials published in 2008. However, the estimates for injectable naltrexone were based solely on the original Russian clinical trial (Krupitsky, 2011). The study, thereby, determined the transition probabilities by treatment to be .0062 for methadone, .0090 for buprenorphine and .0087 for injectable naltrexone and opioid use in treatment to be .5940 for methadone, .6250 for buprenorphine and .1000 for injectable naltrexone.

- Based on a 24-week model, patients expected to remain opioid-free longer for injectable naltrexone than MMT and BMT (56, 49 and 96 days) during treatment, assumed to be associated with post-treatment abstinence. Patients treated with BMT had slightly lower predicted rates of opioid use while on treatment than MMT (45% of days using opioids versus 47%), but those on injectable naltrexone had only 6% of days using opioids.
- The average cost per patient over study period (including drop-outs) was least for MMT, \$1,390.98, BMT (\$1,837.40) and most for Injectable Naltrexone (\$4,287.73).
- When considering both effectiveness and costs, BMT is predicted to be dominated by MMT. The predicted incremental cost-effectiveness ratio (ICER) of injectable naltrexone compared to MMT is approximately \$72 per opioid-free day gained.
- **Research Conclusions:** The base case results suggest that injectable naltrexone is cost-effective if state health payers are willing to pay at least \$72 per opioid-free day gained, about the cost of treating three patients with methadone for 1 day.

Jawa, R., Tin, Y., Nall, S., Calaterra, S.L., Savinkina, A., Marks, L.R., Kimmel, S.D., Linas, B.P., Barcoas, J.A. (2023). Estimated Clinical Outcomes and Cost-effectiveness Associated with Provision of Addiction Treatment in US Primary Care. JAMA Network Open, 6(4), doi:10.1001/jamanetworkopen.2023.7888.

This study estimated the long-term clinical outcomes, costs, and cost effectiveness of using buprenorphine and harm reduction kits in primary care settings for individuals who inject opioids. The study utilized a model called the Reducing Infections Related to Drug Use Cost-Effectiveness (REDUCE), that simulated three treatment strategies: standard primary care services with referral to external addiction care, standard primary care services plus onsite buprenorphine prescribing with referrals to offsite harm reduction kits, and standard primary care plus onsite buprenorphine prescribing and harm reduction kits. Within each model scenario it was assumed that all patients began the simulation without any medications for opioid use disorder. Race and ethnicity were not factored into the analysis due to limitations of the data used to create the model. The simulated sample had an average age of 44 years and were 69% male.

- Standard primary care with referrals to external addiction care resulted in 1,162 overdose deaths per 10,000 people. Standard primary care with both buprenorphine prescriptions only and buprenorphine prescriptions with harm reduction kits resulted in 160 fewer deaths per 10,000 people.
- Standard primary care with referrals to external addiction care had the highest mortality rates for infective endocarditis (38.94%) and severe skin and soft tissue infections (5.75%).

Standard care with buprenorphine prescriptions had a mortality rate of 2.10% for infective endocarditis and 36.34% for severe skin and soft tissue infections. Buprenorphine plus onsite harm reduction kits had a mortality rate of 2.11% for infective endocarditis and 36.46% for severe skin and soft tissue infections.

- Compared to standard care, integrating buprenorphine alone extended life expectancy by .16 years and buprenorphine with harm reduction extended life expectancy by .17 years. With the increase in life expectancy hospitalizations rose by 1,454 for buprenorphine only and by 1,169 for buprenorphine with harm reduction kits.
- While providing buprenorphine and harm reduction services increased costs, of the three scenarios, standard care with buprenorphine prescriptions and harm reduction kits was found to be the most cost-effective strategy and cost a PCP practice \$13,000 over a five-year period. Standard care with buprenorphine only was found to be the most expensive and least effective from a cost benefit perspective.
- **Research Conclusions:** The findings of the study show that providing buprenorphine and harm reduction services with standard primary care improve clinical outcomes and increases life expectancy however there providing these services increases costs for PCP practices. Despite the increase in costs, providing buprenorphine with harm reduction kits was found to be the most cost effective in terms of costs and treatment outcomes when examined over a 5-year span.

Jones, C.M., Shoff, C., Blanco, C., Losby, J.L., Ling, S.M., and Compton, W.M. (2024). Overdose, Behavioral Health Services, and Medications for Opioid Use Disorder After a Nonfatal Overdose, JAMA Internal Medicine. Doi:10.1001/jamainternmed.2024.1733.

This cohort study examined the effects of medications for opioid use disorder, naloxone, and behavioral health services have on Medicare recipients 12 months after a nonfatal drug overdose. The study sample was composed of 136,762 Medicare fee for service beneficiaries aged 18 years or older who experienced a nonfatal overdose from January 2020 through December 2021. The study sample were mostly women (58.6%), had an average age of 68.2 years, identified as non-Hispanic White (78.8%), and lived in a metropolitan area (78.9%).

- 4.1% of Medicare recipients received any type of MOUD, 6.2% of Medicare recipients filled a naloxone prescription 12 months after a nonfatal drug overdose.
- 1% of participants died of a fatal drug overdose, while 17% experienced a second nonfatal drug overdose. Opioids were involved in 72.2% of fatal drug overdoses.
- Filling a naloxone prescription, receiving methadone, receiving buprenorphine, and receiving behavioral health assessments or crisis services were associated with reduced odds of a fatal drug overdose in the 12 months following a non-fatal overdose.
- **Research Conclusions:** The findings of this study show that 12 months after experiencing a nonfatal overdose, a small percentage of Medicare recipients received medication for opioid use disorder or had a naloxone prescription filled. The findings of the study suggest that access to medications for opioid use disorder, naloxone prescription filling, and behavioral health services may lower the odds of an additional overdose and overdoses that involve opioids.

Kakko, J., Svanborg, K.D., Kreek, M.J., Heilig, M. (2003). 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomized, placebo- controlled trial. The Lancet. 361, 662-668. doi: [https://doi.org/10.1016/S0140-6736\(03\)12600-1](https://doi.org/10.1016/S0140-6736(03)12600-1).

This random control trial assessed the one-year efficacy of buprenorphine combined with intensive psychosocial therapy for treatment of heroin dependence. Between May 2000 and April 2001, newly admitted inpatients in the chemical dependence unit of Maria Clinic in Sweden, older than 20 years old, opioid dependent for one year, and did not fulfill Sweden's legal criteria for methadone maintenance treatment were enrolled into the study.

Participants were randomly assigned to receive daily 16mg doses of buprenorphine for 12 months (n=20) or tapered six-day regiment of buprenorphine followed by a placebo (n=20). All participants were enrolled in cognitive behavioral group therapy to prevent relapses, weekly individual counseling, and submitted three weekly urine drug screens. Both treatment groups were primarily male, 30 years of age and had hepatitis c infection.

- After one year, 75% of the buprenorphine group retained treatment. Four participants were involuntarily discharged due to continued drug use observed through urine screens. One participant voluntarily dropped out.
- All 20 participants of the placebo group were involuntarily discharged due to continued drug use observed through urine screens.
- **Research Conclusions:** Research findings show that buprenorphine combined with cognitive behavioral therapy appears to help patients retain treatment and lower the odds of continued heroin use compared to cognitive therapy alone.

Kanervo, M.M., Tupola, S.J., Nikkola, E.M., Rantakari, K.M., Kahila, H.K. (2022). Buprenorphine-naloxone, buprenorphine, and methadone throughout pregnancy in maternal opioid use disorder. Acta Obstetrica et Gynecologica Scandinavica. 102(3), 313-322. <https://doi.org/10.1111/aogs.14497>.

This population-based study compared the pregnancies, births, and newborn outcomes of women treated with buprenorphine/naloxone, buprenorphine, and methadone to treat opioid use disorder in Finland. Between January 1, 2021 through December 31, 2018, 172 pregnant women in opioid maintenance treatment were recruited for the study, however 103 pregnant women were dropped from the study because their opioid maintenance treatment was started, changed, or discontinued during pregnancy. 69 pregnant women remained, however the analytic sample dropped to 67 pregnant women due to one mother having a pair of twins and one still birth. The remaining 67 pregnant women were divided into three groups based upon their opioid maintenance treatment: 37 pregnant women were treated with buprenorphine/naloxone, 15 were treated with buprenorphine, and 15 were treated with methadone. The women were observed throughout their entire pregnancy and data was collected on their demographics, health, and substance use (collected through a self-report survey and voluntary urine tests).

- The daily dose of medication was reduced in 62% of women towards the end of their pregnancy. The most common dose reduction occurred among women treated with buprenorphine (79%) and the least common dose reductions occurred amongst women treated with methadone (40%).
- Combining self-reports and urine drug screens, the drug abuse rate for the length of the study was 51% amongst the women during pregnancy.

- Drug abuse was significantly common amongst women who were treated with methadone, reportedly during the third trimester 80% of women used illicit drugs. 22% and 20% of women reported illicit drug use during their treatment of buprenorphine only and buprenorphine naloxone respectively.
- Women in the methadone treatment were likely to use benzodiazepines (72%), cannabis (53%), and stimulants (40%).
- 96% of newborns were born to full term and in good condition, however 22% had a small for gestational age diagnosis. Women who gave birth to small gestational aged newborns were mostly women treated with methadone (33%) followed by buprenorphine (20%), and buprenorphine naloxone (19%).
- The need for pharmacological treatment for newborns with neonatal opioid withdrawal syndrome was needed most for women who were treated with methadone (87%) compared to both buprenorphine groups (56%).
- **Research Conclusions:** The findings of the study suggest that buprenorphine-based medication, specifically buprenorphine naloxone is the safest pharmacological treatment for women to receive during pregnancy to increase the likelihood of a healthy newborn. The study findings show that illicit drug use was common amongst all treatment groups, especially methadone, which suggests that patients should be closely followed up and monitored during treatment.

Kelty, E, 2017, Fatal and non-fatal opioid overdose in opioid dependent patients treated with methadone, buprenorphine or implant naltrexone.

In Western Australia, opioid dependent patients who were treated with methadone, buprenorphine, or injectable naltrexone were studied to compare the rates of fatal and serious but non-fatal opioid overdose and to identify the risk factors involved in fatal opioid overdoses. Data was collected by matching state mortality and hospital data among the three opioid treatments.

- During the first 28 days of treatment, rates of non-fatal opioid overdose were high across all three groups.
- Fatal opioid overdoses in patients who were treated with methadone was significant compared to zero recorded fatal overdoses amongst patients taking injectable naltrexone and buprenorphine.
- After the first 28 days, buprenorphine was observed to be the most protective medication against non-fatal opioid overdoses.
- Men had an elevated risk of fatal overdose when using injectable naltrexone compared to men who were treated with methadone.
- After the treatment was concluded, gender, hospitalizations with a diagnosis of opioid poisoning, and cardiovascular or mental health problems were significant predictors of fatal opioid overdose.
- **Research Conclusions:** Rates of fatal and non-fatal opioid overdose was not significantly different in patients treated with methadone, buprenorphine, or injectable naltrexone. Gender and past hospitalizations can be used as identifiers to determine patients who are at high risk of fatal opioid overdose.

Kennedy, M.C., Crabtree, A., Nolan, S., Mok, W.Y., Cui, Z., Chong, M., Slaunwhite, A., Ti, L. (2022). Discontinuation and tapering of prescribed opioids and risk of overdose among people on long-term opioid therapy for pain with and without opioid use disorder in British Columbia, Canada: A retrospective cohort study. PLOS Medicine. <https://doi.org/10.1371/journal.pmed.1004123>.

This retrospective cohort study investigated the relationship between discontinuation and tapering of prescription opioids to the risk of overdose for individuals receiving long term opioid therapy for pain with and without an opioid use disorder diagnosis in British Columbia, Canada. The study sample was composed of 14,037 of individuals aged 14 to 74 years old, who received provincial health insurance who had at least one long term episode (90 days or greater) of being prescribed opioid treatment for pain between October 3, 2014, through June 30, 2018. Of the 14,037 individuals in the study, 13,327 did not have an opioid use disorder diagnosis, 483 were diagnosed with opioid use disorder but were not receiving opioid agonist treatment, and 227 individuals were diagnosed with opioid use disorder and received opioid agonist treatment.

- Over the course of four years, 530 (3.8%) individuals experienced at least one overdose event.
- 12,812 individuals experienced at least one discontinuation event, while 9,861 (70.3%) individuals experienced at least one tapering event during the four-year study.
- Discontinuation of opioid treatment for pain was associated with an increased risk of overdose among individuals who had not been diagnosed with an opioid use disorder, individuals diagnosed with an opioid use disorder with opioid agonist treatment, and individuals diagnosed with opioid use disorder and had not received opioid agonist treatment.
- Tapering opioid treatment for pain was associated with a decreased risk of overdose among individuals diagnosed with opioid use disorder and had not received opioid agonist treatment.
- A noted limitation of this study was that study authors were unable to determine whether drugs used in overdose events were illicit and/or prescribed.
- **Research Conclusions:** The study found that individuals who are in long term therapy for pain that discontinue opioid treatment are at an increased risk of overdoses. On the other hand, tapering opioid treatment for pain was associated with a decreased risk of overdose for individuals who had not been prescribed opioid agonist treatment. These findings suggest that avoiding abrupt discontinuation and providing tapering strategies are more beneficial to prevent overdoses.

Kessel, J. B., Castel, L. D., & Nemecek, D. A. (2018). Clinical and cost outcomes of buprenorphine treatment in a commercial benefit plan population. The American Journal of Pharmacy Benefits, 10(1), 84–89. https://ajpblive.s3.amazonaws.com/_media/_pdf/AJPB_0102_2018_Kessel.pdf

This study compares cost and patient outcomes among three different types of treatment for addicted individuals: buprenorphine with induction, buprenorphine without induction, and no buprenorphine. The induction group was started on buprenorphine in the induction phase

and continued to maintenance (or as long as treatment lasted). Inclusion criteria for the induction group consisted of diagnosis of opioid dependence, the Healthcare Common Procedure Coding System procedure code H0033 (defined as “oral medication administration, direct observation”), and a physician provider. Individuals were considered undergoing induction whether or not they used all three authorized induction sessions. The non-induction group received buprenorphine, as seen in pharmacy claims, but not for induction. Instead, this group received it as part of detoxification or while hospitalized (i.e., no induction or implied maintenance). The non-induction group was identified as those who received physician services and buprenorphine within the study interval but without an H0033 claim. The no-treatment group was actually “no treatment with buprenorphine.” This group had treatment as usual (i.e., inpatient or outpatient, detoxification, rehabilitation), but did not receive buprenorphine at any point. The study sample was 648 Cigna customers.

- Treatment with buprenorphine (both induction and non-induction) was associated with significantly reduced inpatient utilization (81.8% vs. 43.1%) and lower total medical, behavioral health, outpatient, and pharmacy costs (cost ratio, 0.52:1).
- With buprenorphine, there was a cost and utilization shift from inpatient toward outpatient, and an observed shift in pharmacy claims from medical to behavioral health services, with an observed cost ratio of 1.58:1 for total pharmacy and 2.26:1 for non-psychotropic pharmacy.
- **Research Conclusions:** This study supports the use of buprenorphine with and without induction to decrease inpatient use and to lower medical, health, and pharmacy costs.

Kilmas, J., Hamilton, M., Gorfinkel, L., Adam, A., Cullen, W., Wood, E. (2021). Retention in opioid agonist treatment: a rapid review and meta-analysis comparing observational studies and randomized controlled trials. *Systematic Reviews*, 10(216). <https://doi.org/10.1186/s13643-021-01764-9>.

This meta-analysis examined the retention rates of randomized controlled trials and observational studies that compared methadone and buprenorphine. Studies included in this meta-analysis included adults 18 years or older with opioid use disorder. The analysis included 13 studies of which 10 were randomized controlled trials with a mean dose of 60.46mg/day of methadone and 7.79 mg/day of buprenorphine. The three observational studies had a mean dose of 69.27mg/ of methadone and 8.84 mg/day of buprenorphine.

- Average retention rates for buprenorphine varied widely among random controlled trials (20-82.5%) and 20.2-78.3%.
- Methadone average retention rates varied widely among random controlled trials (30.7-83.8%) and observational studies (48.3-74.8%).
- There were no significant differences between methadone and buprenorphine when examining length of time retained in the study,
- **Research Conclusions:** The results of this meta-analysis appear to suggest that methadone and buprenorphine both have a wide variation treatment retention and that there is not much of a difference between their rates of retention when comparing the two medications in both randomized controlled trails and observational studies.

Kinsky, S., Houck, P.R., Mayes, K., Loveland, D., Daley, D., & Schuster, J.M. (2019). A comparison of adherence, outcomes, and costs among opioid use disorder Medicaid patients treated with buprenorphine and methadone: A view from the payer perspective. *Journal of Substance Use and Addition Treatment*, 104, 15-21. DOI: <https://doi.org/10.1016/j.jsat.2019.05.015>.

This study investigated the adherence, costs, and emergency department non-fatal drug related overdose among Medicaid recipients treated with buprenorphine and methadone. The study examined a sample of 1,184 Medicaid recipients who had physical and behavioral health insurance and were newly treated with methadone and buprenorphine. Participants treated with naltrexone and received both methadone and buprenorphine during the study period were excluded. Participants treated with methadone (n=212) and buprenorphine (n=972) were demographically similar in that most were female (55.7% vs 54.5%) and White (88.2% vs 91.6%). However, participants who were treated with methadone were significantly older (38.8 vs 35.3 years) and were in an urban area.

- 49.1% of methadone treated participants were adherent to treatment for six months compared to 40.8% of buprenorphine treated participants.
- Participants 40 years old or older and women were significantly associated with having lower risk of non-adherence.
- Emergency department non-fatal drug related overdoses were highest among participants who were non adherent for six months.
- Participants 40 years or older, women, and participants living in high socioeconomic deprivation areas were least likely to experience an overdose.
- Participants receiving buprenorphine increased pharmacy costs by \$219 while methadone decreased pharmacy costs by \$23.
- Participants who were adherent to methadone decreased costs by \$13.27, while non adherent methadone participants increased costs by \$1,173.50.
- Participants adherent to buprenorphine increased costs by \$533.20, while non adherent buprenorphine participants increased costs by \$474.94.
- **Research Conclusions:** The results of this study show that methadone increases the likelihood of adherence for six months compared to buprenorphine. Additionally, individuals over 40 years or older and women have the lowest risk of non-adherence to methadone and buprenorphine treatment amount Medicaid enrollees. Examining the cost of care between buprenorphine and methadone, methadone was found to be the cheaper however nonadherence was found to increase the cost of care.

Kinlock, T.W., Gordon, M.S., Schwartz, R.P., O'Grady, K., Fitzgerald, T.T., Wilson, M. (2007). A randomized clinical trial of methadone maintenance for prisoners: results at 1-month post-release. *Drug and Alcohol Dependence*. 91(2-3), 220-227. Doi: [10.1016/j.drugalcdep.2007.05.022](https://doi.org/10.1016/j.drugalcdep.2007.05.022).

This randomized control trail investigated the effectiveness of methadone maintenance treatment among incarcerated individuals with a heroin addiction prior to incarceration. Study participants were males who were being held at a Baltimore prerelease facility after being incarcerated for at least one year, met criteria for methadone maintenance treatment during their incarceration, diagnosed with heroin dependence at the time of incarceration and had been dependent on heroin the year prior to incarceration. Study participants were

randomized into three treatment conditions: counseling in prison only (n=64), counseling in prison with immediate access to methadone maintenance treatment upon release but no methadone maintenance treatment in prison (n=66), and counseling in prison with initiation of methadone maintenance in prison with a continuation of treatment in the community by the same provider immediately upon release (n=70). Most study participants across all three treatment groups were African American, did not complete high school, were between 35-45 years of age, were previously incarcerated, began using heroin in their late teens, and used heroin and committed a crime everyday within the 30 days prior to incarceration.

- 7.8% of the counseling only group, 50% of the counseling in prison with methadone maintenance after release, and counseling and methadone maintenance during incarceration attended community treatment one month after release. These outcomes were found to be statistically significant.
- 63% of the counseling only group, 41% of the counseling and methadone maintenance after incarceration, and 28% of the counseling and methadone maintenance during incarceration group tested positive for opioids one month after release.
- During the study there were ten serious adverse events that included nine hospitalizations and one narcotic overdose death. Only one hospitalization for constipation was considered being related to the counseling and methadone maintenance after incarceration treatment group.
- **Research Conclusions:** The study found that providing methadone maintenance prior to or immediately after release from prison increases the likelihood for individuals to enter community treatment and not use opioids one month after release compared to receiving counseling only while incarcerated and no methadone after release. Receiving methadone and counseling while incarcerated reduced opioid use the most.

Klaire, S., Zivanovic, R., Barbic, S.P., Sandhu, R., Matthew, N., & Azar, P. (2018). Rapid Micro-Induction of Buprenorphine/naloxone for Opioid Use Disorder in an Inpatient Setting: A Case Series. American Journal on Addiction. Doi:10.1111/ajad.12869.

This study presented two cases of patients from the same hospital who started buprenorphine/naloxone treatment using a micro-induction technique. Case 1 involved a 33-year-old woman who was hit by car with a history of severe opioid use disorder, severe alcohol disorder, hepatitis C, and fetal alcohol spectrum disorder, and used .5 grams of heroin per day, and was taking heroin provided from friends during her inpatient stay prior to the start of buprenorphine/naloxone treatment. This patient was initially given .25mg of buprenorphine/naloxone every four hours. Case 2 involved a 40-year-old man who was found unresponsive at a residential drug treatment facility. This patient had a history of severe opioid use disorder, severe stimulant use disorder, used intranasal heroin daily, and had not been taking prescription medication prior to treatment. This patient initially received .5 mg of buprenorphine every three hours.

- After the day 1 dosage, Case 1 patient was given a double dosage of buprenorphine/naloxone until day 4. On day 5 the patient began a single 16mg dose that continued for the rest of her inpatient stay. The patient experienced no increase in withdrawal symptoms, no cravings for opioids and denied ongoing illicit use of heroin for the rest of during her inpatient stay.
- After the day 1 dosage, Case 2 patient began a doubled dose of buprenorphine/naloxone on their second day. On day 3 the dosage was consolidated to

a single 12mg dose. The patient reported no withdrawal, pain, or cravings. The patient was discharged back to the residential treatment facility on a daily 12mg dose of buprenorphine/naloxone dose.

- **Research Conclusions:** Rapid micro induction of buprenorphine/naloxone offers an alternative way to begin buprenorphine/naloxone treatment and to avoid withdrawal symptoms.

Klein, A. A., & Seppala, M. (2019). Medication-assisted treatment for opioid use disorder within a 12-step based treatment center: Feasibility and initial results. *Journal of Substance Abuse Treatment*, 104, 51–63.

<https://doi.org/10.1016/j.jsat.2019.06.009>.

This study observed opioid use disorder patients who were enrolled in either a residential or day treatment program. The patients participated in a 12-step treatment program and were given the option to receive MAT medication. Out of the 253 patients who participated in the study, 68% were male, 61% were between 21 and 30 years old, and 96% were Caucasian. The MAT medications available were buprenorphine/naloxone, oral naltrexone, and injectable naltrexone (patients had to switch to oral naltrexone due to costs). Post-treatment outcome data, which included craving, opioid withdrawal, residential treatment completion, continuing care compliance, medication compliance, substance use frequency, and 12 step meeting attendance, was gathered at 1 and 6 months.

- 71% of the patients elected to take medication alongside the 12-step program.
- Patients who had higher levels of craving and severe withdrawal symptoms were more likely to choose buprenorphine/naloxone as their preferred MAT medication.
- Medication compliance rates at 1 month were 81%, followed by 59% at 6 months.
- Patients who were compliant with medication were more likely to be abstinent from illicit drugs and alcohol compared to the patients who were noncompliant.
- Patients who took no medication were more likely to maintain abstinence compared to patients who were noncompliant with oral naltrexone.
- There were no significant findings observed between medication compliance and craving, or 12-step meeting attendance.
- **Research Conclusions:** It is feasible to administer MAT medications within the context of 12-step-based treatment. Taking MAT medications as prescribed within the 12-step model leads to favorable treatment outcomes.

Kolb, E. 2021. Patient satisfaction with clinic-based medication pick up: Addressing pharmacy-level challenges to buprenorphine access.

This study examined patient satisfaction among patients participating in a pharmacy program that coordinated buprenorphine delivery and provision to patients during office visits instead of requiring patients to fill prescriptions at their local pharmacies. Voluntary and anonymous surveys were given to 714 buprenorphine prescribed patients who were being treated at 15 office based opioid treatment clinics that utilized the pharmacy program. The survey consisted of 16 questions that evaluated the patient's satisfaction with the pharmacy program and their prior retail pharmacy experience.

- 91.7% (n=655) of patients reported that they were more likely to make their treatment appointments and stick to their treatment plan now that the need to go to a pharmacy to fill their prescription was no longer necessary.
- 77.6% (n=529) of patients found it difficult to get to their pharmacies because of transportation and excessive time spent at the pharmacy.
- 56.8% (n=386) patients felt stigma and shame while going to a retail pharmacy.
- 37.1% (n=252) patients found their pharmacies did not reliably stock their medication.
- **Research conclusions:** Survey findings show that most patients preferred the convenience of receiving their medication from their treatment visit instead of having to visit a retail pharmacy. The survey also revealed barriers and attitudes that patients had felt during pharmacy visits which may have impacted their access to medication.

Konova, A., Lopez-Guzman, S., Urmache, A., Ross, S., Louie, K., Rotrosen, J., & Glimcher, P. (2019). Computational Markers of Risky Decision-making for Identification of Temporal Windows of Vulnerability to Opioid Use in a Real-world Clinical Setting. JAMA Psychiatry.

DOI:<https://doi.org/10.1001/jamapsychiatry.2019.4013>.

This study examined the changes in decision making processes preceding a person's opioid use. 70 patients from a New York City addiction therapy center were studied for 7 months with a max of 15 sessions per person. The patients were made up of 12 women and 58 men with an average age of 44 years old. At each session, the participant completed a clinical assessment to measure their anxiety, craving, withdrawal, and adherence to medication, and then they were asked to complete a betting game that offered a known risk and an unknown risk in order to measure the patients decision making. A control group of 55 participants who did not have an opioid use disorder were given 1-5 sessions per person and were given the same assessments. The data of the control group was used to create a baseline comparative group.

- Of the 553 sessions completed by participants, 252 (45.7%) sessions were directly preceded by opioid use events.
- Patients with high levels of drug craving on their clinical assessments were more likely choose risky unknown decisions. These patients were 85% more likely to use opioids within a week.
- There were no significant differences in the level of unknown risk tolerance observed between the patients and control groups, but the patient group was more tolerant of taking more known risks.
- **Research Conclusions:** The capturing of risky decision making combined with clinical work can be helpful in being able to detect a person's vulnerability to reusing opioids.

Korthuis, P.T., King, C., Cook, R.R., Khuyen, T.T., Kunkel, L.E., Bart, G., Nguyen, T., Thuy, D.T., Bielavitz, S., Nguyen, D.B., Tam, N.T.M., & Giang, L.M. (2021). HIV clinic-based buprenorphine plus naloxone versus referral for methadone maintenance therapy for treatment of opioid use disorder in HIV clinics in Vietnam (BRAVO): an

open-label, randomized, non-inferiority trial. The Lancet. 8(2),67-76, [https://doi.org/10.1016/S2352-3018\(20\)30302-7](https://doi.org/10.1016/S2352-3018(20)30302-7).

This open label trial investigated whether HIV clinic-based buprenorphine plus naloxone treatment for opioid use disorder was a better treatment method than methadone maintenance therapy for achieving HIV viral suppression in Vietnam. Between July 27, 2015 and February 12, 2018, 281 patients with HIV and opioid use disorder were randomly assigned to receive HIV clinic-based buprenorphine plus naloxone or methadone maintenance therapy in six HIV clinics in Vietnam. Participants were mainly male (n=272) and had a mean age 38.3 years, 68% of participants were receiving antiretroviral treatment prior to the study, and all participants were using heroin at the start of the study.

- Viral suppression improved from baseline to 12-month follow up for the HIV clinic-based buprenorphine plus naloxone group (69% to 81%) and the methadone maintenance therapy group (66% to 93%).
- Medication retention was lower for the buprenorphine plus naloxone group than the methadone maintenance therapy group at 12-month follow up (40% vs 65%).
- Participants new to antiretroviral treatment reported feeling uncomfortable visiting an HIV clinic, fearing their HIV status would be made public. Researchers believe HIV related stigma may have played a part in lower viral suppression and opioid substitution treatment adherence.
- Participants in the buprenorphine plus naloxone group reported more serious adverse events than the methadone maintenance group (7% vs 3%). Ten participants died in the trial: seven in the buprenorphine group and three in the methadone maintenance group, which included three heroin overdoses and three AIDS related deaths.
- **Research Conclusions:** Buprenorphine plus naloxone appears to be a less effect treatment method than methadone maintenance. Buprenorphine plus naloxone treatment improved viral suppression but did not significantly improve treatment retention and caused more adverse events and deaths when compared to methadone maintenance. Due to the study setting taking place in HIV clinics, HIV related stigma among the participants may have influenced their actions during the study.

Kotake, K., Hosokawa, T., Tanaka, M., So, R., Banno, M., Kataoka, Y., Shiroshita, A., Hashimoto, Y. (2024). Efficacy and safety of alcohol reduction pharmacotherapy according to treatment duration in patients with alcohol dependence or alcohol use disorder: A systematic review and network meta-analysis. Addiction, 119(5), 815-832. <https://doi.org/10.1111/add.16421>.

This systematic review and meta-analysis evaluated the efficacy and safety of pharmacotherapy to reduce alcohol use among patients with alcohol use disorder and alcohol dependence. A total of 55 random controlled trials that examined 15 pharmacological treatments were reviewed. The outcomes of interest for this review included heavy drinking days, total alcohol consumption, adverse events, and days without drinking. Of the 55 studies, 41 studies evaluated individuals with alcohol dependence and 14 assessed individuals with alcohol use disorder. Among the 15 examined pharmacological treatments, 13 studies were conducted with naltrexone, 9 with baclofen and nalmefene, 8 with topiramate, 5 with varenicline, 4 with zonisamide, 2 with extended-release naltrexone and gabapentin, and one study each for acamprosate, carbamazepine, levetiracetam, pregabalin or valproate.

- For long term efficacy, nalmefene was the only reviewed medication that was more effective than a placebo in reducing heavy drinking days and total alcohol consumption at 24 weeks.
- For short term efficacy, topiramate was the only reviewed medication that was more effective than the placebo for short term heavy drinking days and increased days without drinking.
- Of the reviewed medication, Baclofen was the only medication that was effective for short-term lowering of total alcohol consumption.
- None of the reviewed medications outperformed the placebo for short term and long-term alcohol use reduction.
- For long term drug safety, only nalmefene was associated with a high frequency of adverse events compared to the placebo.
- **Research Conclusions:** This systematic review suggests that nalmefene, topiramate, and baclofen have some effectiveness in heavy drinking of alcohol and total alcohol consumption, with nalmefene being the only reviewed medication with long term effectiveness, however nalmefene has a high frequency of adverse events. This systematic review appears to suggest that the two FDA approved medications, Naltrexone and acamprosate, are not as effective in the short and long term as nalmefene, but they are safer to use. These findings suggest that there may be a trade off between long term efficacy and safety when thinking about prescribing medications for alcohol use disorder.

Krebs, E., Enns, B., Evans, E., Urada, D., Anglin, M. D., Rawson, R. A., Hser, Y., & Nosyk, B. (2017). Cost-effectiveness of publicly funded treatment of opioid use disorder in California. *Annals of Internal Medicine*, 168(1), 10–19.
<https://doi.org/10.7326/M17-0611>

This study sought to determine the cost-effectiveness of opioid agonist treatment for all treatment patients in comparison to the observed standard of care in California's publicly funded treatment system. The researchers accessed 2006–2010 data from publicly funded treatment and criminal justice records in the state.

- **Research Conclusions:** In their model-based analysis, they concluded that immediate access to agonist therapy resulted in a \$78,257 per-patient savings and more quality-adjusted life years than the typical standard of care (medically managed withdrawal). This would amount to a lifetime savings of up to \$3.8 billion based on 2014 patient data, the researchers reported. The projected savings are based largely on the effects of treatment retention and reduced criminal justice costs.

Krupitsky, E., Blokhina, E., Zvartau, E., Verbitskaya, E., Lioznov, D., Yaroslavl'tseva, T., Palatkin, V., Vetrova, M., Bushara, N., Burakov, A., Masalov, D., Mamontova, O., Langleben, D., Poole, S., Gross, R., & Woody, G. (2019). Slow-release naltrexone implant versus oral naltrexone for improving treatment outcomes in people with HIV

who are addicted to opioids: A double-blind, placebo-controlled, randomised trial. The Lancet HIV, 6(4), e221–e229. [https://doi.org/10.1016/S2352-3018\(18\)30362-X](https://doi.org/10.1016/S2352-3018(18)30362-X).

This Russian phase 3 study was a double-blind, double-dummy trial with 200 people seeking treatment for HIV and opioid dependence assessed over 12 months. Researchers assessed HIV and addiction treatment outcomes over the next 12 months. All participants were not on HIV treatment or had not been on it for the past year, and had viral loads over 1,000 copies per ml. The researchers randomly assigned participants to receive the naltrexone implants under the skin every 12 weeks along with daily placebo oral naltrexone (100); the other group (100) received oral naltrexone 50 mg/day along with a placebo implant. All were offered biweekly drug counseling and treated with antiretroviral therapies.

- Forty-six people in the implant group remained on an antiretroviral therapy (ART) regimen compared to 32 in the oral drug group.
- Sixty-six people in the implant group had viral loads less than 400 copies per ml compared to 50 in the oral group.
- The implant group also remained in addiction treatment without relapsing for a longer period of time (32 weeks vs. 20 weeks).
- **Research Conclusions:** Naltrexone implants proved more effective at helping HIV-positive patients with an opioid addiction reduce relapse and have better HIV-related outcomes compared to those taking naltrexone orally.

Krupitsky, E., Nunes, E. V., Ling, W., Illeperuma, A., Gastfriend, D. R., & Silverman, B. L. (2011). Injectable extended-release naltrexone for opioid dependence: A double-blind, placebo-controlled, multicentre randomised trial. The Lancet, 377(9776), 1506–1513. [https://doi.org/10.1016/S0140-6736\(11\)60358-9](https://doi.org/10.1016/S0140-6736(11)60358-9).

A total of 250 young white men who had been addicted to heroin for 10 years were randomized to receive Vivitrol (126) or placebo injection (124) within one week following detoxification and then every month thereafter as well as biweekly individual drug counseling. The outcome measure studied was confirmed abstinence based on negative urine tests and no self-reports of use.

- More of the Vivitrol group completed the study (53.2% vs. 37.9%).
- Vivitrol group had increased opioid-free weeks (90% vs. 35%).
- Vivitrol group had more confirmed abstinence (35.7% vs. 22.6%).
- Statistically significant differences were also observed for all secondary outcomes, including self-reported opioid-free days, opioid craving scores, number of days of treatment retention, and relapse to physiological opioid dependence.
- No overdose events, suicide attempts, or deaths were reported during the double-blind 24-week treatment phase of the pivotal trial or during the 1-year open-label extension.
- **Research Conclusions:** Vivitrol met U.S. Food and Drug Administration (FDA) criteria to be approved for the treatment of OUD in addition to alcohol use disorder, for which it was approved 4 years earlier.

Kudrich, C., Hurd, Y.L., Salsitz, E., Wang, A. (2022). Adjunctive Management of Opioid Withdrawal with the Nonopioid Medication Cannabidiol. Cannabis and Cannabinoid Research. 7(5). <https://doi.org/10.1089/can.2021.0089>.

This literature review examined the use of cannabidiol, a nonintoxicating portion of the cannabis plant to be used in treatment for managing opioid withdrawal syndrome. 41 research articles were reviewed that examined the use of cannabidiol in a clinical setting to treat opioid withdrawal.

- Cannabidiol was reported to have several therapeutic benefits which include acting as an antidepressant, anti-inflammatory, and reduction of opioid cravings.
- Cannabidiol was well tolerated by patients had no significant adverse effects even when co administered with opioid agonists.
- Most studies of included in this literature review were preclinical studies or were small clinical trials.
- **Research Conclusions:** This literature review suggests that cannabidiol has the therapeutic benefits and is well tolerated to be considered as a form of treatment for opioid withdrawal. Due to the fact that most of the studies in the review are based on small clinical trials, large scaled clinical trials are needed to further examine the uses of cannabidiol on managing opioid withdrawal.

Lalani, E., Menon, R., Mufti, M.A., Kumfa, C., Raji, M. (2023). Mirtazapine: A One-Stop Strategy for Treatment of Opioid Withdrawal Symptoms. Cureus, 15(8), doi: 10.7759/43821.

This literature review presents research articles to support the efficacy of using mirtazapine as a one drug solution to treat a variety of opioid withdrawal symptoms. The study reviews the effects that mirtazapine has on nausea and vomiting, diarrhea, anxiety, jitteriness, and depression, insomnia, anorexia, and low appetite, itching, tremors, and cravings.

- The reviewed studies found that Mirtazapine to be more effective than Lofexidine due to its ability to alleviate the most distressing symptoms of withdrawal.
- Clinical benefits to the use of Mirtazapine include reducing costs while improving medication adherence and the minimization of polypharmacy.
- Readers should take note that all the studies reviewed in this article were all picked for their positive review of mirtazapine.
- **Research Conclusions:** This literature review presented evidence to support the use and benefits of the use of Mirtazapine as a one drug solution to treat opioid withdrawal symptoms. Studies were agreement that Mirtazapine can significantly alleviate withdrawal symptoms, improve costs, and may work better than medications that are popularly used to treat withdrawal.

Lancaster, K.E., Mollan, K.R., Hanscom, B.S., Shook-Sa, B.E., Ha, T.V., Dumchev, K., Djoerban, Z., Rose, S.M., Latkin, C.A., Metzger, D.S., Go, V.F., Dvoriak, S., Reifeis, S.A., Piwowar-Manning, E.M., Richardson, P., Hudgens, M.G., Hamilton, E.L., Eshleman, S.H., Susami, H., Chu, V.A., Djauzi, S., Kiriazova, T., Nhan, D.T., Burns, D.N., Miller, W.C., & Hoffman, I.F. (2021). Engaging People who inject Drugs Living

with HIV in Antiretroviral Treatment and Medication for Opioid Use Disorders: Extended Follow-up of HPTN 074. Open Forum Infectious Diseases.
<https://doi.org/10.1093/ofid/ofab281>.

This 52-week clinical trial reported the outcomes from testing the usage of an intervention combining antiretroviral therapy, medication for opioid use (primarily methadone), and viral suppression for patients with opioid use disorder and HIV. Participants were recruited from Kiev, Ukraine (n=187), Jakarta, Indonesia (n=121), and Thai Nguyen, Vietnam (n=194) where they were randomly assigned to receive standard care (n=376) or the study intervention (n=126). Participants were 18-60 years old, HIV positive, and were active injection drug users. During the study participants who dropped out were allowed to reenroll. Standard care participants who expressed a need for additional supports were allowed to join the intervention group at reenrollment. After the 52-week period of the study, 85 participants in the intervention group were randomly selected to continue their intervention services for an additional 52 weeks. Standard care participants who did not receive ART or medication for opioid use but were still in need of services were also selected to join the 52-week study extension and were able to receive the intervention group services. Findings reported from this study are from the 52-week extension.

- 327 participants reenrolled in the study, of which 94 participants from standard care opted to receive the intervention services.
- From week 52 to week 104 the usage of antiretroviral therapy, medication for opioid use disorder, and viral suppression decreased amongst participation in the intervention group.
- The group of participants who were need of support increased their usage of antiretroviral therapy, medication for opioid use disorder and viral suppression from reenrollment to the end of the study extension.
- **Research Conclusions:** Research findings suggest that the usage of an intervention combining antiretroviral therapy, medication for opioid use disorder, and viral suppression will decrease over time. However, individuals who needed supports and had not used antiretroviral therapy and medication of opioid use disorder significantly benefited from the combined intervention of antiretroviral therapy, medication for opioid use disorder, and viral suppression

Larochelle, M. R., Bernson, D., Land, T., Stopka, T. J., Wang, N., Xuan, Z., Bagley, S. M., Liebschutz, J. M., & Walley, A. Y. (2018). Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: A cohort study. *Annals of Internal Medicine*, 169(3), 137–145. <https://doi.org/10.7326/M17-3107>

This study investigated the use of medications for opiate use disorder after an opioid overdose and their associated with mortality. It used 7 individually linked data sets from Massachusetts government agencies to obtain 17,568 Massachusetts participants without cancer who survived an opioid overdose between 2012 and 2014. Exposure to medication (methadone, buprenorphine, and naltrexone) was identified at monthly intervals and examined as a monthly time-varying exposure variable to predict time to all-cause and opioid-related mortality.

Results show that in the 12 months after a nonfatal overdose, 11% of participants enrolled in methadone maintenance for a median of 5 months, 17% received buprenorphine for a median of 4 months, and 6% received naltrexone for a median of 1 month. Among the entire cohort, all-cause mortality was 4.7 deaths per 100 years and opioid-related mortality was 2.1 deaths per 100 years.

- Both methadone and buprenorphine were associated with decreased all-cause mortality and opioid-related mortality. No associations were identified between naltrexone and mortality as patients did not continue taking the medication after the first month.
- Only a minority of opioid overdose survivors received either buprenorphine or methadone despite the life-saving benefits of both.
- **Research Conclusion:** Providing ongoing agonist medication after an overdose will reduce mortality. After overdosing, individuals are more likely to continue agonist medications and naltrexone.

Latif, Z., Benth, J. Š., Solli, K. K., Opheim, A., Kunoe, N., Krajci, P., Sharma-Haase, K., & Tanum, L. (2019). Anxiety, depression, and insomnia among adults with opioid dependence treated with extended-release naltrexone vs buprenorphine-naloxone: A randomized clinical trial and follow-up study. JAMA Psychiatry, 76(2), 127–134. <https://doi.org/10.1001/jamapsychiatry.2018.3537>.

This Norway study compared extended-release naltrexone (XR-NTX) with opioid agonist treatment (Suboxone 16 mg/d) for effects on symptoms of anxiety, depression, and insomnia to determine if XR-NTX unmasks or reinforces current comorbid symptoms of anxiety, depression, or insomnia compared with opioid agonist treatment. In this prospective randomized clinical trial, 159 men and women aged 18 to 60 years with opioid dependence were randomized to 12 weeks of treatment with either XR-NTX or combined buprenorphine/naloxone (BP-NLX) followed by a 9-month, open-label treatment study with participant choice of one of these two drugs. The study was conducted at outpatient addiction clinics in five urban hospitals in Norway, with the clinical trial performed from November 1, 2012, to October 23, 2015, and the follow-up study completed on July 23, 2016. All analyses were conducted using an intention-to-treat sample. Every 4 weeks, symptoms of anxiety and depression were assessed using the 25-item Hopkins Symptom Checklist, and symptoms of insomnia were assessed using the Insomnia Severity Index.

- Participants (66.0%) completed the trial.
- For the clinical trial period, no overall differences were detected between treatment groups for anxiety or depression, but the insomnia score was significantly lower in the XR-NTX group.
- In the follow-up period, no overall differences could be detected for anxiety, depression, or insomnia between participants continuing with and participants switching to XR-NTX. No significant sex differences between the two treatment groups were detected.
- **Research Conclusions:** Comorbid symptoms of anxiety, depression, or insomnia in abstinence-motivated persons with opioid dependence should not prevent persons for initiating or switching from treatment with an opioid agonist to treatment with XR-NTX.

Lee, J. D., Friedmann, P. D., Kinlock, T. W., Nunes, E. V., Boney, T. Y., Hoskinson, R.A., Jr., Wilson, D., McDonald, R., Rotrosen, J., Gourevitch, M. N., Gordon, M., Fishman, M., Chen, D. T., Bonnie, R. J., Cornish, J. W., Murphy, S. M., & O'Brien, C. P. (2016). Extended-release naltrexone to prevent opioid relapse in criminal justice offenders. *New England Journal of Medicine* 374(13), 1232–1242. <https://doi.org/10.1056/NEJMoa1505409>.

This study compares a 24-week course of injectable naltrexone (Vivitrol) with a course of usual treatment (brief counseling and referrals for community treatment programs) among adult criminal justice offenders with a history of opioid dependence.

- The injectable naltrexone group (153) was associated with a rate of opioid relapse that was lower than that with usual treatment (155), 43% vs. 64% of participants, as well as a longer median time to relapse (10.5 vs. 5.0 weeks) and a higher rate of negative urine samples (74% vs. 56%).
- Over the total 78 weeks observed, there were no overdose events in the extended-release naltrexone group of 153, but seven out of 155 in the usual-treatment group.
- **Research Conclusions:** In this trial involving criminal justice offenders, extended-release naltrexone was associated with a rate of opioid relapse that was lower than that with usual treatment. Opioid-use prevention effects waned after treatment discontinuation.

Lee, J.D., Grossman, E., Truncali, A., Rotrosen, J., Rosenblum, A., Magura, S., Gourevitch, M.N. (2012). Buprenorphine-Naloxone Maintenance Following Release from Jail. *Substance Abuse*, 33(1), 40-47. <https://doi.org/10.1080/08897077.2011.620475>.

This study compared treatment retention and ongoing opioid use among patients who were released from jail and received primary care buprenorphine treatment from a public New York City hospital to a group of patients who were community referrals. All study patients were opioid dependent adults who were seeking office-based buprenorphine treatment. 32 patients were from an opioid treatment program at New York City Rikers Island jail facility, while 110 patients were referred from inpatient detoxification facilities and clinics in the community with participation in the study being their first time treated with buprenorphine. Of the patients that came from the jail treatment program, most were male (97%), Hispanic (66%), had no insurance (47%), and used heroin in the last seven days or at arrest (100%). The community referred patients were mostly male (78%), White non-Hispanic (53%), had Medicaid (65%), and used heroin in the last seven day or at arrest (65%). Patients with insurance were able to fill their buprenorphine prescriptions at community pharmacies, while uninsured patients received free medication from the study hospital pharmacy. Follow up hospital visits assessed on going drug use through self-reports and urine screens.

- The mean treatment duration was 37 weeks among patients from the jail treatment program and 33 weeks amongst community referral patients.
- The mean time of treatment before dropping out was 21 weeks among patients from the jail treatment program and 17 weeks amongst community referral participants.
- Ongoing opioid use continued at a steady proportion amongst both patient groups with no significant difference between both groups.

- **Research Conclusions:** The outcomes of this study appear to show that providing a pipeline of continued care from a jail-based treatment program to the community is an effective treatment model when compared to nonincarcerated individuals referred to the same treatment center, however considerations should be taken with understanding these study outcomes. Most of the study sample of incarcerated individuals were uninsured thus this could receive their medication for free and could receive it at the study hospital, this may have helped have promote higher retention rates amongst patients released from jail. Another point of consideration is that patients from jail were already stable and induced onto buprenorphine in a controlled environment prior to the study compared to community patients who were new to treatment and were being induced to buprenorphine for the first time. This difference between the two patient groups may have helped treatment outcomes favor patients released from jail.

Lee, J. D., Nunes, E. V., Novo, P., Bachrach, K., Bailey, G. L., Bhatt, S., Farkas, S., Fishman, M., Gauthier, P., Hodgkins, C. C., King, J., Lindblad, R., Liu, D., Matthews, A. G., May, J., Peavy, K. M., Ross, S., Salazar, D., Schkolnik, P., . . . & Rotrosen, J. (2018). Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): A multicentre, open-label, randomised controlled trial. *The Lancet*, 391(10118), 309–318. [https://doi.org/10.1016/S0140-6736\(17\)32812-X](https://doi.org/10.1016/S0140-6736(17)32812-X)

This study compared randomly assigned to buprenorphine/naloxone (N=287) and injectable naltrexone (N=283) for a 24-week program. The primary outcome was opioid relapse-free survival during 24 weeks of outpatient treatment. Relapse was 4 consecutive weeks of any non-study opioid use by urine toxicology or self-report, or 7 consecutive days of self-reported use.

- Injectable naltrexone was as effective as buprenorphine/naloxone among those who received the injections—52% of those who started on it relapsed over the course of the 24-week study, compared with 56% of those who received buprenorphine/naloxone.
- However, more than a quarter (28%) of those assigned to the naltrexone group dropped out before they even took their first injection while most of those assigned buprenorphine/naloxone (94%) received their first dose of medication.
- Fifteen individuals (5.3%) had 18 overdose events when they had taken the extended-release naltrexone, compared to 8 individuals (1.7%) with 10 overdose events among those who took buprenorphine/naloxone.
- Five fatal overdoses occurred during the 24-week study (two in the injectable naltrexone group, .071%, and three in the buprenorphine group, 1.04%)
- **Research Conclusions:** It is more difficult to initiate patients to injectable naltrexone than buprenorphine/naloxone and this negatively affected overall relapse. However, once initiated, both medications were equally safe and effective.

Lee, J.D., Malone, M., McDonald, R., Cheng, A., Vasudevan, K., Tofighi, B., Garment, A., Porter, B., Goldfeld, K.S., Matteo, M., Mangat, J., Katyal, M., Giftos, J., MacDonald, R. (2021). Comparison of Treatment Retention of Adults With Opioid Addiction Managed With Extended-Release Buprenorphine vs Daily Sublingual Buprenorphine-

Naloxone at Time of Release From Jail. Journal of American Medical Association. 4(9). Doi:10.1001/jamanetworkopen.2021.23032.

This randomized open label study compared treatment retention among adults released from jail receiving sublingual buprenorphine naloxone versus those receiving extended-release buprenorphine during an 8-week period. Participants were adults who were diagnosed with opioid use disorder, incarcerated in a New York City jail with a known release date, and were prescribed sublingual buprenorphine naloxone. 52 individuals agreed to participate in the study, of which 26 were given extended-release buprenorphine and 26 continued to receive sublingual buprenorphine. Follow ups were conducted at weeks 1,2,4,5, and 8 either in person at the Bellevue Hospital in Manhattan, by phone if in person attendance was not possible, or in the event of reincarceration, at the jail medical clinic. Study participants were primarily men (n=45 [87%]), mean age of 42 years of age, 77% used heroin prior to incarceration, 58% reported prior buprenorphine use, and 35% received community buprenorphine treatment prior to incarceration.

- There were no reported instances of extended release diversion in jail (stolen or missing doses or extraction post injection)
- Barriers that impacted extended-release buprenorphine in jail included lack of knowledge, opposition to needles, preference to sublingual buprenorphine.
- In jail, extended-release buprenorphine was time and labor saving compared to sublingual buprenorphine.
- 18 extended-release buprenorphine participants retained treatment in the community at week eight vs only 9 sublingual buprenorphine patients.
- Seven extended-release buprenorphine patients switched to sublingual buprenorphine due to complaints of burning and pain during extended-release buprenorphine administration and general preference for sublingual buprenorphine.
- 55.3% of extended-release buprenorphine participants tested negative for nonprescribed opioids vs 38.4% among sublingual buprenorphine participants. Majority of positive opioid tests involved heroin and fentanyl.
- **Research Conclusions:** Study findings show that extended-release buprenorphine decreases the likelihood of nonprescribed opioid use and increased treatment retention post release compared to sublingual buprenorphine. Despite the positive treatment outcomes from extended release buprenorphine, lack of knowledge and general preference for sublingual buprenorphine were common barriers to the treatment.

Leighty, A.E., Ansara, E.D. (2019). Treatment outcomes of long-acting injectable naltrexone versus oral naltrexone in alcohol use disorder in veterans. Mental Health Clinician. 9(6), 392-396. <https://doi.org/10.9740/mhc.2019.11.392>.

This retrospective study compared the difference in time till relapse between patients taking long-acting naltrexone and oral naltrexone. Data were obtained from electronic charts of US veterans with alcohol use disorder who were treated at a VA clinic in Indiana and were prescribed oral or long-acting naltrexone from August 1, 2016, to July 31, 2018. Participant requirements included being 21 years or older, a diagnosis of alcohol use disorder or alcohol dependence, receiving treatment in the Substance Use Disorder Recovery Program at the VA clinic, and abstinence from alcohol at the time of medication initiation. 410

patients were identified for having a prescription of either naltrexone medication, but 361 patients were excluded for not fulfilling all participant requirements. Of the remaining 49 patients, 33 were prescribed oral naltrexone and 16 were prescribed long-acting naltrexone. 16 of the 33 oral naltrexone patients were randomly selected to be included in the study analyses to keep a 1:1 ratio with the long-acting naltrexone group. The demographic characteristics of both medication groups were similar. Most patients were male (84%), white (63%), and had a co-occurring diagnosis of depression (59%).

- The median time till relapse for long-acting naltrexone was significantly longer compared to oral naltrexone (150.5 days vs 50.5 days).
- There were no significant differences between the two groups concerning safety outcome, other substance use, or patient adherence.
- **Research Conclusions:** Study findings show that long acting naltrexone provides an increased time till relapses when compared to oral naltrexone among US veterans with alcohol use disorder. The outcomes of this study may not be truly reflective of this population due to most identified participants being cut from the study for not fulfilling all study requirements.

Leslie, D. L., Milchak, W., Gastfriend, D. R., Herschman, P. L., Bixler, E. O., Velott, D. L., & Meyer, R. E. (2015). Effects of injectable extended-release naltrexone (XR-NTX) for opioid dependence on residential rehabilitation outcomes and early follow-up. *American Journal on Addictions*, 24(3), 265–270. <https://doi.org/10.1111/ajad.12182>.

This retrospective study of 7,687 persons released from residential treatment facilities in Pennsylvania examined the short-term outcomes among patients receiving injectable naltrexone in terms of treatment completion and engagement in aftercare compared to those who did not receive the injection before release from residential treatment. Although 598 of the patients were recommended for Vivitrol, only 168 received it.

- Those who received Vivitrol were less likely to leave residential treatment against medical advice (4.8% vs. 30.2%).
- Those who received Vivitrol were more likely to attend their first post-discharge outpatient visit, 37.7% vs. 19.7%. These differences remained significant after controlling for demographic variables.
- **Research Conclusions:** Receiving injectable naltrexone while in residential opioid treatment improves treatment retention and continuation of aftercare outpatient treatment, but residential patients proved reluctant to receive it.

Lewer, D., Eastwood, B., White, M., Brothers, T.D., McCusker, M., Copeland, C., Farrell, M., Petersen, I. (2021). Fatal opioid overdoses during and shortly after hospital admissions in England: A case-crossover study. *Plos Medicine*. <https://doi.org/10.1371/journal.pmed.1003759>.

This case crossover study investigated if there is an elevated risk of opioid related death during hospital admission and after discharge. Data on 13,609 opioid related deaths of individuals in England 18-64 years old from January 1, 2010, to December 2019 were obtained from the UK office for National Statistics and Hospital Episode Statistics database. Patient characteristics two years prior to death, during hospital admission, and 14 days after

discharge were compared. 91.4% of the death were of white ethnicity, 71.8% male, median age at death was 42 years old, and 44.6% lived in a deprived neighborhood.

- 85.5% of deaths did not occur in the hospital or within 14 days of discharge. 4.8% of occurred in the hospital following admission due to drug poisoning. 1.7% of deaths occurred during hospital admission for a reason other than drug poisoning. 8% of deaths occurred within 14 days after discharge.
- Days 1 to 14 of hospital admission had a similar risk of opioid related deaths as being out in the community. 15 or more days spent in the hospital were associated with a lower risk of opioid related deaths.
- The risk of opioid related death was significantly higher amongst people discharged after a psychiatric admission and for people who left the hospital against medical advice.
- **Research Conclusions:** Study findings suggest that hospitalizations and discharges are associated with a small increase in the likelihood of an opioid related death. Longer hospital stays were associated with lowered risk of opioid related deaths, while leaving the hospital against medical advice increased the likelihood of an opioid related death upon discharge.

Lillie, K.M., Shaw, J., Jansen, K.J., Garrison, M.M. (2020). Buprenorphine/Naloxone for Opioid Use Disorder Among Native and American Indian People. Journal of Addiction Medicine. 2020 Oct. <https://doi.org/10.1097/adm.0000000000000757>.

This study identified variables that were associated with buprenorphine/naloxone retention among Alaska Native and American Indian people with opioid use disorder. Electronic health records of 241 Alaska Native and American Indian adults who received buprenorphine/naloxone treatment for opioid use disorder were analyzed from January 1, 2015 to December 21, 2019.

- 63% of the 240 patients retained buprenorphine/naloxone treatment for 90 days, 51% at 6 months, and 40% at 1 year.
- Younger age and having co-occurring substance use were associated with an increased rate of buprenorphine/naloxone treatment discontinuation.
- **Research Conclusions:** Across the Alaska Native and American Indian population buprenorphine/naloxone treatment retention decreases over time. However, younger people and people with co-occurring substance use are at a higher risk of discontinuing treatment. More attention should be considered to patients to prevent treatment discontinuation.

Lim, S., Cherian, T., Katayl, M., Goldfeld, K.S., McDonald, R., Wiewel, E., Khan, M., Krawczyk, N., Braunstein, S., Murphy, S.M., Jalali, A., Jeng, P.J., MacDonald, R., Lee, J.D. (2022). Association between jail-based methadone or buprenorphine treatment for opioid use disorder and overdose mortality after release from New York City jails. Addiction. doi.org/10.1111/add.16071.

This retrospective cohort study assessed the impact of in jail medication for opioid use disorder involving New York City jail inmates after release. The study analyzed the electronic health records of 15,797 diagnosed opioid use disorder adults who were released

from New York City jails into the community from 2011 through 2017. Majority of the participants were male (82%) and had an average age of 42 years, arrested for a misdemeanor related offense (52%), non-Hispanic Black or Hispanic (74%), and single (79%). In jail medication for opioid use disorder was most common among females, participants who experienced homelessness, injection drug users, had cocaine use disorder, and had a visited the emergency department three months prior to their release. Overdose deaths involved heroin, fentanyl, and cocaine. Study participants were grouped into a MOUD and an out of treatment group which was based upon if medication for opioid use disorder was received during the last three days prior to their release from jail.

- One month post release the MOUD group experienced seven overdose deaths while the out of treatment group experienced 27 deaths.
- One year post release the MOUD group experienced 41 overdose deaths while the out of treatment group experienced 70 deaths.
- One year after post release the MOUD group experienced 98 All-cause deaths which malignant neoplasms (n=14), heart disease (n=11), and HIV/AIDS (n=6) as the most common causes. The out of treatment group experienced 121 All-cause deaths with malignant neoplasm (n=10), heart disease (n=8), and homicide (n=7) as the most common causes.
- **Research Conclusions:** Study findings suggest that providing individuals medication for opioid use disorder in jail prior to their release back into the community will lower their risk of overdose and All-cause mortality after one year than not providing medication. These findings further suggest that despite the lower risk of mortality, medication for opioid use disorder is not widely provided to all individuals in jail who are diagnosed with opioid use disorder. To lower the risk of death of individuals upon release into the community, medication for opioid use disorder should have increased availability.

Lin, L.A., Fortney, J.C., Bohnert, A.S., Couglin, L.N., Zhang, L., Piette, J.D. (2021). Comparing telemedicine to in-person buprenorphine treatment in U.S. veterans with opioid use disorder. Journal of Substance Abuse Treatment. <https://doi.org/10.1016/j.jsat.2021.108492>.

This retrospective cohort study compared the use of telehealth delivery of buprenorphine and in person buprenorphine delivery among U.S. veterans. Trends data from the Veterans Health Administration from 2012 to 2019 were examined. The gathered data was used to compare demographic and clinical characteristics of patients who received telehealth buprenorphine treatment and those who received in person buprenorphine treatment.

- The use of telehealth buprenorphine treatment increased from 2.29% in 2012 to 7.96% in 2019.
- Compared to in person buprenorphine patients, telehealth buprenorphine patients were more likely to be female and white.
- Telehealth buprenorphine patients were more likely to be treated at community-based outpatient clinics and to live in rural areas.
- **Research Conclusions:** Among U.S. veterans, telehealth to provide buprenorphine treatment increased from 2012-2019 but remained low. Telehealth buprenorphine

treatment appears be more widely used for those who live in rural environments and those that attend community-based clinics rather than at large medical centers.

Lincoln, T., Johnson, B. D., McCarthy, P., & Alexander, E. (2018). Extended-release naltrexone for opioid use disorder started during or following incarceration. *Journal of Substance Abuse Treatment*, 85, 97–100. <https://doi.org/10.1016/j.jsat.2017.04.002>.

This study investigates the Hampden County Correctional Center's initiation of injectable naltrexone prior to release from incarceration followed by linking participants to community treatment providers compared to persons provided the medication after release. Of initial 67 released, 47 received the medication approximately 7 days prior to release. Utility of the program was measured by retention rates of 4, 8, and 24 weeks.

- Rate of retention at week 4 was higher in the pre-release injection group: 55% versus 25%; week 8: 36% versus 25%; and week 24: 21% versus 15%.
- Three patients in the pre-release group died from overdoses, all 3–5 months after release and 2.5 or more months after their last injection, compared to none of the 20 in the post-release comparison group.
- **Research Conclusions:** Receiving XR-NTX prior to jail release increases the treatment retention rate compared to those receiving the injections after release. The rate of overdose deaths and treatment attrition support the expansion of treatment prior to release.

Ling, W., Hillhouse, M., Ang, A., Jenkins, J., & Fahey, J. (2013). Comparison of behavioral treatment conditions in buprenorphine maintenance. *Addiction*, 108(10), 1788–1798. <https://doi.org/10.1111/add.12266>.

This randomized controlled trial compared the effectiveness of four behavioral treatment conditions provided with buprenorphine and medical management (MM) for the treatment of opioid dependence. After a 2-week buprenorphine induction/stabilization phase, participants were randomized to one of four behavioral treatment conditions provided for 16 weeks: Cognitive Behavioral Therapy (CBT=53); Contingency Management (CM=49); both CBT and CM (CBT+CM=49); and no additional behavioral treatment (NT=51). Study activities occurred at an outpatient clinical research center in Los Angeles, California. Included were 202 male and female opioid-dependent participants. The primary outcome was opioid use, measured as a proportion of opioid-negative urine results over the number of tests possible. Secondary outcomes included retention, withdrawal symptoms, craving, other drug use, and adverse events.

- No group differences in opioid use were found for the behavioral treatment phase (Chi square=1.25, $p=0.75$), for a second medication-only treatment phase, or at weeks 40 and 52 follow-ups. Analyses revealed no differences across groups for any secondary outcome.
- **Research Conclusions:** There remains no clear evidence that cognitive behavioral therapy and contingency management reduce opiate use when added to buprenorphine and medical management in opiate users seeking treatment.

Ling, W., Nadipelli, V.R., Aldridge, A.P., Ronquest, N.A., Solem, C.T., Chilcoat, H., Albright, V., Johnson, C., Learned, S.M., Mehra, V., & Heidbreder, C. (2018). Remission

from chronic opioid use- Studying environmental and socio-economic factors on recovery (RECOVER): Study design and participant characteristics. *Contemporary Clinical Trials*, 76, 93-103, <https://doi.org/10.1016/j.cct.2018.11.015>.

Ling, W., Nadipelli, V.R., Aldridge, A.P., Ronquest, N.A., Solem, C.T., Chilcoat, H., Albright, V., Johnson, C., Learned, S.M., Mehra, V., & Heidbreder, C. (2020). Recovery From Opioid Use Disorder (OUD) After Monthly Long-acting Buprenorphine Treatment: 12-Month Longitudinal Outcomes from RECOVER, an Observational Study. *Journal of Addiction Medicine*, 10.1097/ADM.0000000000000647.

RECOVER, an observational study, reported on opioid use abstinence and changes in quality of life of participants with moderate to severe opioid use who participated in an extended release buprenorphine clinical trial from 39 community treatment sites across 17 US states. Participants were given a monthly extended release buprenorphine injections over 12 months. After completing or discontinuing the injections, the participants were then entered into the RECOVER observational phase. During observation, participants supplied self-report assessments and urine screens every 3 months. After the observation, there was a 12 month follow up in which all participants of the 24-month observation were eligible to participate in as long as they were not deceased or incarcerated. 533 participants were enrolled in the study. The participants were predominantly male (66%), white (56.2%), mean age of 42 years old, and 67% completed high school or had a GED. At the 12-month follow up the sample size decreased to 425 participants.

- 48.8% of participants received all 12 extended release buprenorphine injections, 33% received up to 5 injections, and 18% received 6 to 11 injections. 251 (47%) participants dropped out of the study.
- After receiving the monthly injection phase of RECOVER, 207 (38.9%) participants continued to seek medication assisted treatment. Of those 207 participants receiving medication assisted treatment, 196 (95%) participants received buprenorphine, and 146 (75%) of those participants continuing to use extended release buprenorphine.
- Participants who received all 12 injections were 75% more likely to sustain abstinence from opioids. Participants who received 2 or less injections were 25% likely to sustain abstinence from opioids.
- 50.8% of participants who participated in the 12-month follow up reported no opioid use after the 24-month observation.
- 6-12 months of extended release buprenorphine and being a female were associated with sustaining abstinence at the 12-month follow up. Previous use of pharmacotherapy for opioid use disorder and being 30 years or older were associated with non-abstinence.
- The percentage of participants reporting none/minimal depression increased from 30.2% at the pretrial screening of RECOVERY to 74% at the 12-month follow up.
- The percentage of participants currently employed increased from 20.3% at RECOVERY pretrial to 48.3% at the 12-month follow up.
- **Research Conclusions:** 12 months after participating in the RECOVER study, participants reported positive outcomes for abstinence, depression, and employment.

These findings suggest that pharmacologic treatments have a significant impact in the treatment and relapse prevention for opioid use disorder.

Ling, W., Nadipelli, V.R., Solem, C.T., Ronquest, N.A., Yeh, Y., Learned, S.M.,...Heidbreder, C. (2020). Effects of monthly buprenorphine extended-release injections on patient-centered outcomes: A long-term study. Journal of Substance Abuse Treatment. 110,1-8, doi: <https://doi.org/10.1016/j.jsat.2019.11.004>.

This 12-month open label safety study evaluated extended release buprenorphine's effects on health status, quality of life, employment, healthcare utilization, medication satisfaction, treatment effectiveness, and addiction severity. Study participants were 18 to 65 years old who were seeking treatment for moderate or severe opioid use disorder. Participants who had other substance use diagnoses or positive urine screens for other substances were excluded from the study. The participants were able to enroll by either taking 12 monthly extended release buprenorphine or enroll into a 24-week placebo-controlled group with 6 monthly extended released buprenorphine injections.

- 412 participants began the extended buprenorphine treatment but 206 participants (50%) discontinued the study. Participant being lost to follow up (80 participants) and withdrawal of consent (67 participants) were the most common reasons.
- Significant improvements were observed from baseline to study exit for the participants health status and quality of life.
- The proportion of participants employed increased by 7% from baseline to the end of the study (44.2% to 51.2%).
- During the length of the study a total of 21 hospitalizations, 140 emergency room visits, and 923 outpatient service visits were reported.
- At the end of the study 88% of the participants were satisfied with treatment.
- **Research Conclusions:** Results from the study support the use of extended release buprenorphine can lead to positive outlooks to health and life and high treatment satisfaction

Lintzeris, N., Dunlop, A.J., Haber, P.S., Lubman, D.I., Graham, R., Hutchinson, S., Arunogiri, S., Hayes, V., Hjelmstrom, P., Svedberg, A., Peterson, S., Tiberg, F. (2021). Patient-Reported Outcomes of Treatment of Opioid Dependence With Weekly and Monthly Subcutaneous Depot vs Daily Sublingual Buprenorphine A randomized clinical trial. Journal of American Medical Association. 4(5). doi: [10.1001/jamanetworkopen.2021.9041](https://doi.org/10.1001/jamanetworkopen.2021.9041).

This open label randomized clinical trial compared patient satisfaction between depot buprenorphine and sublingual buprenorphine among adults with opioid use disorder. Participants were recruited from six drug treatment centers in Australia from October 2019 to May 2020. 119 participants were randomly assigned to receive weekly or monthly depot buprenorphine (n=60) or daily sublingual buprenorphine (n=59) over 24 weeks. Participants visited one of the six study site clinics for dosing except for the sublingual buprenorphine group who could receive their dose from a study approved pharmacy.

- After 24 weeks, depot buprenorphine was found to be significantly more satisfying to use than sublingual buprenorphine due to treatment convenience.

- There were no significant treatment differences such as illicit opioid use, withdrawal, and cravings between the two treatment groups.
- 39 participants (65%) in the depot buprenorphine group experienced 117 adverse events and 12 participants in the sublingual buprenorphine group experienced 21 adverse reactions. No participants discontinued medication or withdrew from the study because of adverse events.
- All participants had been treated with sublingual buprenorphine prior to the start of the study. The findings of this study may not truly represent outcomes of patients who are new to buprenorphine treatment.
- **Research Conclusions:** Depot buprenorphine and sublingual buprenorphine provided similar treatment outcomes, but depot buprenorphine was found to provide greater satisfaction due its convenience. Due to all the participants having been familiar with sublingual buprenorphine, it is difficult to generalize these findings for other adults with opioid use disorder.

Liu, J., Grewen, K., Gao, W. (2022). Evidence for the normalization effects of medication for opioid use disorder on functional connectivity in neonates with prenatal opioid exposure. Journal of Neuroscience. Doi: 10.1523/JNEUROSCI.2232-21.2022.

This study characterized the neural effects of prenatal opioid and other drug exposure (PODE) on neonatal brain function. Of the 109 newborns examined in this study, 42 were PODE, 39 had prenatal exposure to drugs excluding opioids, and 28 were drug free. To compare neural effects, the newborns were separated into groups based on where their mother's received medication for opioid use disorder (n=31) or received no treatment (n=11).

- PODE newborns had the most significant alterations to the reward frontal section of the brain compared to the newborns with exposure to drugs and drug free newborns.
- Medication for opioid use disorder was associated with a significant reduction of PODE related alterations to the limbic and frontal brain connections.
- **Research Conclusions:** The findings of this study shows that there are significant changes in the reward section of the brain and brain connectivity among newborns with prenatal opioid and other drug exposure. Mothers who use medications for opioid use disorder can reduce prenatal opioid and other drug exposure brain alterations in their newborns.

Lofwall, M. R., Walsh, S. L., Nunes, E. V., Bailey, G. L., Sigmon, S. C., Kampman, K. M., Frost, M., Tiberg, F., Linden, M., Sheldon, B., Oosman, S., Peterson, S., Chen, M., & Kim, S. (2018). Weekly and monthly subcutaneous buprenorphine depot formulations vs daily sublingual buprenorphine with naloxone for treatment of opioid use disorder: A randomized clinical trial. JAMA Internal Medicine, 178(6), 764–773. <https://doi.org/10.1001/jamainternmed.2018.1052>

This study compared weekly and monthly subcutaneous (SC) buprenorphine depot formulations with daily sublingual (SL) combination of buprenorphine and naloxone in the

treatment of opioid use disorder. This outpatient, double-blind, double-dummy randomized clinical trial was conducted at 35 sites in the United States from December 29, 2015, through October 19, 2016. Participants were treatment-seeking adults with moderate-to-severe opioid use disorder. Randomization to daily SL placebo and weekly (first 12 weeks; phase 1) and monthly (last 12 weeks; phase 2) SC buprenorphine (SC-BPN group) or to daily SL buprenorphine with naloxone (24 weeks) with matched weekly and monthly SC placebo injections (SL-BPN/NX group). Primary end points tested for noninferiority were response rate (10% margin) and the mean proportion of opioid-negative urine samples for 24 weeks (11% margin). Responder status was defined as having no evidence of illicit opioid use for at least 8 of 10 prespecified points during weeks 9 to 24, with two of these at week 12 and during month 6 (weeks 21–24). The mean proportion of samples with no evidence of illicit opioid use (weeks 4–24) evaluated by a cumulative distribution function (CDF) was an a priori secondary outcome with planned superiority testing if the response rate demonstrated noninferiority. A total of 428 participants (263 men [61.4%] and 165 women [38.6%]; mean [SD] age, 38.4 [11.0] years) were randomized to the SL-BPN/NX group (N=215) or the SC-BPN group (N=213).

- The response rates were 31 of 215 (14.4%) for the SL-BPN/NX group and 37 of 213 (17.4%) for the SC-BPN group, a 3.0% difference.
- The proportion of opioid-negative urine samples was 1,099 of 3,870 (28.4%) for the SL-BPN/NX group and 1,347 of 3,834 (35.1%) for the SC-BPN group, a 6.7% difference.
- The CDF for the SC-BPN group (26.7%) was statistically superior to the CDF for the SL-BPN/NX group.
- Injection site adverse events (none severe) occurred in 48 participants (22.3%) in the SL-BPN/NX group and 40 (18.8%) in the SC-BPN group.
- **Research Conclusions:** Compared with SL buprenorphine, depot buprenorphine did not result in an inferior likelihood of being a responder or having urine test results negative for opioids and produced superior results on the CDF of no illicit opioid use.

Luo, S.X., Feaster, D.J., Liu, Y., Balise, R.R., Hu, M., Bouzoubaa, L., Odom, G.L., Brandt, L., Pan, Y., Hser, Y., VanVeldhuisen, P., Castillo, F., Calderon, A.R., Rotrosen, J., Saxon, A.J., Weiss, R.D., Wall, M., Nunes, E.V. (2023). Individual-Level Risk Prediction of Return to Use During Opioid Use Disorder Treatment. JAMA Psychiatry. doi:10.1001/jamapsychiatry.2023.3596.

This study was based upon a decision analytical model to help create an individual level prediction tool to predict the risk of return to opioid use among individuals with opioid use disorder. Study authors created the model by using data from 3 multicenter randomized clinical trials that lasted for at least 12 weeks from 2006 to 2016. In total all three clinical trials consisted of 2,199 participants, with most participants identifying as male (66.9%), White (70.4%), and an average age of 35.3 years. All participants were treated with either methadone, buprenorphine, or extended-release naltrexone. The study determined return to opioid use as four consecutive weeks of missing or positive urine screen results by week 12 of treatment.

- Participants with weekly negative urine screen results in the 3 weeks after treatment initiation were at a 13% risk of return of opioid use compared to 85% of participants with 3 weeks of missing or positive urine screens during the same time frame.

- Study data was limited and was unable to examine how race could potentially play a factor in return to opioid use.
- **Research Conclusions:** The study findings appear to suggest that the use of a prediction model may have some uses to determining risk of return to opioid use, however there should be future considerations made to examine how demographic factors play a role in a return to opioid use.

Lynch, F.L., McCarty, D., Mertens, J., Perrin, N.A., Green, C.A., Parthasarathy, S., Dickerson, J.F., Anderson, B.M., & Pating, D. (2014). Costs of care for persons with opioid dependence in commercial integrated health systems. *Addiction Science and Clinical Practice*, 9(16). <https://doi.org/10.1186/1940-0640-9-16>.

This retrospective cohort study examined how buprenorphine affects medical care, addiction medicine services, and costs. Study data were obtained from two large nonprofit health systems that provided addiction medicine treatment and comprehensive medical care. Study participants were grouped into three treatment groups: buprenorphine plus counseling, counseling only (two or more sessions with no medication, and little or no addiction treatment (one or fewer counseling sessions and no medication). Study enrollment included participants with an opioid use disorder diagnosis who had two or more health system service encounters from 2007-2008. A total of 6,040 participants were enrolled in the study of which 52% were female. The treatment group counseling only included 2,280 participants, 1,814 participants received little or no addiction treatment, and 1,946 participants received buprenorphine plus counseling.

- Participants who received buprenorphine plus counseling had significantly lower total health care costs compared to participants with little or no addiction treatment (\$13,578 vs \$31,035).
- Total health care costs did not significantly differ between participants who received buprenorphine plus counseling and counseling only.
- Participants who received little to no addiction services significantly used primary care, other medical visits, and emergency services more than participants who received buprenorphine plus counseling treatment.
- Participants who received counseling only used less inpatient detoxification and significantly used more primary care visits, other medical visits, and mental health visits than participants who received buprenorphine and counseling.
- **Research Conclusions:** Receiving buprenorphine and counseling or counseling alone reduced general healthcare costs compared to little or no addiction treatment.

Macleod, J., Steer, C., Tilling, K., Cornish, R., Marsden, J., Millar, J., Hickman, M. (2019) Prescription of benzodiazepines, z-drugs, and gabapentinoids and mortality risk in people receiving opioid agonist treatment: Observational study based on the UK Clinical Practice Research Datalink and Office for National Statistics death records. *PLOS Medicine*. <https://doi.org/10.1371/journal.pmed.1002965>.

This study in the United Kingdom examined the data from the Clinical Practice Research Datalink of 12,118 patients with opioid dependence who were prescribed opioid agonist treatment between the years of 1998 to 2014. The study investigated if the prescription of benzodiazepines in patients receiving opioid agonist treatment represented an increased risk of mortality despite the fact that its use also increased opioid medicine treatment duration. Data from the Office for National Statistics was used to determine the patients who died and their cause of death. Data of patients who had taken benzodiazepines in their

treatment were compared to patients who had taken z-drugs and gabapentinoids. The latter two groups of drugs are for sleep and neurological pain.

- 657 deaths were recorded across all three medication groups with 42% of the deaths of the patients involved benzodiazepines, 19.7% involved z drugs, and 7.6% involved gabapentinoid.
- Benzodiazepines were involved in 61.9% of drug related poisonings compared to 31% and 8.8% among z-drugs and gabapentinoids.
- Benzodiazepines and Z drugs were both associated with an increased duration of methadone (466 days and 483 days) and buprenorphine treatments (234 days and 266 days).
- **Research Conclusions:** Despite staying in treatment for longer periods of time, patients who use benzodiazepines are at an increased risk of death from overdosing. The findings suggest that prescribing benzodiazepines to opioid dependent patients should be avoided.

Macmadu, A., Adams, J.W., Bessey, S.E., Brinkley-Rubinstein, L., Martin, R.A., Clarke, J.G., Green, T.C., Rick, J.D. & Marshall, B.D. 2021. Optimizing the impact of medications for opioid use disorder at release from prison and jail settings: A microsimulation modeling study. International Journal of Drug Policy. doiL 10.1016/j.drugpo.2020.102841.

The study developed a microsimulation model to simulate a population of 55,000 persons at risk of opioid overdose in Rhode Island. It compared the effect of providing naltrexone only and the effect of providing all three MOUD at release on cumulative overdose death over eight years compared to standard of care with limited MOUD.

- Model predicted 2,385 opioid deaths between 2017 and 2024.
- Extended-release naltrexone averted 103 deaths for a 4.3% reduction.
- All three MOUD averted 139 deaths for a 5.8% reduction.
- Among those with prior incarceration, extended release naltrexone averted 22.8% deaths and all three averted 31.6% deaths.
- **Research Conclusion:** Expanded use of MOUD in prison and jail can reduce overdose mortality but real-world impact will vary by levels of incarceration, treatment enrollment, and post-release retention.

Macmadu, A., Goedel, W.C., Adams, J.W., Brinkley-Rubinstein, L., Green, T.C., Clarke, J.G., Martin, R.A., Rich, J.D., Marshall, B. (2020). Estimating the Impact of Wide Scale Uptake of Screening and Medications for Opioid Use Disorder in US Prisons and Jails. Drug and Alcohol Dependence. 208. <https://doi.org/10.1016/j.drugalcdep.2020.107858>

This study examined the impact of screening and treatment with medication for opioid use disorder on the mortality rate of released prisoners in US prisons and jails. Data was collected from the National Center for Vital Statistics of each US state, the Bureau of Justice Statistics, and relevant literature to create a Monte Carlo simulation of treatment scenarios in US prisons and jails in 2016. The scenarios that were simulated were (1) all persons who receive medications for opioid use disorder while incarcerated, and (2) all persons who

receive medication for opioid use disorder while incarcerated and are retained in treatment post release. For each scenario, the simulation was repeated 10,000 times for each state.

- In scenario 1, if all persons received medication for opioid use disorder while incarcerated in 2016, approximately 1,840 lives would have been saved nationally. It was estimated that 668 lives would have been saved per 10,000 persons incarcerated.
- In scenario 2, if all persons received medication for opioid use disorder while incarcerated and were retained in treatment post release in 2016, 4,400 lives would have been saved nationally. 1,609 lives would have been saved per 10,000 persons incarcerated.
- A noted limitation of this study was the estimated rates of reductions in opioid mortality used in the simulation were derived from studies in England and Australia, which may differ from the US in terms of treatment capacity, healthcare access, and medication treatments available thus affecting an estimated US mortality rate.
- **Research Conclusions:** Prison and jail-based programs that provide medication or opioid use disorder have the potential to reduce opioid related overdose deaths. However, prison and jail-based treatment with retention after post release provides a greater impact in reduction of opioid related overdose deaths.

Magura, S., Lee, J. D., Hershberger, J., Joseph, H., Marsch, L., Shropshire, C., & Rosenblum, A. (2009). Buprenorphine and methadone maintenance in jail and post-release: A randomized clinical trial. *Drug and Alcohol Dependence*, 99(1–3), 222–230. <https://doi.org/10.1016/j.drugalcdep.2008.08.006>

This study introduced buprenorphine maintenance in a large urban jail, Rikers Island in New York City. Heroin-dependent men not enrolled in community methadone treatment and sentenced to 10–90 days in jail (N=116) were voluntarily randomly assigned either to buprenorphine or methadone maintenance, the latter being the standard of care for eligible inmates at Rikers.

- Buprenorphine and methadone maintenance completion rates in jail were equally high. Buprenorphine patients were less likely than methadone patients to withdraw voluntarily from medication while in jail (3% vs. 16%).
- The buprenorphine group reported for their designated post-release treatment in the community significantly more often than did the methadone group (48% vs. 14%). Consistent with this result, prior to release from Rikers, buprenorphine patients stated an intention to continue treatment after release more often than did methadone patients (93% vs. 44%).
- There were no post-release differences between the buprenorphine and methadone groups in self-reported relapse to illicit opioid use, self-reported re-arrests, self-reported severity of crime or re-incarceration in jail.
- **Research Conclusions:** After initiating opioid agonist treatment in jail, continuing buprenorphine maintenance in the community appears to be more acceptable to offenders than continuing methadone maintenance.

Maradiaga, J. A., Nahvi, S., Cunningham, C. O., Sanchez, J., & Fox, A. D. (2016). “I kicked the hard way. I got incarcerated.” Withdrawal from methadone during incarceration and subsequent aversion to medication assisted treatments. *Journal of Substance Abuse Treatment*, 62, 49–54. <https://doi.org/10.1016/j.jsat.2015.11.004>

The study conducted semi-structured interviews with 21 formerly incarcerated individuals with opioid use disorder in community substance abuse treatment settings. Interviews were audio recorded, transcribed, and analyzed using a grounded theory approach. Themes that emerged upon iterative readings of transcripts were discussed by the research team. The three main themes relating to methadone were: 1) rapid dose reduction during incarceration, 2) discontinuity of methadone during incarceration, and 3) post-incarceration aversion to methadone.

- Participants who received methadone maintenance treatment prior to incarceration reported severe and prolonged withdrawal symptoms from rapid dose reductions or disruption of their methadone treatment during incarceration.
- The severe withdrawal during incarceration contributed to a subsequent aversion to methadone and adversely affected future decisions regarding reengagement in medication-assisted treatment.
- **Research Conclusions:** Though medication-assisted treatment (MAT) is the most efficacious treatment for opioid use disorder, current penal policy, which typically requires cessation of MAT during incarceration, may dissuade individuals with opioid use disorder from considering and engaging in MAT after release from incarceration.

Mariani, J.J., Dobbins, R.L., Heath, A., Gray, F., Hassman, H. (2023). Open-label investigation of rapid initiation of extended-release buprenorphine in patients using fentanyl and fentanyl analogs. The American Journal on Addictions. <https://doi.org/10.1111/ajad.13484>.

This study was a secondary analysis of an open label pilot study to evaluate rapid induction of extended-release buprenorphine for the treatment of participants with treating opioid use disorder who have used fentanyl. Study participants were seeking opioid use disorder treatment from an inpatient treatment in New Jersey from August 2019 through May 2020, were 18 years or older, abstained from short acting opioid for at least 6 hours and long-acting opioids for 24 hours prior to study enrollment. 24 participants enrolled in the study of which 17 were positive for fentanyl at study enrollment and seven were negative for fentanyl. Fentanyl positive individuals were mostly female (58.8%), White (58.8%), and had an average age of 43.8 years. Individuals who were not positive for fentanyl were mostly male (71.4%), were Black or White (42.9%), and had an average of 30.7 years. Participants received a single 4mg dose of transmucosal buprenorphine followed by a 300mg injection of extended-release buprenorphine an hour later. Participants continued the study for 6 months of which they received six monthly injections.

- 12 individuals (10 fentanyl positive and 2 fentanyl negative) received all six buprenorphine injections.
- After 12 hours post extended-release buprenorphine injection individuals experienced mild or no active withdrawal symptoms. No participants in the study experienced severe withdrawal.
- There were no serious adverse events that resulted in the discontinuation of the study.
- **Research Conclusions:** The findings of this study appear to show that the use of a rapid 1-day induction of an extended-release buprenorphine injection to treat individuals with opioid use disorder who have used fentanyl is safe to use and causes mild or no withdrawal symptoms.

Mark, T.L., Treiman, K., Padway, H., Heneretty, K., Tzeng, J., Gilber, M. (2021). Addiction Treatment and Telehealth: Review of Efficacy and Provider Insights During the COVID-19 Pandemic. Psychiatric Services. <https://doi.org/10.1176/appi.ps.202100088>.

This study examined research evidence on the efficacy of telehealth delivered substance use disorder treatment and the experience of providers using telehealth during the COVID-19 pandemic in California. Telehealth efficacy and effectiveness information was collected through reviews of published studies, a survey of addiction treatment organization in California, and interviews with treatment providers and stakeholders. Eight studies were reviewed that consisted of randomized controlled trials that compared telehealth treatment to in person substance use disorder treatment. The provider survey was given to 412 providers in California who accepted Medicaid or county funding of which 100 responded. The stakeholder interviews were semi structured phone interviews conducted from September to November 2020 with leaders in addiction treatment organizations (n=12), government officials who oversee California Medicaid and public sector addiction treatment (n=9), behavioral health telephone helpline staff (n=4), emergency department providers (n=3), and emergency department technicians (n=2).

- Half of the reviewed studies found no significant differences in treatment adherence and retention between telehealth and in person treatment.
- Three studies found that telehealth can be effectively used for medication management for opioid use disorder. The patients in these studies received medication management through telehealth from a physician and received routine in person treatment for drug testing, counseling, and other general medical and mental health services as needed.
- 28% of survey respondents believed telehealth removed treatment barriers completely, 36% believed moderate, 13% felt a little bit, 10% believed barriers were not at all removed, and 12% responded not applicable because their patient attendance was not affected by telehealth during the pandemic.
- Survey respondents believed that in person treatment was more effective than telemedicine for all treatment services except for individual counseling.
- Stakeholder interviews identified rural residents and patients with limited access to public transportation, and families with young children were people who benefited the most from telehealth.
- Access to broadband and people who are not comfortable with use of technology were common barriers that stakeholders identified.
- **Research Conclusions:** Research articles suggest that telemedicine can be just as effective as in person treatment in retaining patients and managing medication. However, providers in California are not confident that telemedicine is as effective as in person treatment and does not quite solve all the barriers that patients have in retaining treatment.

Marsch, L.A. (1998). The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: a meta-analysis. *Addiction*, 93(4), 515-532. Doi: 10.1046/j.1360-0443.1998.9345157.x.

This meta-analysis presented evaluation data from studies regarding the use of psychopharmacological interventions to treat opiate substance abuse. This meta-analysis examined 11 studies (2,056 participants) investigating the use of methadone maintenance treatment on illicit opioid use, eight studies (1,797 participants) on methadone maintenance treatment on HIV risk behaviors, and 24 studies (7,173 participants) investigating the use of methadone maintenance on criminal activities. Participants involved in these studies had an opiate dependent substance abuse diagnosis without a concurrent psychiatric diagnosis.

- There were statistically significant relationships between methadone maintenance treatment and the reduction of illicit opiate use, HIV risk behaviors and drug and property related criminal behaviors.
- Methadone maintenance treatment was most effective in reducing drug related criminal behaviors; however, the effects were moderate in reducing illicit opioid use and drug and property related criminal behaviors, and small to moderate effects in reducing HIV risk behaviors.
- **Research Conclusions:** The findings of the meta-analysis appear to show that there are statistically significant relationships between methadone maintenance treatment and the reduction of illicit opioid use, HIV risk behaviors, and drug and property related criminal behaviors. While there were statistically significant effects found between methadone maintenance treatment and HIV risk behaviors, illicit opioid use, and criminal behavior, the level of effectiveness of methadone maintenance for each outcome varied.

Marsden, J., Stillwell, G., Jones, H., Cooper, A., Eastwood, B., Farrell, M...Hickman, M. (2016) Does exposure to opioid substitution treatment at prison release reduce the risk of death? A prospective, observational study in England. The Lancet. 388(11), doi: [https://doi.org/10.1016/S0140-6736\(16\)32247-4](https://doi.org/10.1016/S0140-6736(16)32247-4)

This study investigated if prison based opioid substitution treatment (OST) , either methadone or buprenorphine, reduced the risk of death due to the prisoner's exposure to the program and through community drug treatment post release. The sample included adult prisoners with opioid use disorder from 39 prisons (32 male and 7 female) in England that provided opioid substitution treatment. Upon release participants were placed in either the OST exposed group or the OST unexposed group if they did not receive OST, or had withdrawn from OST, or had a low dose of medication. The two groups were not randomly assigned,

- 82.1% (n=12,260) of the sample entered the study once and the remaining 17.9% (n=2,194) entered the study between 2 to 7 times due to re-incarceration.
- Within the first year of release there were 160 deaths. 102 (63.8%) of the deaths were drug related poisoning, 13 liver disease due to viral hepatitis or alcohol, 5 drug injection related infection, 8 cardiovascular disease, 3 were other non-communicable diseases.
- Within the first 4 weeks of prison release the OST exposed group experienced 6 all-cause mortality deaths and the OST unexposed group experienced 18 all-cause mortality deaths.
- Within the first 4 weeks of prison release 3 the OST exposed group experienced 3 drug related poisoning deaths and OST unexposed group experienced 15 drug related poisoning deaths.

- After the first four weeks of prison release there were no significant difference between all cause deaths or drug related poisoning between the OST exposed and unexposed group.
- Within the first 4 weeks 6,140 participants were admitted into drug treatment programs. The OST exposed group was 2 times more likely to enter treatment than the OST unexposed group.
- There was no statistical difference between admittance into a drug program and the risk of all cause mortality or drug related poisoning.
- **Research Conclusions:** Prison based opioid substitution treatment is effective in the first 4 weeks after release. People with opioid use disorder who stop or reduce their treatment during their incarceration are at an increased risk of death after release if they start using drugs again.

Marsden, J., Stillwell, G., Jones, H., Metcalfe, C., Cooper, A., Eastwood, B., Farrell, M., Lowden, T., Maddalena, N., Metcalfe, C., Shaw, J., & Hickman, M. (2017). Does exposure to opioid substitution treatment in prison reduce the risk of death after release? A national prospective observational study in England. *Addiction*, 112(8), 1408–1418. <https://doi.org/10.1111/add.13779>

This United Kingdom–based study investigated if receiving Suboxone or methadone before release increases or decreases risk of death after release. The study used observational data from more than 15,000 prison releases in the UK among 12,260 individuals with opioid use disorder according to the prison electronic database for those who sought treatment. Authors collected data from September 2010 to October 2014 in 39 prisons that provided treatment as part of the Integrated Drug Treatment System, which included medication for opioid use disorder. Individuals volunteered to be prescribed medication or not, based on feedback from a clinical assessment and their preference. Officials attempted to link all individuals in the prison-based drug treatment with services post-release. More than half were taking a medication on the day of their release.

- This real-world study of medications for opioid use disorder in the prison population in the UK showed that being prescribed methadone or Suboxone at clinically meaningful levels was associated with a substantially lower likelihood of death, including but not limited to drug overdose death, in the first month after release.
- The Medication group had a 75% lower likelihood of death.
- The Medication group had an 85% lower likelihood of drug overdose death.
- The Medication group had 2.5 times greater odds of attending a treatment appointment in the month after release.
- It seems, however, that the Medication group's propensity to attend treatment after prison may be accounted for by their greater overall severity, which could make them more willing to engage in treatment.
- Death rates between the groups were similar after the first month.

Martin, E., Maher, H., McKeon, G., Patterson, S., Blake, J., Chen, K.Y. (2022). Long-acting injectable buprenorphine for opioid use disorder: A systematic review of impact of use on social determinants of health. Journal of Substance Abuse Treatment. doi: <https://doi.org/10.1016/j.jsat.2022.108776>.

This systematic review describes the effects and perspectives of long-acting injectable buprenorphine on abstinence, accessibility, employment, gender, and social relationships. Three randomized controlled trials, one open label safety study, two case series, and six qualitative studies that examined patient perspectives towards long-acting injectable buprenorphine were reviewed. The reviewed articles included a total of 2,293 participants with either current or past opioid use disorder, average age range of 36 to 52 years old, 60% male, and 50% White.

Seven studies found that participants believed long-acting injectable buprenorphine would have a positive impact on their autonomy to reduce illicit opioid use. However, some participants believe using the medication would erode their autonomy by holding them hostage and prevent them from using other opioids.

- Most participants noted that long-acting injectable buprenorphine eased travel, daily adherence, lack of need for daily medication or regular trips to the pharmacy.
- Four studies that explored retention of long-acting injectable buprenorphine found that it ranged from 50%-73%.
- Seven of the nine studies that examined employment found that removing the need to go to get a daily medication pickup was helpful in getting and maintaining a job.
- Four studies examined long-acting injectable buprenorphine within the criminal justice system found that it may be more helpful in reducing opioid cravings which would reduce opioid use disorder related crimes.
- Twelve studies that explored social functioning found that participants felt that long-acting injectable buprenorphine would offer freedom from being chained to services and allow them to get on their lives and spend their time on other activities in life and feel more normal like the general population.
- Two studies found that women preferred long-acting injectable buprenorphine than men because it was discreet and believes it to be a good treatment
- **Research Conclusions:** The findings of this review found overwhelmingly positive psychosocial feedback from the individuals who are prescribed long-acting injectable buprenorphine. Long-acting injectable buprenorphine helps individuals abstain from opioids, increase retention, lower recidivism, and provides a better outlook for employment and social relationships.

Mason, B.J., Heyser, C.J. (2021). Alcohol Use Disorder: The Role of Medication in Recovery. Alcohol Research Current Reviews. 41(1). <https://doi.org/10.35946/arc>

This paper provides an overview of medications currently available to treat alcohol use disorder and how they should be used in treatment. FDA reports, meta-analysis, and evidence-based reviews are used throughout the paper to support its claims.

- Most popular alcohol use disorder medications are acamprosate, naltrexone, and disulfiram. Acamprosate or naltrexone should be used among individuals with moderate

to severe alcohol use disorder who wish to cut down or quit drinking, prefer medication, or have not responded to nonpharmacological treatments. Disulfiram should not be selected as an initial treatment for alcohol use disorder due to the physiological consequences of drinking in combination with this drug.

- Topiramate and gabapentin are generic drugs to treat alcohol use disorder and should be used amongst patients who have a goal in decreasing or quitting drinking and are intolerant to or have not responded to acamprosate and naltrexone.
- Medications for alcohol use disorder provide best results when combined with a comprehensive treatment plan that includes behavioral therapy.
- **Research Conclusions:** This article provided information and suggestions of when to use the most popular FDA approved medication for alcohol use disorder and generic drugs that may be helpful. This paper emphasizes that alcohol use disorder medications should be used in conjunction with behavioral health treatment.

Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD002207. DOI: 10.1002/14651858.CD002207.pub4.

This review compared buprenorphine maintenance to placebo and to methadone maintenance to evaluate its ability to retain people in treatment, suppress illicit drug use, reduce criminal activity, and lower mortality. The review consisted of 31 randomized control trials that included 5,430 participants.

- Compared to the placebo, buprenorphine was superior in retaining participants at low, medium, and high doses, however only high dose buprenorphine was more effective than the placebo in suppressing illicit opioid use.
- Methadone was more likely to retain more patients than low dose buprenorphine, however there was no difference in retention between methadone and medium and high doses of buprenorphine.
- There was no difference in illicit opioid use between buprenorphine and methadone.
- **Research Conclusions:** Study findings show that buprenorphine at various doses is more effective in retaining patients in treatment than a placebo, but patients should receive high doses of buprenorphine to suppress illicit opioid use. However, compared to methadone, buprenorphine at low doses is not effective in retaining patients. Medium and high doses of buprenorphine have comparable treatment retention compared to methadone.

McCarty, D., Bougatsos, C., Chan, B., Hoffman, K.A., Priest, K.C., Grusing, S., Chou, R. (2021). Office-Based Methadone Treatment for Opioid Use Disorder and Pharmacy Dispensing: A Scoping Review. The American Journal of Psychiatry. <https://doi.org/10.1176/appi.ajp.2021.20101548>.

This review assessed outcomes from randomized trials and controlled observational studies that focused on treating opioid use disorder patients with methadone in office-based settings. Reviewed studies were based in the United States and other developed countries.

Of the 18 studies that were reviewed, six were randomized controlled trials, eight were observational studies, and four were articles that discussed the use of pharmacies to dispense methadone.

- Office based methadone was preferred among patients and increased patients' likelihood of remaining in treatment with low rates of drug use.
- Office based methadone was associated with higher treatment satisfaction and greater improvements in patients' quality of life.
- Study authors noted that the participants in the reviewed studies were highly stable patients and outcomes may not be representative of the target population.
- **Research Conclusions:** Office based methadone treatment was viewed favorably among patients and increased their likelihood of retaining treatment while lowering the rate of drug use.

McCarty, D., Chan, B., Bougatsos, C., Grusing, S., Chou, R. (2021). Interim methadone-Effective but underutilized: A scoping review. Drug and Alcohol Dependence. 225. <https://doi.org/10.1016/j.drugalcdep.2021.108766>.

This review summarized interim methadone use (medication only) and other strategies used to minimize wait lists at opioid treatment programs. Six studies that examined interim methadone and three studies that examined alternative strategies were reviewed.

- Clinical trials and observational studies observed reductions in heroin among patients using interim methadone and these patients were more likely to enter opioid treatment programs than participants who were waitlisted and did not use interim methadone.
- Retention rates of patients receiving interim methadone were like patients actively in treatment.
- **Research Conclusions:** Interim methadone appears to be an effective strategy to increase patient likelihood of entering and retaining treatment and reducing heroin usage compared to being placed on a waitlist for treatment.

McPheeters, M., O'Connor, E.A., Riley, S., Kennedy, S.A., Voisin, C., Kuznacic, K., Coffey, C.P., Edlund, M.D., Bobashev, G., and Jonas, D.E. (2023). Pharmacotherapy for Alcohol Use Disorder A Systematic Review and Meta-Analysis. JAMA Network, 330(17), 1653-1665. Doi:10.1001/jama.2023.19761.

This systematic review and meta-analysis compared medication interventions to treat alcohol use disorder. A total of 118 clinical trials that involved 20,976 participants and lasted for at least 12 weeks were reviewed. The primary data outcome from the review was alcohol consumption, which was defined as any alcohol use, return to heavy drinking, and the number of drinks per week.

- Compared to a placebo, 50mg of oral naltrexone was associated with the lowest rate of return to heavy drinking, while injectable naltrexone was associated with fewest drinking days over the past 30 days.
- 11 treatments with acamprosate were needed to prevent one person from returning to any drinking followed by oral and 18 for 50mg of oral naltrexone.
- Compared to a placebo, acamprosate caused higher incidences of diarrhea while naltrexone was more likely to cause nausea and vomiting.

- **Research Conclusions:** This systematic review appears to support that naltrexone may be the best medication to use to treat alcohol use disorder with acamprosate as another viable medication. However, there should be some caution with considering these medications due to gastrointestinal issues in the body that may arise from taking these medications amongst this population.

Meador N. (2010). A comparison of methadone, buprenorphine and alpha2 adrenergic agonists for opioid detoxification: a mixed treatment comparison meta-analysis. Drug and alcohol dependence, 108(1-2), 110–114.

<https://doi.org/10.1016/j.drugalcdep.2009.12.008>.

This systematic review compared the efficacy of buprenorphine, methadone, clonidine, and lofexidine for opioid detoxification across 23 randomized controlled trials and found methadone and buprenorphine to be the most effective, followed by lofexidine and clonidine.

- There were statistically significant higher rates of completion of detoxification treatment observed with buprenorphine compared to clonidine in mixed treatment meta-analysis (OR 3.95, 95% CrI 2.01 to 7.46) and direct comparison analysis (OR 2.22, 95% CrI 1.10 to 4.26).
- Methadone was observed to be associated with significantly higher rates of treatment completion than clonidine in the mixed treatment comparison (OR 2.42, 95% CrI 1.07 to 5.37).
- There were some benefits (i.e., non-statistically significant) for buprenorphine when compared to methadone and lofexidine for treatment completion. A non-significant benefit was observed for methadone compared to lofexidine.
- There were no statistically significant differences between lofexidine and clonidine.
- **Research Conclusions:** Both buprenorphine and methadone found superior to lofexidine or clonidine for completion of detoxification, with buprenorphine found to be superior to methadone.

Molero, Y., Zetterqvist, J., Binswanger, I. A., Hellner, C., Larsson, H., & Fazel, S. (2018). Medications for alcohol and opioid use disorders and risk of suicidal behavior, accidental overdoses, and crime. The American Journal of Psychiatry, 175(10), 970–978. <https://doi.org/10.1176/appi.ajp.2018.17101112>.

This study examines the associations between medications for alcohol and opioid use disorders and suicidal behavior, accidental overdoses, and crime, found in 21,000 Swedish individuals who received treatment.

- For naltrexone, there was a reduction in the hazard ratio for accidental overdoses during periods when individuals received treatment compared with periods when they did not.
- Buprenorphine was associated with reduced arrest rates for all crime categories (i.e., violent, nonviolent, and substance-related) as well as reduction in accidental overdoses.
- For methadone, there were significant reductions in the rate of suicidal behaviors as well as reductions in all crime categories. However, there was an increased risk for accidental overdoses among individuals taking methadone.

- **Research Conclusions:** Medications currently used to treat alcohol and opioid use disorders also appear to reduce suicidality and crime during treatment.

Moore, K. E., Oberleitner, L., Smith, K., Maurer, K., & McKee, S. A. (2018). Feasibility and effectiveness of continuing methadone maintenance treatment during incarceration compared with forced withdrawal. *Journal of Addiction Medicine*, 12(2), 156–162. <https://doi.org/10.1097/ADM.0000000000000381>

This study compared inmates who received methadone maintenance treatment (MMT) prior and during their incarceration to inmates who did not receive any methadone treatment (control group). This study had 184 inmates receiving MMT and 198 inmates who did not receive any services. This study also observed post-release, during re-engagement with community-based MMT programs, 6 months reoffending outcomes amongst the participants.

- Inmates in the MMT group were less likely to receive disciplinary tickets than the inmates in the control group (odds ratio= 0.32).
- The MMT group was observed to have increased engagement with community MMT providers within 1 day of release (odds ratio= 32.04).
- 40.6% of MMT participants re-engaged with services within the first 30 days of post-release compared to the 10.1% of the control group.
- Re-engagement with MMT services was found not to have an association with recidivism.
- A subset of inmates (N=69) who received MMT services post-incarceration from the jail MMT provider was associated with a reduced risk of arrests, new charges, and re-incarceration compared to those who did not re-engage.
- **Research Conclusions:** The results of the study support interventions that facilitate continuity of MMT during and after incarceration. Also engaging with community providers can help improve access to methadone in correctional facilities.

Moore, K.E., Robers, W., Reid, H.H., Smith, K.M.Z., Oberleitner, L., McKee, S.A. (2019). Effectiveness of medication assisted treatment for opioid use in prison and jail settings: A meta-analysis and systematic review. *Journal of Substance Abuse Treatment*, 99, 32-43. <https://doi.org/10.1016/j.jsat.2018.12.003>.

This meta-analysis and systematic review examined the existing literature about the effectiveness of medication assisted treatment delivery in prisons and jails on community substance use treatment engagement, opioid use, recidivism, and health risk behaviors following individuals release from incarceration. Included in this meta-analysis were 18 methadone studies, 3 buprenorphine studies, and 3 naltrexone studies that all took place in correctional settings.

- Studies agreed that providing methadone, buprenorphine, and naltrexone during incarceration led to increased community-based substance use treatment engagement after release.
- Methadone studies found that incarcerated individuals who received methadone while incarcerated were less likely to use opioid after release compared to individuals who did

not receive methadone. Buprenorphine and naltrexone studies were compared to control groups that used methadone and found no significant difference in opioid use post release.

- All studies that examined recidivism did not find any significant difference in recidivism amongst incarcerated individuals receiving methadone, buprenorphine, and naltrexone during incarceration.
- Individuals who received methadone during their incarceration had reduced odds of injection drug use post release. Buprenorphine was found to show no significant difference in health risk behaviors 1 month post release compared to a control group that did not receive medication. Naltrexone was found to increase the ability to achieve and maintain viral suppression when compared to a placebo group.
- **Research Conclusions:** The findings of this meta-analysis and systematic review appear to provide supporting evidence that methadone, buprenorphine, and naltrexone during incarceration can improve community-based substance use treatment engagement, lower illicit opioid use, and improve health outcomes post release. Recidivism was found to not have any significant effects from the use of medications for opioid use disorder.

Morgan, J.R., Schackman, B.R., Weinstein, Z.M., Walley, A.Y., Linas, B.P. (2019). Overdose following initiation of naltrexone and buprenorphine medication treatment for opioid use disorder in a United States commercially insured cohort. Drug and Alcohol Dependence, 200, 34-39. <https://doi.org/10.1016/j.drugalcdep.2019.02.031>.

This retrospective cohort study investigated the effectiveness of medication for opioid use disorder in preventing opioid related overdoses during periods of on and off treatment. A cohort of 46,846 commercially insured participants, diagnosed with opioid use disorder and were prescribed buprenorphine, oral naltrexone, and extended-release naltrexone from 2010 through 2016 in outpatient and office-based settings were identified as the sample for the study. Methadone treatment was excluded from the study because it was not reliably included in the data set that study authors analyzed. Most study participants were prescribed buprenorphine (n=40,441) followed by oral naltrexone (n=7,782), extended release naltrexone (n=1,386). The study cohort were primarily male (62%), median age of 29 years, and 40% were the children or dependent of a primary insurance beneficiary.

- 1,805 participants experienced 2,755 opioid related overdoses during the study period.
- 2,020 opioid related overdoses occurred while participants were not in treatment.
- Participants who were prescribed buprenorphine were significantly at a lower risk of opioid related overdose compared to participants who were treated with oral naltrexone and extended-release naltrexone.
- In the first four weeks after medication for opioid use discontinuation, there were 16 overdoses among those who were treated with extended-release naltrexone, 81 overdoses among participants treated with oral naltrexone, and 200 overdoses among participants treated with buprenorphine.
- **Research Conclusions:** Study findings suggest that buprenorphine treatment reduces the likelihood of an overdose compared to naltrexone, however within the first four

weeks of discontinuation participants treated with buprenorphine are at a higher risk of an overdose compared to the those treated with the various formulations of naltrexone.

Mun, C.J., Finan, P.H., Epstein, D.H., Kowalczyk, W.J., Agage, D., Letzen, J.E., Phillips, K.A., Preston, K.L. (2020). Craving mediates the association between momentary pain and illicit opioid use during treatment for opioid-use disorder: an ecological momentary assessment study. *Addiction*. 116(7), 1794-1804. <https://doi.org/10.1111/add.15344>.

This observational study investigated how momentary pain can impact opioid cravings and illicit opioid use among individuals receiving opioid agonist treatment. 56 adults who qualified for opioid agonist treatment and were seeking treatment at an office-based outpatient clinic in Baltimore Maryland associated with the National Institute on Drug Abuse were identified to participate. Participant data was collected through ecological momentary assessments over the phone. Researchers sent participants fixed and random prompts to report pain severity, stress, negative mood, opioid craving, and illicit opioid use over the course of eight weeks. Pain other than from opioid withdrawal in the past 3 months and pain that is constant or flares up frequently were analyzed for the study findings.

- Momentary pain severity was found to be a predictor of opioid cravings. These opioid cravings increased the likelihood of illicit opioid use.
- **Research Conclusions:** Study findings suggest that momentary pain is indirectly associated with illicit opioid use through opioid cravings.

Murphy, S. M., McCollister, K. E., Leff, J. A., Yang, X., Jeng, P. J., Lee J. D., Nunes, E. V., Novo, P., Rotrosen, J., & Schackman, B. R. (2019). Cost-effectiveness of buprenorphine-naloxone versus extended-release naltrexone to prevent opioid relapse. *Annals of Internal Medicine*, 170(2), 90–98. <https://doi.org/10.7326/M18-0227>

This study sought to provide a cost-effectiveness analysis of daily oral doses of buprenorphine/naloxone vs. monthly extended release naltrexone injections for opioid use treatments. A randomized clinical trial of 570 adults with opioid use disorder from 8 U.S inpatient or residential treatment programs were included in the study. The participants were monitored over the course of 24 weeks with an additional 12-week observation.

- Over the course of the 24-week intervention the extended-release naltrexone treatment cost the health care sector an average of \$5,317 more than buprenorphine/naloxone. The cause of this price difference can be attributed to the longer detoxification period required for extended release naltrexone induction and the higher cost of the medication itself even from savings from fewer required follow-up visits.
- Extended-release naltrexone had higher average total costs for the health care sector at 36 weeks and total societal costs at 24 and 36 weeks.
- Extended-release naltrexone was not associated with significantly better outcomes measured in quality-adjusted life years or abstinent years gained.
- **Research Conclusions:** Buprenorphine/naloxone is typically preferred as a first-line treatment when both options are clinically appropriate.

Nava, F., Manzato, E., Leonardi, C., Lucchini, A. (2008). Opioid maintenance therapy suppresses alcohol intake in heroin addicts with alcohol dependence: Preliminary results of an open randomized study. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 32, 1867-1872. <https://doi.org/10.1016/j.pnpbp.2008.08.019>.

This open randomized study evaluated the efficacy of methadone and buprenorphine to suppress alcohol use among heroin users. 218 participants with a diagnosis for heroin and alcohol dependence were identified to participate in the study. The participants were randomly placed in a methadone treatment group (n=108) or a buprenorphine group (n=110). The two groups were similar characteristically with most participants being male, in their early 30's, living with family or friends, had a four-year history of heroin use, and a two-year history of alcohol abuse. The participants attended an outpatient clinic facility 6 days per week and received one methadone or buprenorphine dose. Methadone was administered orally beginning with an 80 mg dose then progressing to 120mg, 160mg, and 200 mg. Buprenorphine was administered sublingually beginning with 8mg then progressing to a 16mg, 24mg, and 32mg. After three consecutive opioid positive urine screens, the patient was offered a dosage increase. If a participant refused an increase or wanted a decrease, they were dismissed from the study.

- The methadone group had 21 participants to drop out of the study. Seven participants discontinued medication, seven participants experienced drug related side effects, three participants dropped out for unknown reasons, three participants refused a dosage increase, and one participant requested a dosage decrease. The buprenorphine group had 27 participants drop out. Seven participants refused a dosage increase, seven participants experienced drug related side effects, five participants discontinued medication, five participants discontinued for unknown reasons, and three participants requested a dose decrease.
- Both methadone and buprenorphine reduced heroin cravings. 80mg dose of methadone was more effective than 8mg of buprenorphine in reducing heroin cravings. The highest doses of methadone and buprenorphine were equally effective in reducing heroine cravings.
- The lowest doses of methadone and buprenorphine were equally effective in reducing alcohol craving and consumption. The 32mg dose of buprenorphine was more effective than the 200mg dose of methadone in reducing alcohol craving and consumption.
- **Research Conclusions:** Study findings show that methadone and buprenorphine are effective medications to reduce heroin and alcohol cravings among heroin and alcohol dependent users. Buprenorphine appears to be a slightly more effective medication due to its ability to reduce alcohol cravings better than methadone.

Ndegwa S, Pant S, Pohar S, ... & Mierzwinski-Union, M. (2016). Injectable Extended-Release Naltrexone to Treat Opioid Use Disorder. 2017 Aug 1. In: CADTH Issues in Emerging Health Technologies. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health, 163. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK481477/>

This study describes the uses of Vivitrol (extended-release Naltrexone) in treating opioid use disorder and evidence of its usefulness from the results of double blind and randomized control trials of patients with opioid use disorder.

- Compared to buprenorphine and methadone, naltrexone is not associated with the development of tolerance and dependence and lacks the potential for misuse and diversion.
- Because the oral formulation of naltrexone requires daily dosage, this often leads to poor adherence for the medication.
- Before starting Vivitrol an individuals should be opioid free for at least seven to ten days to avoid withdrawal symptoms that may require hospitalization.
- Results from phase III, randomized, double blind trial found that patients who had recently used Vivitrol were more likely to have improved levels abstinence, treatment retention, and reduced opioid cravings compared to a placebo group. About half of participants who received Vivitrol were abstinent from opioids for one year.
- A phase III trial provided evidence that Vivitrol has a high chance of preventing relapses among people in prisons and people with HIV.
- **Research Conclusions:** The study highlights that Vivitrol can increase treatment retention, prevent relapses, and reduce opioid cravings. Additionally Vivitrol is difficult for patients to misuse or divert.

Nunes, E.V., Comer, S.D., Lofwall, M.R., Walsh, S.L., Peterson, S., Tiberg, F., Hjelmstrom, P., and Budilovsky-Kelley, N.R. (2024). Extended -Release Injection vs Sublingual Buprenorphine for Opioid Use Disorder with Fentanyl Use A Post Hoc Analysis of a Randomized Clinical Trial. JAMA Network Open. 7(6). Doi: 10.1001/jamanetworkopen.2024.17377.

This study compared the effectiveness of sublingual buprenorphine-naloxone and extended-release buprenorphine injections in treating opioid use disorder among patients with and without fentanyl use. Study data was obtained from a 24-week phase 3 trial that was conducted in December 2015 through November 2016, with adults between the ages of 18-65 years of age with moderate to severe opioid use disorder, who voluntarily sought treatment. Individuals were excluded from the study if they had prior pharmacotherapy for opioid use disorder 60 days prior to study enrollment and had moderate to severe substance use for psychoactive substances other than opioids or had chronic pain that required opioid treatment. The study sample consisted of 428 individuals with opioid use disorder of which 123 individuals tested positive for fentanyl or nor fentanyl in their urine at baseline.

Individuals who tested positive for fentanyl were more likely to be male (61%), White (73.2%), and identified heroin as their primary opioid (84.6%). Individuals were randomly assigned treatment with sublingual buprenorphine naloxone (n=213) or a weekly and monthly injection of extended-release buprenorphine (n=215).

- 60.2% of fentanyl positive individuals and 56.7% fentanyl negative individuals completed the study. Buprenorphine formulation was insignificant to completing the study.
- Of fentanyl positive individuals, 28.5% who received extended-release buprenorphine and 18.8% who received sublingual buprenorphine naloxone tested negative for opioids by the end of the 24-week study.
- Of the fentanyl negative individuals, 36.7% of individuals who received extended-release buprenorphine and 30.6% of individuals who received sublingual buprenorphine naloxone tested negative for opioid by the end of the 24-week study.

- Of fentanyl positive individuals, 74.6% of individuals who received extended-release buprenorphine and 61.9% of individuals who received buprenorphine naloxone tested negative for fentanyl by the end of the 24-week study. The study found this difference in outcomes to be significant.
- There were no significant differences observed for opioid cravings between fentanyl use and the type of buprenorphine formulation.
- The study found no significant differences in adverse events rates between fentanyl use and buprenorphine formulations.
- **Research Conclusions:** The findings of the study appear to show that the use of sublingual buprenorphine naloxone and extended buprenorphine are effective methods of treatment for individuals with moderate to severe opioid use who have used or not used fentanyl. However, the study findings show that extended-release buprenorphine is the more effective buprenorphine formulation to decrease opioid and fentanyl use.

Nunes, E.V., Scodes, J.M., Pavlicova, M., Lee, J.D., Novo, P., Campbell, A., Rotrosen, J. (2021). Sublingual Buprenorphine-Naloxone Compared With Injection Naltrexone for Opioid Use Disorder: Potential Utility of Patient Characteristics in Guiding Choice of Treatment. The American Journal of Psychiatry. 178(7), 660-671.
<https://doi.org/10.1176/appi.ajp.2020.200060816>.

This multisite randomized trial investigated whether patients' demographics and clinical characteristics were associated with a better response to sublingual buprenorphine-naloxone and extended-release naltrexone. Over the course of 24 weeks, inpatient opioid use disorder patients were randomly assigned to receive buprenorphine naloxone (n=287) or extended-release naltrexone (n=283). Most of the study sample were white, male, average age of 30 years old, and were enrolled in Medicaid or Medicare (n=356). More than half of the participants had a high school degree or less, were unemployed, and had friends or family who used opioids or other illicit drugs. During the study patients received medication management counseling from a doctor or nurse and outpatient counseling recommended by the study site. Buprenorphine naloxone was administered daily while extended-release naltrexone was administered every 28 days.

- 79 of 283 patients (27.9%) failed to initiate extended-release naltrexone, while 17 out of 287 patients (5.9%) failed to initiate buprenorphine naloxone.
- Current probation or parole, preference for treatment with buprenorphine naloxone, and moderate to severe physical pain, randomized into study within 3 days of last opioid exposure were significant indicators for failure to initiate medication.
- Patients living situation was the only significant characteristic that influenced the potential of a relapse. Relapse rate was lower among homeless patients (n=74) who took extended-release naltrexone (51.6%) compared to homeless patients (n=69) using buprenorphine naloxone (70.4%). Among non-homeless patients, relapse rate was lower among those who took buprenorphine naloxone (53.1%) than extended-release naltrexone (70.4%).
- **Research Conclusions:** Research findings show that homelessness was a significant patient characteristic that impacted a chance relapsing during the 24-week study. Homeless patients were less likely to relapse if they were using extended-release naltrexone, while non homeless patients were less likely to relapse if they were taking

buprenorphine naloxone. Researchers assume that homelessness makes it harder for patients to take a daily medication consistently. Patients were most likely to fail at initiating extended-release naloxone depending on their parole/probation status, physical pain severity, preference to use buprenorphine naloxone, and recent opioid use.

O'Brien, C.P., Gastfriend, D.R., Forman, R.F., Schweizer, E., Pettinati, H.M. (2011). Long-term Opioid Blockade and Hedonic Response: Preliminary Data from Two Open-Label Extension Studies with Extended-Release Naltrexone. *American Journal of Addiction*, 20(2), 106-112. Doi: 10.1111/j.1521-0391.2010.00107.x.

This exploratory study investigated whether long-term extended-release naltrexone impacts an individual's experience of pleasure from everyday experiences compared to the experiences of pleasure caused by alcohol. Study participants were recruited from two previous randomized clinical trials that examined the efficacy and safety of extended-release naltrexone in the treatment of alcohol dependency. The first study involved patients receiving treatment from 24 U.S. public hospitals, Veterans Administration clinics, and tertiary care medical centers with a six month follow up. These patients received an 380mg extended-release naltrexone intramuscular injection, 190 mg extended-release naltrexone, or a placebo every four weeks. The second study involved patients at 24 similar treatment sites as the first study, however the follow up period was for one year. Patients of the second study received either a 480 mg extended-release naltrexone injection or a daily 50mg oral naltrexone. The current study investigated pleasure from extended-release naltrexone by administering a 13 item self-report hedonic response questionnaire. The questionnaire asked participants about a range of activities that may produce positive feelings on a scoring range of 1 (not at all) to 5 (very much so). The questionnaire was administered once to patients. Of the 187 patients who participated in one of the randomized clinical trials, 74 patients completed the questionnaire after participation of their randomized study. The patients that agreed to complete the questionnaire were predominantly male (57%), White (85%) and had an average of 47 years, received extended-release naltrexone for 41.5 months.

- 19% of patients reported that they received very much or quite a bit of pleasure from drinking alcohol. 21 of the 74 patients reported that they had not drank alcohol in the past 90 days.
- Patients who did not drink in the past 90 days had significantly higher amounts of pleasure from eating sweets, reading, and shopping compared to those who drank alcohol in the past 90 days.
- Compared to pleasure from drinking alcohol, patients had significantly higher amounts of pleasure from listening to music, sex, reading, being with friends, eating good food, eating spicy food, and playing video games/cards.
- Medication dosage and duration did not have a significant effect on pleasure from alcohol and pleasure from other activities.
- Readers should take note that the study authors did not conduct a baseline hedonic questionnaire so there is no way to determine how these ratings may have changed during extended-release naltrexone treatment.
- **Research Conclusions:** Research findings suggest that treatment with extended-release naltrexone among alcohol dependent patients have pleasurable responses to

everyday activities while decreasing pleasurable experiences to alcohol. It should be noted that the sample consisted of individuals who had been taking extended-release naltrexone for a long period of time and the research findings may not be reflective of the population. Additionally, study authors did not conduct a baseline hedonic questionnaire, thus it is difficult to determine how the questionnaire ratings may have changed during treatment with extended-release naltrexone.

Olfson, M., Wall, M., Wang, S., Crystal, S., & Blanco, C. (2017). Service use preceding opioid-related fatality. *The American Journal of Psychiatry*, 175(6), 538–544. <https://doi.org/10.1176/appi.ajp.2017.17070808>

This study investigated over 13,000 overdose deaths between 2001 and 2007 of those in the Medicaid program who died of an opioid overdose.

Just over 60% of individuals who filled medication prescriptions and died of an opioid overdose were diagnosed with chronic pain. Many were found to have been diagnosed with depression and anxiety.

About one third of those who died had been diagnosed with a drug use disorder in the prior year, but fewer than 5% had been diagnosed with opioid use disorder in the last month.

In the year before death, over 50% of those who died had filled prescriptions for opioids or benzodiazepines, and many had filled prescriptions for both types of medications—“a combination known to increase risk of respiratory depression, the primary cause of death in most fatal opioid overdoses.”

Olfson, M., Zhang, V., Schoenbaum, M., King, M. (2020). Trends in Buprenorphine Treatment in the United States, 2009-2018. *JAMA*. 323(3),276-277. [Doi:10.1001/jama.2019.18913](https://doi.org/10.1001/jama.2019.18913).

This study obtained data from the IQVIA Real World Data Longitudinal prescription database to examine the trends in buprenorphine use in the United States from 2009 to 2018. Individuals from 15-80 years old who had filled 1 or more buprenorphine prescriptions were included in the study. Trends were identified by comparing age groups (15-24-year old's, 25 to 34-year old's, 35 to 44-year old's, 45 to 54-year old's, and 55 to 80 year-old's) and gender (male and female) with length and duration of buprenorphine treatment.

- For the study population the rate of buprenorphine use per 1000 persons increased from 1.97 (n=351,904) to 4.43 (n=1,037,787) from 2009 to 2018.
- 35 to 44-year old's rate of buprenorphine use increased the most out of all age groups from 2.41 to 8.34 per1000 persons.
- 15 to 24-year old's were the only age group to experience a decrease in the rate of buprenorphine use from 1.76 to 1.40 per 1000 persons.
- Male buprenorphine use increased from 2.44 to 5.21 per 1000 persons and female use increased from 1.49 to 2.66 per 1000 persons from 2009-2018.
- Approximately 29.3% (n=133,915) of 15 to 80-year old's used buprenorphine for at least 180 days.
- 28.6% (n=76,162) of males and 30.2% (n=57,753) of females continued buprenorphine use for at least 180 days

- 15-24-year old's (n=41,961) had the lowest number of people continue buprenorphine for at least 180 days. 25-34-year-olds (n=181,067) had the greatest number of people continuing buprenorphine for at least 180 days, followed by 34-44 year old's (n=123,759), 45-54 year old's (n=63,889), and 55-80 year old's (n=46,490).
- **Research Conclusions:** Buprenorphine use and retention is increasing in general among age groups and gender. However there appears to be a treatment gap amongst 15-24-year old's who presented with the lowest buprenorphine use and retention.

Oller, D.A., Thornton, C., Nuzzo, P.A., Fanucchi, L.C. (2021). Buprenorphine Induction in Persons with Opioid Use Disorder Hospitalized with Acute Hepatitis A. Journal of Addiction Medicine. 15(3), 187-190. doi: 10.1097/ADM.0000000000000730.

This retrospective review investigated if buprenorphine/naloxone can be safely initiated among hospitalized patients with acute hepatitis A infection. Data were obtained from 31 hospitalized patients with acute hepatitis A at a hospital in Kentucky from October 2018 to July 2019. Liver function tests and patient tolerability of buprenorphine/naloxone induction were used to measure outcomes.

- There were no significant differences found in the liver function tests between participants who took buprenorphine/naloxone versus those who did not.
- Long term liver function could not be determined due to study design.
- Patients taking buprenorphine/naloxone were likely to report nausea.
- **Research Conclusions:** Study findings suggest that hepatitis A patients can safely take buprenorphine/naloxone without any damages to their liver. Long term effects of buprenorphine/naloxone on the liver were unable to be determined by this study.

Olofsen, E., Algera, M.H., Moss, L., Dobbins, R.L., Groeneveld, G.J., Velzen, M., Niesters, M., Dahan, A., Laffont, C.M. (2022). Modeling buprenorphine reduction of fentanyl-induced respiratory depression. JCI Insight. Do: 10.1172/jci.insight.156973.

This study aimed to characterize buprenorphine and fentanyl's interaction with mu opioid receptors and to determine if buprenorphine can prevent respiratory depression among opioid naïve individuals and individuals who chronically use high doses of opioids. The study was divided into two parts. Part 1 was conducted amongst 14 opioid naïve participations (7 men and 7 women with an average of 24 years old) and parts 2 was conducted with 8 participants with chronic opioid use (3 men and 5 women with an average age of 42 years old). During both parts, participants went through two periods of randomly receiving a continuous I.V. infusion of buprenorphine or a placebo with four escalating fentanyl IV. doses.

- Buprenorphine use caused mild respiratory depression, while high doses of fentanyl caused notable respiratory depression and apnea.
- Participants who had chronic opioid use had a higher tolerance to the respiratory effects of fentanyl use compared to the opioid naïve participants.
- High doses of buprenorphine created a protective effect against high dose fentanyl to prevent respiratory depressions.

- **Research Conclusions:** The study found that even though buprenorphine may cause respiratory depression, it can create the body from further respiratory depression caused by fentanyl. Additionally, participants with chronic opioid use have a high tolerance towards the respiratory effects of fentanyl.

Park, B. (2022). Buprenorphine Extended-Release SC Injection Under Review Again for Opioid Use Disorder. Medical Professionals Reference.

<https://www.empr.com/home/news/drugs-in-the-pipeline/buprenorphine-extended-release-sc-injection-under-review-again-for-opioid-use-disorder/>.

This reference discusses the FDA's decision rereviewing Brixadi, a weekly and monthly extended release subcutaneous injection of buprenorphine. The FDA compared a phase 3 trial of Brixadi in comparison to sublingual buprenorphine/naloxone among patients with moderate to severe opioid use disorder over the course of 24 weeks.

- The use of Brixadi yielded a higher percentage of negative opioid tests than sublingual buprenorphine/naloxone from weeks 4 to 24.
- Some participants who received Brixadi experienced mild to moderate injection site reactions. Besides injection site reactions, Brixadi was observed to have a similar safety profile as oral buprenorphine.
- **Research Conclusions:** Brixadi is a new medication that is currently being reviewed by the FDA to treat with opioid use. Results from a phase 3 trial appear to suggest that Brixadi is as safe as oral buprenorphine and may be better than sublingual buprenorphine/naloxone.

Park, T., Larochelle, M., Saitz, R., Wang, N., Bernson, D., Walley, A.Y. (2020). Associations between prescribed benzodiazepines, overdose death, and buprenorphine discontinuation among people receiving buprenorphine. Addiction, doi: <https://doi.org/10.1111/add.14886>.

This retrospective study examined 63,389 Massachusetts residents who received buprenorphine in treatment from January 2012 to December 2015. The data collected were used to observe the existence of a relationship between benzodiazepine prescription to fatal opioid overdose, non-fatal opioid overdose, all-cause mortality, and buprenorphine discontinuation.

- Of the 63,289 people that received a buprenorphine prescription, only 24% filled at least one of their prescriptions during treatment.
- 31% of 183 overdose deaths that were reported occurred when the person used buprenorphine during treatment.
- Receiving benzodiazepines increased the person's risk of fatal opioid overdose, nonfatal opioid overdose, all-cause mortality, but it decreased the likelihood that a person would discontinue buprenorphine.
- **Research Conclusions:** Even though the use of benzodiazepines decreases the chances of buprenorphine discontinuation, it is associated with an increase in death related to overdosing.

Pearce, L.A., Min, J.E., Piske, M., Zhou, H., Homyra, F., Slaunwhite, A., Irvine, M., McGowan, G., Nosyk. (2020). Opioid agonist treatment and risk of mortality during opioid overdose public health emergency: population based retrospective cohort study. The BMJ, 368. doi:10.1136/bmj.m772.

This retrospective study estimated the risk of mortality for individuals on and off opioid agonist treatment (OAT) and how OAT mortality risk has been affected by fentanyl and other synthetic opioids. Data was obtained from 5 health administrative databases used to identify OAT dispensations, deaths and their underlying causes, hospital admissions, services provided by practitioners under universal insurance, and all levels of ambulatory care in British Columbia, Canada. The sample included all OAT recipients during the study period with at least one OAT dispensation between January 1st 1996 to September 30th 2018. OAT recipients were then followed from the date of their first OAT dispensation to administrative loss (no record of any kind of service for at least 66 months before the end of the study) or their death. 55,347 individuals were identified during the study window as OAT recipients. 7,030 (12.7%) all-cause deaths were reported in the sample.

- Risk of mortality was substantially lower during periods on OAT (2,197 deaths) than off OAT (4,833 deaths). While on and off OAT, buprenorphine /naloxone (on OAT:87 deaths; off OAT: 570 deaths) reported significantly less deaths than methadone (on OAT: 2,085; off OAT: 4,237).
- Mortality rates were highest among individual under 20 years old, HIV (positive or unknown), and with hepatitis C.
- The risk of mortality was highest in the week after stopping treatment for both methadone and buprenorphine/naloxone. The risk of mortality was 2.6 times higher for methadone than buprenorphine a week after stopping treatment.
- Prior the rise fentanyl the risk of mortality off OAT was 2.1 times higher than on OAT. The increased prevalence of fentanyl made the risk of mortality off OAT 3.4 times more likely than on OAT.
- **Research Conclusions:** Study findings provide evidence that OAT is an effective intervention to lower the risk of mortality for people with opioid use disorder. The effectiveness of OAT is displayed further as the mortality rate of individuals on OAT remained low with the increased prevalence of fentanyl.

Peck, K.R., Ochalek, T.A., Badger, G.J., Sigmon, S.C. (2020) Effects of interim buprenorphine treatment for opioid use disorder among emerging adults. Drug and Alcohol Dependence. 208, Doi: 10.1016/j.drugalcdep.2020.107879

This study compared the treatment outcomes for opioid use disorder between emerging adults (18-25-year old's) and older adults (26 years and above). 35 individuals (10 emerging adults, 25 older adults) participated in the study who were receiving technology assisted interim buprenorphine treatment. Interim buprenorphine treatment consisted of 12 weeks of buprenorphine maintenance with bimonthly clinic visits and technology assisted monitoring. At study intake emerging adults presented with a greater level of severity of intravenous drug use, employment, legal, psychiatric problems than older adults.

- There was no significant difference in the percentage of negative urine screens for illicit opioids at week 4(emerging adults 90% vs older adults 88%), week 8 (emerging adults 80% vs older adults 76%), and week 12 (emerging adults 60% vs older adults 68%).

- Emerging adults significantly improved their scores on Beck Anxiety Scale, Beck Depressions Inventory, and Addiction Severity Index than older adults.
- The limitations of this study included the small sample size, lack of racial diversity in the sample, and the length of treatment duration.
- **Research Conclusions:** Despite emerging adults having a higher severity of presenting problems prior to treatment, a low burden type of intervention appears to be an effective treatment method for this age group.

Pergolizzi, J.V., Annabi, H., Gharibo, C., & LeQuang, J.A. (2018). The Role of Lofexidine in Management of Opioid Withdrawal. Pain and Therapy, 8, 67-78. <https://doi.org/10.1007/s40122-018-0108-7>

This study reviewed 20 research articles published over the past 10 years to evaluate the role of the alpha-2 adrenergic agonist lofexidine in managing opioid withdrawal.

- Lofexidine was found to be as effective as another non-opioid, clonidine, but with fewer side effects. Both lofexidine and clonidine are associated with less severe withdrawal symptoms, longer time in treatment, and higher rates of treatment completion than placebo.
- One study in the review found that lofexidine dosing in opioid detoxification centers was higher than manufacturer recommendations in just over half (54.7%) of cases: 0.8 mg/day versus the recommended 0.2–0.4 mg/day. The survey found no evidence that this higher starting dose influenced outcomes. In addition, this study found that most people stopped lofexidine after 10 days versus the recommended 14 days.
- When compared to placebo, lofexidine was significantly more likely to cause low blood pressure (hypotension), dizziness, dry mouth, and slow heart rate (bradycardia).
- **Research Conclusions:** Lofexidine is superior to clonidine for withdrawal management with less side effects. Individuals who might especially benefit from the non-opioid lofexidine in their efforts to discontinue opioids include those experiencing withdrawal symptoms and find opioids worsen their pain (opioid-induced hyperalgesia) or are pregnant or lactating, among others

Pytell, J.D., Whitley, P., Passik, S.D., Bundy, W.L., Dawson, E., Saloner, B. (2023). Association of Patients' Direct Addition of Buprenorphine to Urine Drug Test Specimens with Clinical Factors in Opioid Use Disorder. Jama Psychiatry. doi:10.1001/jamapsychiatry.2023.0234.

This cross-sectional study investigated the characteristics associated with the direct addition of buprenorphine to urine drug test samples amongst buprenorphine prescribed patients with opioid use disorder. Between January 1, 2017, through April 30, 2022, 507,735 urine samples from 58,476 patients were obtained. Males provided 261,210 (51.4%) of the samples and 137,254 (37.7%) of the patients were between the ages of 25 to 34 years old.

- 9,546 (1.9%) urine samples from 4,550 patients were suggestive to have had the direct addition of buprenorphine to the sample.

- Urine samples that were opioid positive with and without stimulants were associated with the direct addition of buprenorphine, whereas urine samples that were opioid negative and stimulant positive were not associated with direct buprenorphine to the sample.
- Patients who were between the ages of 35 to 44 years and attended primary care were the most likely to have direct buprenorphine added to the urine sample.
- Patients living in the South Atlantic portion on the United States were most likely to have direct buprenorphine added the sample, while patients living in New England were least likely.
- **Research Conclusions:** Study findings show that the addition of buprenorphine directly to a urine sample was often associated with opioid positivity and the sample being collected at a primary care setting. The behavior of adding buprenorphine to urine samples suggest that treatment is not working effectively among patients who are continuing illicit drug use. These study findings suggest that there needs to be better practices in place to detect and address patients adding buprenorphine to their samples.

Ranapurwala, S. I., Shanahan, M. E., Alexandridis, A. A., Proescholdbell, S. K., Naumann, R. B., Edwards, D., & Marshall, S. W. (2018). Opioid overdose mortality among former North Carolina inmates: 2000–2015. *American Journal of Public Health, 108*(9), 1207–1213. <https://doi.org/10.2105/AJPH.2018.304514>.

This study examined the differences in the rate of opioid deaths that occur between North Carolina inmates and North Carolina residents. The study also examined the factors that were associated with post-release opioid overdose for the prisoners. The study collected data from 229,275 inmates from 2000–2015. From the inmate data that was collected, a total of 1,329 died from opioid overdose after their release.

- At 2 weeks, 1 year, and complete follow-up after release, the risk of opioid overdose death was 40, 11, and 8.3 times, respectively, more likely to occur than in the general North Carolina resident population.
- At 2 weeks, 1 year, and complete follow-up, prisoners were 74, 18, and 14 times, respectively, more likely to experience heroin overdose death than regular North Carolina residents.
- Former inmates within 2 weeks after release, aged between 26 to 50 years old, white, with more than 2 prison terms, who received in-prison mental health and substance abuse treatment were at the greatest risk for opioid overdose death.
- **Research Conclusion:** Former inmates are highly vulnerable to opioids after their release and need additional preventative measures.

Randall-Kosich, O., Andracka-Christou, B., Totaram, R., Alamo, J., Nadig, M. (2019) Comparing Reasons for Starting and Stopping Methadone, Buprenorphine, and Naltrexone Treatment Among a Sample of White Individuals With Opioid Use Disorder. *Journal of Addiction Medicine*. Epub ahead of print

This study identified why people start and stop medications for opioid use disorder including methadone, buprenorphine, and extended release naltrexone. 31 white participants who had a history of opioid use disorder were interviewed over the phone.

- Participants had primarily learned about methadone and buprenorphine from other people with opioid use disorder and saw how the methadone and buprenorphine worked on their peers.
- Methadone was perceived as a last resort type of medication.
- Participants learned about naltrexone after receiving information from health practitioners.
- Preventing medication dependence was the leading factor as to why participants stopped using opioid medications.
- Stigma and external pressure were the leading causes as to why participants stopped using buprenorphine and methadone but not naltrexone.
- **Research Conclusions:** Peers with medication for opioid use disorder experience may be trusted sources of information for individuals seeking opioid use treatment. Further research will be needed to see if a peer support specialist with medication for opioid use disorder experience combined with formal substance use disorder treatment will lead to more individuals taking medication for opioid use disorder, retain patients in treatment longer, and improve opioid use disorder treatment outcomes.

Ray, L.A., Meredith, L.R., Kiluk, B.D., Walthers, J., Carroll, K.M., Magill, M. (2020). Combined Pharmacotherapy and Cognitive Behaviors for Adults With Alcohol or Substance Use Disorder A systematic Review and Meta-analysis. JAMA Network Open. 3(6). doi:10.1001/jamanetworkopen.2020.8279.

This meta-analysis provides an up-to-date review of CBT paired with pharmacotherapy to treat alcohol use/ substance use disorder. The studies included in this review were used to compare CBT and pharmacotherapy treatment with 3 different treatment types: (1) CBT and pharmacotherapy compared to usual care (e.g., clinical management and nonspecific therapy), (2) CBT and pharmacotherapy compared to specific therapy (e.g., motivational enhancement therapy, contingency management, and 12 step facilitation) with pharmacotherapy, and (3) CBT and pharmacotherapy with usual care compared to usual care and pharmacotherapy. Studies included in the meta-analysis were written in English, peer reviewed and published from Jan 1, 1990 through July 21, 2019, treatment was cognitive behavioral or relapse prevention based with pharmacotherapy, and the participants were adults 18 years or above with criteria for alcohol use disorder or other drug use disorder. This review included 30 articles that had sample sizes that ranged from 30-917 participants, primary substance targeted for treatment was alcohol (15[50%]), cocaine (7[23]), and opioids (6[20%]), mean participant age was 39 years old, 72% of participants were male, participants were 66% white, 35% black, and 9% Latinx, and pharmacotherapy medications included naltrexone hydrochloride and/or acamprosate sodium (42%), methadone hydrochloride or combined buprenorphine hydrochloride and naltrexone (18%), disulfiram (8%), and a mixture of pharmacotherapies (32%)

- CBT and pharmacotherapy were found to have more statistically significant treatment outcomes than usual care.
- CBT and pharmacotherapy had no unique benefit when compared to a specified treatment with pharmacotherapy

- CBT and pharmacotherapy with usual care compared to usual care with pharmacotherapy had no clear findings based upon study outcomes.
- **Research Conclusions:** The findings of the review suggest that clinicians should choose an addiction treatment that includes pharmacotherapy plus CBT or a specific evidence-based therapy, rather than usual clinical management or nonspecific counseling services. CBT paired with pharmacotherapy and usual treatment requires further investigation to understand CBT's impact fully.

Rich, J. D., McKenzie, M., Larney, S., Wong, J. B., Tran, L., Clarke, J., Noska, A., Reddy, M., & Zaller, N. (2015). Methadone continuation versus forced withdrawal on incarceration in a combined US prison and jail: A randomised, open-label trial. *The Lancet*, 386(9991), 350–359. [https://doi.org/10.1016/S0140-6736\(14\)62338-2](https://doi.org/10.1016/S0140-6736(14)62338-2).

This study investigates the effect of forced withdrawal from methadone upon incarceration on risk behaviors and engagement with post-release treatment. Inmates of the Rhode Island Department of Corrections who were enrolled in a methadone maintenance treatment (MMT) program in the community at the time of arrest—and wanted to continue treatment during incarceration and on release—were assigned to either continue their treatment or be forced to withdraw from methadone. Participants in the continued-methadone group were maintained on their methadone dose at the time of their incarceration (with dose adjustments as clinically indicated). Patients in the forced-withdrawal group followed the standard withdrawal protocol of receiving methadone for 1 week at the dose at the time of their incarceration, then a tapered withdrawal regimen. (For those on a starting dose >100 mg, the dose was reduced by 5 mg per day to 100 mg, then reduced by 3 mg per day to 0 mg; for those on a starting dose ≤100 mg, the dose was reduced by 3 mg per day to 0 mg.) Between 2011 and 2013, 283 prisoners were randomly assigned to the study. After exclusions, 114 participants were in the continued methadone group and 109 in the forced-withdrawal group.

- Participants that continued methadone were more than twice as likely to return to a community methadone clinic within one month of release than those forced off methadone in prison (96% vs. 78%).
- **Research Conclusions:** This study showed that forced withdrawal from methadone on incarceration reduced the likelihood that prisoners would re-engage in MMT after release. Continuation of MMT during incarceration could lead to greater treatment retention after release.

Saloner, B., Whitley, P., Dawson, E., Passik, S., Gordon, A.J., Stein, B.D. (2023). Polydrug use among patients on methadone medication treatment: Evidence from urine drug testing to inform patient safety. *Addiction*, 118(8), 1549-1556. <https://doi.org/10.1111/add.16180>.

This retrospective cohort study examined the trends of illicit substance use among patients first year of receiving methadone treatment for opioid use disorder. The study examined urine drug test results from January 1, 2017, through December 31, 2021 of 16,386 unique patients living in Alaska, Arizona, Florida, Illinois, Kentucky, Minnesota, New Mexico, Ohio, Virginia, and Washington. All treatment sites that obtained urine samples, submitted the samples to Millennium Health, a third-party laboratory, for testing. The study sample were mostly males (50.7%), had Medicaid insurance (77%), had a median age of 38 years, and Kentucky provided the most samples (31%).

- From 2018 through 2021, positivity rates increased for fentanyl (13.1%-53%), methamphetamine (10.6%-27.2%), cocaine (13.8%-19.5%). Heroin positivity rates initially increased from 6.94% in 2017 to 9.72% in 2020 but decreased in 2021 (6.45%).
- Positive screens for fentanyl were significantly likely occur amongst men, patients older than 35 years of age, living in Ohio, and have Medicaid insurance.
- Positive screens for heroin were significantly likely to occur amongst male patients, patients living in Alaska, and patients that had Medicaid insurance.
- Positive screens for methamphetamines were more likely to occur amongst patients living in Alaska and patients that had Medicaid insurance.
- Positive screens for cocaine were more likely to occur amongst patients living in Ohio and patients who had Medicaid insurance.
- **Research Conclusions:** The findings of this study appear to show that even though patients are receiving methadone treatment for opioid use disorder there is still illicit drug use that is occurring, with fentanyl being the most likely used drug. While this study took place in multiple states, the urine samples were aggregated so differences among states were not determined.

Saloner, B., Whitley, P., LaRue, L., Dawson, E., Huskey, A. (2021). Polysubstance Use Among Patients Treated With Buprenorphine From a National Urine Drug Test Database. Journal of the American Medical Association. 4(9). doi: 10.1001/jamanetworkopen.2021.23019.

This retrospective study described the trends of nonprescribed substance use among individuals with opioid use disorder who initiated buprenorphine pharmacotherapy. 150,000 urine drug test results from January 1, 2013, to December 31, 2019, for buprenorphine prescribed patients 18 years or older who attended treatment centers across all 50 U.S. states were analyzed. Of the 150,000 samples, 82,107 sample were from male patients, 77,300 sample were from patients younger than 35 years old. 44,220 patients had Medicaid, 23,725 private insurance, 7,279 Medicare, 12,395 uninsured, and 62,381 were unknown.

- Throughout the length of the study, 128,240 samples were positive for buprenorphine and 71,373 were positive for one or more non prescribed substances.
- The positivity rate of non-prescribed substances was highest among patients receiving treatment from substance use disorder treatment centers. Alcohol positivity and marijuana positivity was highest among patients attending primary care practices.
- Younger patients were more likely to be positive for fentanyl and heroin, while older individuals were more likely to be positive for benzodiazepines, alcohol, and oxycodone.
- Compared to patients with private health insurance, patients with Medicaid had higher positivity rates for other substances.
- Patients who were positive for buprenorphine were significantly less likely to be positive for other opioids compared to patients who tested negative for buprenorphine.
- **Research Conclusions:** Research findings show that patterns of nonprescribed substance use among patients prescribed buprenorphine varied widely based upon patient characteristics and treatment setting.

Samples, H., Noweles, M.A., Williams, A.R., Olfson, M., Crystal, S. (2023). Buprenorphine After Nonfatal Opioid Overdose: Reduced Mortality Risk in Medicare Disability Beneficiaries. American Preventive Medicine. 1-11. <https://doi.org/10.1016/j.jamepre.2023.01.037>.

This longitudinal, retrospective cohort study examined the association between buprenorphine and opioid use disorder related psychosocial services with the risk of opioid involved overdose deaths in the year after a nonfatal opioid involved overdose. A random sample of 81,616 Medicare Part D beneficiaries between the age ages of 18-64 years old who had a nonfatal opioid overdose treated in inpatient or in an emergency department setting between 2008 through 2016 were analyzed. The study sample was primarily female (57.3%), between the ages of 50-59 (41.7%), White (80.9%), lived in the South (42.7%), and had chronic pain (57.6%).

- At the time of follow-up 9,439 participants died, of those deaths 2,430 were drug related with 2,512 deaths involving opioids.
- 93.5% of opioid deaths were unintentional.
- Between deaths that were opioid involved and non-opioid involved, opioid related deaths were primarily males, aged 50 years or older, and White.
- Buprenorphine was associated with a 62% reduction in the risk of opioid involved overdose a year after a nonfatal overdose.
- Fewer than 1 in 20 individuals received buprenorphine treatment in the subsequent year after a nonfatal overdose.
- Due to the study using data for Medicare Part D patients, data may not be representative of all adults in this population.
- **Research Conclusions:** Study findings show that buprenorphine treatment was associated with a significant reduction in the risk of an overdose, however very few individuals received buprenorphine treatment in the year following a non-fatal overdose. The lack of buprenorphine treatment suggests that accessing buprenorphine treatment may be extremely difficult for the people who need it most.

Samples, H., Williams, A. R., Olfson, M., & Crystal, S. (2018). Risk factors for discontinuation of buprenorphine treatment for opioid use disorders in a multi-state sample of Medicaid enrollees. Journal of Substance Abuse Treatment, 95, 9–17. <https://doi.org/10.1016/j.jsat.2018.09.001>

Samples, H., Williams, A.R., Crystal, S., Olfson, M. (2020). Impact of long-Term Buprenorphine Treatment on Adverse Health Care Outcomes in Medicaid. Health Affairs, 39(5), 747-755. <https://doi.org/10.1377/hlthaff.2019.01085>

These studies analyzed Medicaid insurance claims to characterize the risk factors that are attributed to the discontinuation of buprenorphine treatment and to compare adverse health outcomes of long-term continuous buprenorphine use vs short-term buprenorphine use. The sample to determine the risk factors of discontinuing buprenorphine treatment included adults who were 18 years and above who were diagnosed with opioid use and had 6 months without a buprenorphine claim prior to the start of the study. The sample to compare

adverse health outcomes included adults 18 years or older who had buprenorphine treatment for at least 6 months.

- In determining risk factors of buprenorphine discontinuation, over one-quarter of the sample discontinued buprenorphine in the first month of treatment (N=4,928; 28.4%) and most discontinued before 180 days (N=11,189; 64.6%).
- Risk factors for discontinuation included: a lower initial buprenorphine dose (≤ 4 mg), male sex, younger age, minority race/ethnicity, comorbid substance use disorder (alcohol, non-opioid drugs), hepatitis C, opioid overdose history in the 6-month baseline period, any in-patient care in the 6-month baseline period.
- Continuous buprenorphine treatment of 15 months or more had lower all cause inpatient hospitalizations, emergency department visits, opioid related hospital use, and opioid related hospital use when compared to those who discontinued buprenorphine treatment at 6-9 months.
- **Research Conclusions:** These findings suggest that long term buprenorphine use provides more positive adverse health outcomes. There is a need to address barriers to treatment to help increase retention. Additional attention to these treatment barriers can help increase treatment retention amongst minorities, younger individuals, and those with additional SUDs.

Samples, H., Williams, A.R., Crystal, S., Olfson, M. (2020). Psychosocial and behavioral therapy in conjunction with medication for opioid use disorder: Patterns, predictors, and association with buprenorphine treatment outcomes. Journal of Substance Abuse Treatment. doi: <https://doi.org/10.1016/j.jsat.2022.108774>.

This study observed the outcomes of psychosocial and behavioral therapy services within the first six months of buprenorphine initiation. Additionally, this study identified characteristics there are associated with these treatment patterns. From 2013-2018, Medicaid claims data of 61,976 adults between 18-64 years old who initiated buprenorphine for at least seven days were analyzed.

- There were three service patterns of psychosocial and behavioral therapy received by participants that study authors noticed: none (73.8%), low intensity (17.2%), and high intensity (9%).
- Compared to individuals who did not seek therapy, individuals who received low intensity and high intensity services were more likely to have a behavioral health diagnosis and received medical treatment for an opioid overdose prior to buprenorphine initiation.
- The risk of buprenorphine discontinuation was low amongst individuals with low and high intensity services compared to those who did not receive therapy.
- Individuals who had high intensity services had the highest risk of an opioid related health care event including opioid overdose during buprenorphine treatment.
- **Research Conclusions:** Research findings show that concurrent therapy services may help with buprenorphine discontinuation. It should be noted that most study participants did not receive psychosocial and behavioral therapy after initiating buprenorphine treatment, so the study findings may not be accurate.

Santo, T., Clark, B., Hickman, M., Grebely, J., Campbell, G., Sordo, L., Chen, A., Tran, L., Bharat, C., Padmanatha, P., Cousins, G., Dupouy, J., Kelty, E., Muga, R., Nosyk, B., Min, J., Pavarin, R., Farrell, M., Degenhardt, L. (2021). Association of Opioid Agonist Treatment With All-Cause Mortality and Specific Causes of Death Among People With Opioid Dependence: A systematic Review and Meta- analysis. *Journal of American Medical Association Psychiatry*. doi: 10.1001/jamapsychiatry.2021.0976.

This systemic review investigated the association between the time of receiving opioid agonist treatment to an individual's mortality. 15 randomized clinical trials and 36 observational studies that included data on all-cause mortality among individuals with opioid use disorder while receiving and not receiving opioid agonist treatment.

- Among the observational studies, the rate of all-cause mortality for individuals receiving opioid agonist treatment was half of the rate observed among individuals who discontinued opioid agonist treatment.
- Individuals enrolled in methadone MAT were at a higher risk of mortality during the first four weeks of treatment than those enrolled in buprenorphine MAT.
- All-cause mortality was six times higher after four weeks of stopping opioid agonist treatment than those who continued their MAT.
- Opioid agonist treatment was associated with a lower risk of mortality during incarceration and after release.
- **Research Conclusions:** Findings show that opioid agonist treatment is an intervention that lowers the risk of mortality but treatment retention during the first four weeks is crucial. Providing access opioid agonist treatment to individuals while they are incarcerated was found to significantly lower the risk of mortality.

Santos, G.M., Ikeda, J., Coffin, P., Walker, J., Matheson, T., Ali, A., McLaughlin, M., Jain, J., Arenander, J., Vittinghoff, E., Batki, S. (2022). Targeted Oral Naltrexone for Mild to Moderate Alcohol Use Disorder Among Sexual and Gender Minority Men: A Randomized Trial. *American Journal of Psychiatry*. 179(12), 915-926. Doi:10.1176/appi.ajp.20220335.

This double-blind placebo control trial investigated the efficacy of the use of oral naltrexone in sexual and gender minority men who binge drink and have mild to moderate alcohol use disorder. Study authors recruited 120 sexual and gender minority men in San Francisco, California to receive a 50 mg dose of oral naltrexone or a placebo with weekly counseling for 12 weeks. The study sample characteristics include 54% White men, 59% college educated or above, 48% full time employed, 26% HIV positive, median age of 37 years, 22% of the sample was positive for marijuana, no participants were positive for opioids, 91% have health insurance, and 85% have a regular health care provider, and 87% had never been hospitalized for an alcohol related problem.

- 93% of the study sample retained treatment by the end of the study, of which 90% of the naltrexone and 95% of the control group completed the study.
- On average naltrexone participants reported taking their medication 71% of days of which they craved alcohol or anticipated heavy drinking. The control group took their medication 76% of the time when craving alcohol or anticipating heavy drinking.

- Adverse events between the naltrexone and control groups were similar across both groups and were unrelated with the study or its medication.
- Naltrexone significantly reduced the reported number of binge drinking days and the number of drinks per month compared to the placebo group after 12 weeks.
- **Research Conclusions:** Studying findings show that naltrexone was an effective medication to reduce alcohol consumption among sexual and gender minority men with mild to moderate alcohol use disorder.

Saucier, R., Wolfe, D., & Dasgupta, N. (2018). Review of case narratives from fatal overdoses associated with injectable naltrexone for opioid dependence. *Drug Safety*, 41(10), 981–988. <https://doi.org/10.1007/s40264-018-0653-3>.

This study investigated overdose risk following the last injection of naltrexone administered in order to determine the time period of concern for fatal overdose associated with the medication. This study conducted a case review of Vivitrol spontaneous reports (October 2010–March 2016) in the FDA Adverse Event Reporting System Case narratives to identify overdose deaths among patients. Although cause of death was unknown in 46% of the 263 deaths obtained, 52 deaths met the case definition of fatal overdose.

- Of the 28 deaths with known times of dose and death, 22 occurred within 2 months of last Vivitrol injection (median 46 days) and 5 occurred within 28 days.
- **Research Conclusions:** Findings suggest that the majority of reported deaths were occurring a few weeks after the effect of the last shot had worn off, not as a result of individuals attempting to overcome the blocking effects of the medication.

Saxon, A. J., Akerman, S. C., Liu, C. C., Sullivan, M. A., Silverman, B. L., & Vocci, F. J. (2018). Extended-release naltrexone (XR-NTX) for opioid use disorder in clinical practice: Vivitrol's Cost and Treatment Outcomes Registry. *Addiction*, 113(8), 1477–1487. <https://doi.org/10.1111/add.14199>

This study reports on outcomes for extended-release naltrexone (XR-NTX) in Vivitrol's Cost and Treatment Outcomes Registry, analyzing 295 enrolled patients for baseline characteristics and quality-of-life outcomes found at 32 U.S. treatment centers from 2011 and 2013.

- On average, patients received five injections. The median number of injections administered within 6 months was higher in patients who at baseline were employed (3 vs. 2) or had private insurance (5 vs. 2).
- The six-injection patients at baseline were more likely to meet normal/minimal mental illness criteria and attend school and less likely to report recent drug use. Compared to the subgroups receiving only one, two, or three injections, the six-injection group demonstrated improvements in employment, mental health and psychosocial functioning, and decreases in opioid craving, drug use and drug-related behaviors.
- **Research Conclusions:** Better mental health, higher education, and lower recent drug use at baseline are associated with greater treatment duration among opioid-dependent people receiving XR-NTX. In turn, longer treatment duration is associated with lower relapse rates and improved outcomes generally.

Schepis, T. S., Simoni-Watsila, L., & McCabe, S. E. (2018). Prescription opioid and benzodiazepine misuse is associated with suicidal ideation in older adults. *International Journal of Geriatric Psychiatry*, 34(1), 122–129. <https://doi.org/10.1002/gps.4999>.

This study explored whether there is a significant connection between opioid and benzodiazepine use and misuse with suicidal ideation in the past year in the United States with adults 50 years and older. Data from the 2015 to 2016 National Survey on Drug Use and Health were used. Each of the participants were asked, “At any time in the past 12 months, did you seriously think about trying to kill yourself?” The participants were then categorized based on use, misuse, and no use in the past year. There were 17,608 participants, 53.2% female and 43.2% were 65 years or older. Of the 17,608 participants, 17,114 were used for this study. The 494 participants excluded from the study refused the questions or presented bad data to the questions.

- There was a significantly higher rate of suicidal ideation presented in participants who misused both benzodiazepines and opioids (25.4%) than participants who misused opioids (8.3%) or benzodiazepines (8.8%) solely. Only 2.2% of respondents of the no misuse category reported having suicidal ideation in the past year.
- **Research Conclusions:** Past year opioid and/or benzodiazepine misuse increases the likelihood of suicidal ideation in adults 50 years and older. These results suggest that older adults who get screened for opioids and benzodiazepines would benefit from getting screened for suicidal ideation as well.

Schiff, D.M., Nielsen, T.C., Hoepfner, B.B., Terplan, M., Hadland, S.E., Bernson, D., Greenfield, S.F., Bernstein, J., Bharel, M., Reddy, J., Taveras, E.M., Kelly, J.F., Wilens, T.E. (2021). Methadone and Buprenorphine Discontinuation among Postpartum Women with Opioid Use Disorder. *American Journal of Obstetrics and Gynecology*. <https://doi.org/10.1016/j.ajog.2021.04210>.

This retrospective cohort study examined the discontinuation of methadone and buprenorphine amongst women with opioid use disorder a year after giving birth and common characteristics associated with discontinuation. The administrative data of Massachusetts women who received methadone and buprenorphine during the month of their delivery between 2011-2014 were obtained. The administrative data provided information on methadone and buprenorphine use, demographic, psychosocial, prenatal, and delivery characteristics.

- Of the 2,314 women who received methadone and buprenorphine upon delivery, 1,484 (64.1%) women continued to receive medication 12 months after giving birth.
- 34% of women continued methadone and buprenorphine if they started medication a month before delivery and 80% of women continued if medication was used throughout their entire pregnancy.
- Nonwhite women, and incarceration during pregnancy and postpartum were strongly associated with methadone and buprenorphine discontinuation.
- **Research Conclusions:** Majority of women continued to use medication for opioid use disorder a year after giving birth, however race, prenatal use of medication, and incarceration status were significant factors for discontinuation. These findings suggest

that expanding the access to medication for opioid use disorder for prenatal women and women in the criminal justice system may improve postpartum women's treatment for opioid use disorder.

Shulman, M., Greiner, M.G., Tafessu, H.M., Opara, O., Ohrtman, K., Potter, K., Hefner, K., Jelstrom, E., Rosenthal, R., Wenzel, K., Fishman, M., Rotrosen, J., Ghitza, U.E., Nunes, E.V., and Bisaga, A. (2024). Rapid Initiation of Injection Naltrexone for Opioid Use Disorder A Stepped-Wedge Cluster Randomized Clinical Trial. JAMA Network Open. 7(5). Doi: 10.1001/jamanetworkopen.2024.9744.

The Surmounting Withdrawal to Initiate Fast Treatment (SWIFT) trial is a 70 week randomized controlled trial that compared the effectiveness of rapid extended-release naltrexone initiation procedures (1 day of buprenorphine at minimum dose, 1 opioid free day, and ascending low doses of naltrexone and adjunctive medications for opioid withdrawal) to standard procedures (5 day buprenorphine taper followed by 7-10 days opioid free period) at community-based inpatient addiction treatment centers. SWIFT was implemented in 6 geographically diverse community inpatient addiction treatment centers across the United States. At the start of the trial and at every 14-week interval, one site was randomly assigned to switch from their standard extended-release naltrexone initiation procedure to a rapid initiation procedure, however one site maintained the standard procedure throughout the length of the study. Upon inpatient admission, patients received the treatment centers initiation procedure that was currently assigned to them. After inpatient admission, patients were referred to outpatient addiction clinics according to each sites standard procedure and were followed for eight outpatient weeks. The study originally recruited 3,993 patients who expressed interest in extended-release naltrexone treatment, however 2,443 patients did not attempt extended-release naltrexone initiation due to preferring buprenorphine (n=848), preferred methadone (n=1085), and preferred withdrawal management with no medication for opioid use disorder (n=280). 415 patients attempted to initiate extended-release naltrexone with 225 patients at sites that were assigned rapid procedures and 190 patients at sites that were assigned standard procedures. Most patients were female (50.6%), average age of 33.6 years, and 69.9% White.

- 62.7% of patients at rapid procedure treatment centers received extended-release naltrexone compared to 35.8% of patients at standard procedure centers.
- The most common reasons that patients did not receive a first dose of extended-release naltrexone was because they left the inpatient unit early (61.9% rapid procedure vs 70.5% standard procedure), decided to begin with buprenorphine or methadone (21.4% rapid procedure vs 20.5% standard procedure), or withdrawal symptoms were too uncomfortable (14.3% rapid procedure vs 4.9% standard procedure).
- Withdrawal symptoms did not significantly differ among either treatment condition.
- Adverse events were infrequent, however they occurred more often at centers implementing rapid procedures (6.7% rapid procedures vs 1.6% standard procedures).
- Research Conclusions: The findings of the study show that patients are more likely to initiate extended-release naltrexone under rapid procedures, however patients appear to experience uncomfortable withdrawal symptoms and experience more adverse events compared to standard procedures. For treatment centers that consider using rapid procedures, intensive medical management and safety monitoring is needed.

Schuman-Olivier, Z., Borodovsky, J. T., Steinkamp, J., Munir, Q., Butler, K., Greene, M. A., Goldblatt, J., Xie, H. Y., & Marsch, L. A. (2018). MySafeRx: A mobile technology platform integrating motivational coaching, adherence monitoring, and electronic pill dispensing for enhancing buprenorphine/naloxone adherence during opioid use disorder treatment: A pilot study. *Addiction Science & Clinical Practice*, 13, 21. <https://doi.org/10.1186/s13722-018-0122-4>.

The study examines the feasibility, usability, and acceptability of MySafeRx—a mobile technology platform integrating motivational coaching, adherence monitoring, and electronic pill dispensing designed to address the challenges of office-based opioid treatment (OBOT) with buprenorphine/naloxone (B/N). The MySafeRx platform integrates electronic pill dispensers, text messaging, and videoconferencing to provide supervised self-administration of medication and daily motivational coaching through an Android app interface. High-risk early adults (18–39 years old) who were enrolled in OBOT with B/N and had documented illicit opioid use in the past month during opioid agonist therapy (N=12) participated in a 28-day single-arm observational study of the MySafeRx platform in addition to standard care.

- Two-thirds of participants who completed the study achieved an average of > 5 days per week of supervised B/N self-administration. Visual confirmation of medication adherence was demonstrated for an average of 72% of study days among all participants.
- All participants achieved platform technical proficiency within 60 minutes, reporting good levels of usability and acceptability. Illicit opioid abstinence rates confirmed by urine toxicology increased by 53% during MySafeRx but fell 43% within 3 weeks post-intervention.
- **Research Conclusions:** The MySafeRx medication adherence and remote coaching mobile platform is acceptable and can be feasibly implemented in real-world opioid use disorder treatment settings during high-risk periods (i.e., initial stabilization, after illicit opioid lapse), resulting in reduced illicit opioid use; however, the effect did not last after intervention completion, suggesting longer duration or extended taper of program may be needed.

Scott, C.K., Grella, C.E., Dennis, M.L., Carnevale, J., LaVallee, R. (2022). Availability of best practices for opioid use disorder in jails and related training and resource needs: findings from a national interview study of jails in heavily impacted counties in the U.S. *Health and Justice*, 10, 36. <https://doi.org/10.1186/s40352-022-00197-3>.

This study examines the best practices for addressing opioid use disorder for individuals in jail and the trainings, resources, and technical assistance needed to expand best practices for this population. The study sample consisted of individuals from the top 97 counties that accounted for 50% of all opioid overdose deaths nationally along with a individual from 147 counties that had high opioid related over dose deaths per 100,000 people above the national average. Within the selected counties, 250 jails were identified to take part in the study. Majority of the jails were associated with a sheriff's office or county (95%), housed both males and females (96%), and contract out for services (72%). Jails were provided a structured survey to assess availability and accessibility of opioid withdrawal management, screening, and assessment to identify opioid use problems, eligibility, reasons for use, and restrictions on use of medications for opioid use disorder, and re-entry planning and services. Respondents from the jails were mainly jail administrators (54%), medical/behavioral health directors (18%), health services administrators (8%),

program/service directors (6%), and other administrative staff (14%). Data were obtained from 185 of the 244 (76%) targeted counties and 185 of 250 (74%) of jails. Jails that did not provided data were more likely to be from counties with residents who lived below the federal poverty line, have a high population incarceration rate for females, males, and white non-Hispanics.

- 70% of jail respondents indicated that each of then opioid use disorder best practices were available in their jails ranging from 71% of jails providing clinical assessment to 96% providing overdose prevention. However, the specific services that jails provided under each best practice category greatly varied.
- For best practice at discharge, 72% of jails indicated that they provided some collaborative activities with community medication for opioid use disorder.
- Jails that followed best practice guidelines the most were more likely to have a higher Hispanic population, fewer individuals living in poverty, and lower jail admissions. Urbanicity and proximity to a medication for opioid use disorder provider was insignificant.
- To increase training, technical assistance, and resources majority of jails responded that they need more funds were their largest need. Specifically, funds were need for medication (81%), clinical staff (80%), diversion prevention (76%), transportation (65%), and medication for opioid use disorder in the community (61%).
- Regarding clinical capacity, most jails needed medical staff (71%), training on how to match their clients with an appropriate type of medication (62%), and how to switch between medications (60%).
- **Research Conclusions:** The findings of the study show that most jails have are incorporating opioid use disorder best practices, however jails do not provide all the services that represent each best practice category. Funding, staffing, and medication education are common barriers that impact jail's ability to follow through with opioid use disorder best practice services.

Sigmon, S. C., Ochalek, T. A., Meyer, A. C., Hruska, B., Heil, S. H., Badger, G. J., Rose, G., Brooklyn, J. R., Schwartz, R. P., Moore, B. A., & Higgins, S. T. (2016). Interim buprenorphine vs waiting list for opioid dependence. *The New England Journal of Medicine*, 375(25), 2504–2505. <https://doi.org/10.1056/NEJMc1610047>

This pilot study evaluates the efficacy of interim regimen of buprenorphine for reducing opioid use among 50 people on waiting lists for entry into opioid treatment.

- Participants receiving interim buprenorphine treatment showed a higher percentage of urine specimens negative for opioids than those not receiving treatment at 4 weeks (88% vs. 0%), at 8 weeks (84% vs. 0%), and at 12 weeks (68% vs. 0%).
- **Research Conclusions:** Results suggest that interim buprenorphine dosing could reduce drug-related risks when comprehensive treatment is not available.

Silva, M.J., Coffee, Z.H., Yu, C.H. (2021). Prolonged Cessation of Chronic Opioid Analgesic Therapy A Multidisciplinary Intervention. *The American Journal of*

Managed Care. Accessed November 3 2021, Prolonged Cessation of Chronic Opioid Analgesic Therapy: A Multidisciplinary Intervention (ajmc.com).

This retrospective review study presented outcomes from the Focus on Opioid Transitions (FOOT Steps) program, an intervention to help patients with chronic, noncancer pain (CNCP) cease chronic opioid analgesic therapy (COAT) reliance by using a combination of group interventions and medication management. Data was collected from electronic health records and California Prescription Drug Monitoring Program of patients who participated in the FOOT Steps program from October 2017 to December 2019. Participants were selected through a semi-structured motivational interview between the participant and program clinician. 109 participants were admitted into the study by fulfilling study criteria of voluntarily consenting to participate in FOOT Steps for the purpose of COAT cessation, diagnosis of CNCP, used COAT daily at the time of admission or struggled to maintain opioid cessation, and tried and failed or plateaued on a previous opioid wean. Demographic information on participants was limited but included 69% female, 30% with Medicare insurance, 25% workers compensation, 10% on Medicaid, and majority of participants identified their work status as disabled or retired.

- 98 participants ceased COAT by program graduation. Reasons that participants did not complete the program included adverse events caused by withdrawal symptoms, adverse events caused by buprenorphine, and changes in patient care plans that required a return to COAT.
- 63 and 64 participants maintained their medication regiment after program graduation or continued to make progress on their own by weaning off buprenorphine entirely at 6 months respectively.
- Some participants who maintained successful COAT cessation showed a brief return to opioid use. Electronic health records show that these patients underwent surgical procedures necessitating a limited exposure to opioids.
- **Research Conclusions:** Study findings show that the interventions used in the FOOT Steps program provide successful strategy to promote COAT cessation among patients with chronic noncancer pain.

Sittambalam, C.D., Radhika, V., Ferguson, R.P. (2014). Buprenorphine Outpatient Outcomes Project: can Suboxone be a viable outpatient option for heroin addiction? Journal of community Hospital Internal Medicine Perspectives. 4(2). doi: 10.3402/jchimp.v4.22902

The rate of emergency department visits and hospitalizations, legal issues, and quality of life were evaluated to determine if suboxone was a viable treatment option for active heroin users. 220 active heroin users 18-67 years old were recruited to begin suboxone treatment during hospitalization. Majority of participants were under 50 years old (72%), 85% identified as African American, 63% male, and 79% were unemployed. Once participants were discharged from the hospital they were observed as outpatient patients where they maintained suboxone and received counseling. Data was collected through electronic medical records, Maryland state legal records, and counseling records.

- 137 (62%) participants were in the study for less than one month, 46 (21%) remained for 1-3 months, and 37 (17%) participants stayed in the study for more than three months.

- The rate of hospitalizations and emergency room visits decreased by 45 and 35% respectively, after participants began taking suboxone. 51% of the participants who remained in the study for more than three months never had a hospitalization after taking suboxone.
- Total number of legal charges increased among participants from the year prior taking suboxone (n=221) and after taking suboxone (n=237).
- Participant quality of life improvement was proportional to their length of suboxone use.
- **Research Conclusions:** Retaining participants for this study was difficult but the longer that participants remained in the study to take suboxone there was an increase in quality of life and more positive treatment outcomes. However, taking suboxone did not have an impact on criminal charges.

Smith, J.T., Sage, M., Szeto, H., Myers, L.C., Lu, Y., Martinez, A., Kipnis, P., Liu, V.X. (2022). Outcomes After Implementation of a Benzodiazepine-Sparing Alcohol Withdrawal Order Set in an Integrated Health Care System. Journal of the American Medical Association. 5(2). doi: 10.1001/jamanetworkopen.2022.0158

This retrospective study evaluated the changes in medication use and outcomes after implementation of a revised treatment program aimed at lowering benzodiazepine use amongst inpatients with alcohol withdrawal syndrome across 21 hospitals in a Northern California health care system. At study entry, participants with a low risk for alcohol withdrawal syndrome and low severity were given supportive treatment with thiamine and multivitamins. Patients who entered treatment with a high-risk for alcohol withdrawal syndrome or were currently experiencing alcohol withdrawal syndrome were given anticonvulsant and alpha agonist medications with benzodiazepines. Patients with severe alcohol withdrawal syndrome or not responsive to other treatments were administered dexmedetomidine at the start of treatment. Between October 1, 2014, through September 30, 2019, 22, 899 hospital visits that involved alcohol withdrawal syndrome, occurring among 16,323 unique patients were identified and analyzed for the study. Majority of the patients were on average 57.1 years old and were 68.8% men.

- Benzodiazepine use decreased by 17.4% after implementation of the revised benzodiazepine treatment program.
- The use adjunctive medications such as clonidine, gabapentin, phenobarbital, thiamine, and valproic acid significantly increased since the implementation of the revised treatment program.
- Mortality increased after implementation of the revised benzodiazepine treatment program, which study authors attributed to difficulty some participants may have had to changing medications.
- Use of the revised treatment program was associated with a decrease in use of the intensive care unit.
- **Research Conclusions:** The study found that using a revised treatment program to lessen benzodiazepine successfully lowered benzodiazepine use, increased adjunctive medications, and lowered ICU admission. Despite these positive treatment outcomes, patient mortality rate did not decrease.

Smith, K.E., Tillson, M.D., Staton, M., Winston, E.M. (2020). Characterization of diverted buprenorphine use among adults entering corrections-based drug treatment

in Kentucky. Drug and Alcohol Dependence. 208, Doi: 10.1016/j.drugalcdep.2020.107837.

This study examined the prevalence and correlation of illicit buprenorphine use one year prior to incarceration and prior to participating in corrections-based drug treatment. Data was collected from incarcerated adults in Kentucky who voluntarily participated in a 6-month substance abuse treatment program. The participants in the program had a history of alcohol and/or illicit drug use, 60 days of good behavior, and were serving a minimum of 6 months. Participants also had to be Kentucky residents for at least 6 months prior to their incarceration. The participants were separated into two groups, those who used illicit buprenorphine prior to incarceration and those who did not.

- Of the 12,0007 participants in the study, 3,142 (26.2%) of participants reported illicit buprenorphine use prior to their incarceration and used it on average 6.5 months.
- The illicit buprenorphine group were found to be younger in age, white, and male.
- Living in rural and Appalachia Kentucky was a significant characteristic of illicit buprenorphine use.
- 21.8% of the sample reported illicit buprenorphine use 30 days prior to incarceration and using 14.3 days on average.
- Except for alcohol, rates of other illicit drug use were higher among the illicit buprenorphine group of participants when compared to non-illicit buprenorphine users.
- Participants that illicitly used buprenorphine reported a higher occurrence of substance use treatment prior to incarceration than those who did not use buprenorphine (77% vs 68.9%) and they considered drug treatment to be more important (79.4% vs 66.9%).
- Rates of hepatitis C (27.9% vs 13.2%) and B (1.6% vs .7%) were higher amongst the illicit buprenorphine users. HIV (.3%) was equal between both groups.
- **Research Conclusions:** Illicit buprenorphine use in this sample were associated with high risk behaviors, particularly those in rural and Appalachia Kentucky. These finding suggest increased medical care for inmates and an increase in community-based providers or outreach teams to help those in rural areas.

Smyth, B. P., Elmusharaf, K., & Cullen, W. (2018). Opioid substitution treatment and heroin dependent adolescents: Reductions in heroin use and treatment retention over twelve months. BMC Pediatrics, 18, 151. <https://doi.org/10.1186/s12887-018-1137-4>.

This study examined adolescents going through opioid substitution treatment (OST and took place in Dublin, Ireland at an outpatient multidisciplinary adolescent addiction treatment center. One hundred twenty individuals participated in the study; all were all heroin dependent and under 18.5 years old. The participants were given OST with either methadone or buprenorphine, counseling and in some cases family therapy, and two supervised urine screens per week. Participants who continually used heroin or resumed heroin after abstinence were given an increased dosage of medication.

- Heroin abstinence was 21% at 3 months and 46% at 12 months for the participants who stayed in the OST program.
- Heroin use declined significantly from baseline to 3 months and from 3 months to 12 months. Use of other drugs did not change significantly.

- Participants who had a previous psychiatric admission displayed low rates of abstinence. Abstinence was not significantly associated with a higher medication dose. Participants who used cocaine during month 12 were more likely to also use heroin.
- Unplanned exits from the program occurred in 25% of the participants by 120 days into the program.
- Participants who had no children, grew up in families with two parents, were in an intimate relationship with another heroin user and were abstinent from cocaine in pretreatment drug screen had significantly lower rates of unplanned exits from the program.
- **Research Conclusions:** Heroin-dependent adolescents achieved significant reductions in heroin use within 3 months after starting OST and continued to improve over the length of treatment. As with adults, dropouts remain a challenge for this age population. Cocaine use before and during treatment may be a negative prognostic factor.

Socias, M.E., Choi, J., Lake, S., Wood, E., Valleriani, J., Hayahi, K., Kerr, T., Milloy, M.J. (2020). Cannabis use is associated with reduced risk of exposure to fentanyl among people on opioid agonist therapy during a community-wide overdose crisis. Drug and Alcohol Dependence. <https://doi.org/10.1016/j.drugalcdep.2020.108420>.

This study observed the relationship between cannabis use and exposure to fentanyl among people on Opioid Agonist Treatment (OAT). Data was obtained from participants in two illicit drug use cohort studies in a downtown neighborhood of Vancouver Canada. All participants were on OAT for at least six months prior to study start and were given urine drug screens every six months from December 1, 2016 to November 30, 2018. 819 participants were observed in this study and had an average age of 48 years old, 57% male, 59.7% white, and 34.6% lived with HIV.

- Despite being on methadone or buprenorphine maintenance, 431 (53%) participants used fentanyl, 439 (53.6%) used cocaine, and 366 (44.7%) used methamphetamines.
- Fentanyl use was associated with moderate/severe depression, slow-release oral morphine-based OAT, homelessness, and recent opiate or stimulant use.
- Participants who tested positive for cannabis were 9% less likely to use fentanyl compared to those who tested negative for cannabis (47% vs 56%).
- Cannabis users were more likely to be men and use benzodiazepines.
- **Research Conclusions:** Findings appear to suggest that cannabis use is associated with a lower risk of being exposed to fentanyl among people on OAT. However, researchers unable to prove a causal relationship between cannabis use and reduced risk of fentanyl exposure and the study could not account for some unmeasurable variables that could have impacted the results such strain of cannabis, cannabis dose, cannabis use frequency, reason for cannabis use, and method of cannabis administration.

Solli, K. K., Latif, Z., Opheim, A., Krajci, P., Sharma-Haase, K., Benth, J. Š., Tanum, L., & Kunoe, N. (2018). Effectiveness, safety and feasibility of extended-release naltrexone for opioid dependence: A 9-month follow-up to a 3-month randomized trial. *Addiction*, 113(10), 1840–1849. <https://doi.org/10.1111/add.14278>.

This is a follow-up study of a previously published randomized clinical trial conducted in Norway that compared extended-release naltrexone (XR-NTX) to buprenorphine/naloxone (BP-NLX) over 3 months. At the conclusion of the trial, participants were offered their choice of study medication for an additional 9 months. While BP-NLX was available at no cost through opioid maintenance treatment programs, XR-NTX was available only through study participation, probably encouraging almost all participants to choose XR-NTX in the follow-up. The aim of this follow-up study was to compare differences in outcome between adults with opioid dependence continuing XR-NTX and those inducted on XR-NTX for a 9-month period, on measures of effectiveness, safety and feasibility. In this prospective cohort study, participants were either continuing XR-NTX, changed from BP-NLX to XR-NTX or re-included into the study and inducted on XR-NTX treatment. The study was conducted in five urban outpatient addiction clinics in Norway. Opioid-dependent adults continuing (N=54) or inducted on (N=63) XR-NTX. XR-NTX administered as intramuscular injections (380 mg) every fourth week. Data on retention, use of heroin and other illicit substances, opioid craving, treatment satisfaction, addiction-related problems and adverse events were reported every fourth week.

- Nine-month follow-up completion rates were 51.9% among participants continuing XR-NTX in the follow-up and 47.6% among those inducted on XR-NTX after beginning on BP-NLX.
- Opioid abstinence rates were, respectively, 53.7% and 44.4% (not significantly different). No significant group differences were found in use of heroin and other opioids.
- **Research Conclusions:** Opioid-dependent individuals elected to switch from buprenorphine/naltrexone treatment after 3 months to injectable naltrexone treatment for 9 months. Switching to injectable naltrexone after 3 months resulted in similar treatment completion and abstinence rates and similar adverse event profiles to individuals who had been on injectable naltrexone from the start of treatment.

Sordo, L., Barrio, G., Bravo, M. J., Indave, B. I., Degenhardt, L., Wiessing, L., Ferri, M., & Pastor-Barriuso, R. (2017). Mortality risk during and after opioid substitution treatment: Systematic review and meta-analysis of cohort studies. *BMJ*, 357(8103), Article j1550. <https://doi.org/10.1136/bmj.j1550>.

The study compares the risk for all cause and overdose mortality in people with opioid dependence during and after substitution treatment with methadone or buprenorphine and to characterize trends in risk of mortality after initiation and cessation of treatment. Prospective or retrospective cohort studies in people with opioid dependence that reported deaths from all causes or overdose during follow-up periods in and out of opioid substitution treatment with methadone or buprenorphine. There were 19 eligible cohorts, following 122,885 people treated with methadone over 1.3–13.9 years and 15,831 people treated with buprenorphine over 1.1–4.5 years.

- Pooled all-cause mortality rates were 11.3 and 36.1 per 1,000 person years in and out of methadone treatment (unadjusted out-to-in rate ratio 3.20, 95% confidence interval 2.65 to 3.86) and reduced to 4.3 and 9.5 in and out of buprenorphine treatment (2.20, 1.34 to 3.61). In pooled trend analysis, all-cause mortality dropped sharply over the first four

weeks of methadone treatment and decreased gradually two weeks after leaving treatment.

- All-cause mortality remained stable during induction and remaining time on buprenorphine treatment. Overdose mortality evolved similarly, with pooled overdose mortality rates of 2.6 and 12.7 per 1,000 person years in and out of methadone treatment (unadjusted out-to-in rate ratio 4.80, 2.90 to 7.96) and 1.4 and 4.6 in and out of buprenorphine treatment.
- **Research Conclusions:** Retention in methadone and buprenorphine treatment is associated with substantial reductions in the risk for all-cause and overdose mortality in people dependent on opioids. The induction phase onto methadone treatment and the time immediately after leaving treatment with both drugs are periods of particularly increased mortality risk, which should be dealt with by both public health and clinical strategies to mitigate such risk.

Sousa, J.L., Raja, P., Huskamp, H.A., Mehrotra, A., Busch, A.B., Barnett, M.L., & Uscher-Pines, L. (2022). Perspectives of patients receiving telemedicine services for opioid use disorder treatment: A qualitative analysis of user experiences. *Journal of Addiction Medicine*, 16(6), 702-708. Doi: 10.1097/ADM.0000000000001006.

This semi structured qualitative study attempted to understand patients experiences with using telemedicine to treat opioid use disorder. A total of 20 adults, who received 3-5 weeks of telemedicine treatment, were interviewed. Most of the patients lived in the south (65%), lived in an urban area (50%), identified as a woman (60%), were between 25-44 years of age (80%), worked full time (85%), had a history of in person opioid use disorder treatment with medication for opioid use disorder (80%), and did not have a history of telemedicine treatment (60%). The interview questions discussed patients experiences with telehealth and their perceived advantages and disadvantages of telehealth.

- Nearly all patients reported that they appreciated how fast they were able to initiate treatment with telehealth treatment. Most patients were able to be seen by a telehealth opioid use disorder provider within three days after expressing interest. However, one quarter of patients wished they could have been seen sooner due to readiness for behavior changes and transitioning between providers.
- Majority of patients that had experience with in-person treatment felt that they felt more respect, lack of judgement, and provider responsiveness to needs with telehealth providers than with in person providers.
- All patients described telehealth opioid use disorder treatment as straightforward, convenient, and user friendly.
- Three quarters of patients felt that telehealth treatment helped lessen social barriers to opioid use disorder treatment and allowed them to distance themselves from other opioid use disorder patients who could have negatively impacted their recovery.
- **Research Conclusions:** This qualitative study of patients who participated in telehealth opioid use disorder treatment showed that telemedicine provides unique benefits to treatment and provides greater self-satisfaction than what most have experienced from in person treatment. While most patients were able to start telehealth opioid use disorder

treatment within three days, patients were still looking for faster access to treatment to meet their immediate treatment needs.

Springer, S. A., Di Paola, A., Azar, M. M., Barbour, R., Biondi, B. E., Desabrais, M., Lincoln, T., Skiest, D. J., & Altice, F. L. (2018). Extended-release naltrexone improves viral suppression among incarcerated persons living with HIV with opioid use disorders transitioning to the community: Results of a double-blind, placebo-controlled randomized trial. *Journal of Acquired Immune Deficiency Syndromes*, 78(1), 43–53. <https://doi.org/10.1097/QAI.0000000000001634>

This first-ever study of its kind examined whether inmates released on injectable naltrexone were more likely to maintain or improve their HIV viral load suppression. Ninety-three participants were randomized 2:1 to receive 6 monthly injections or placebo starting at release and observed for 6 months each between 2010 and 2016.

- A greater proportion of people who received the extended-release naltrexone ended up getting HIV treatment as well.
- The injectable naltrexone group was more likely than the placebo group to improve viral suppression (VS) (30.3% vs. 18.5%) and maintain VS (30.3% vs. 27.3%), and less likely to lose VS (7.6% vs. 33.3%) by 6 months.
- **Research Conclusions:** Injectable naltrexone improves or maintains VS after release to the community for incarcerated people living with HIV with OUD.

Stone, A.C., Carroll, J.J., Rick, J.D., Green, T.C. (2020). One year of methadone maintenance treatment in a fentanyl endemic area: Safety, repeated exposure, retention, and remission. *Journal of Substance Abuse Treatment*. <https://doi.org/10.1016/j.jsat.2020.108031>

This study assessed treatment outcomes of a 12-month methadone maintenance treatment program in a fentanyl endemic area. 151 newly admitted patients from a Rhode Island methadone maintenance treatment program were observed over 12 months to measure their treatment retention, sustained remission, return to use, methadone dosage, number of days to achieve remission, and mortality.

- 80% (n=121) of patients tested positive for fentanyl at intake
- 75% of patients achieved remission within the 12-month study period
- 53% of patients who were exposed to fentanyl and 47% of patients who were not exposed to fentanyl completed the 12-month treatment program
- 99% of patients who remained in treatment for 12 months achieved remission.
- 4 patients died after leaving treatment prematurely
- **Research Conclusions:** The findings of this study suggest that methadone management treatment is effective in treating patients that have been exposed to fentanyl and is protective against death to exposed patients while in therapy.

Stone, J., Degenhardt, L., Grebely, J., Larney, S., Altice, F.L., Smyrnov, P., Rahimi-Movaghar, A., Alavi, M., Young, A.M., Havens, J.R., Miller, W.C., Hickman, M., Vickerman, P. (2021). Modelling the intervention effect of opioid agonist treatment on

multiple mortality outcomes in people who inject drugs: a three-setting analysis. The Lancet. doi:[https://doi.org/10.1016/S2215-0366\(20\)30538-1](https://doi.org/10.1016/S2215-0366(20)30538-1).

A mathematical model was created to evaluate how opioid agonist treatments such as methadone and buprenorphine could reduce drug related deaths if they were more widely used and were for a longer period. Kyiv Ukraine, Tehran Iran, and Perry County in Kentucky were chosen for this model because of their differences in mortality risk in the community, HIV prevalence, HIV treatment, and proportions of people who inject drugs and use opioid agonist treatment in the community and in prison. The created model considered how many drug related deaths could be prevented if there was no increase in use of opioid agonist treatment, opioid agonist treatment was scaled up by 40% of people who inject drugs in the community, opioid agonist treatment was scaled up by 40% of people who inject drugs and use opioid agonist treatment for 2 years, and opioid agonist treatment was scaled up by 40% of people who inject drugs and are incarcerated.

- Scaling up use of opioid agonist treatment to 40% could avert between 12-24% of all drug related deaths, including 13-19% of overdose deaths.
- Increasing the amount of time individuals use opioid agonist treatment and providing prison based opioid agonist treatment would avert 27-51% of drug related deaths.
- Tehran and Kyiv would experience the greatest reductions in HIV mortality (48-68% deaths averted)
- Reduction in overdose mortality would be experienced most in Perry County Kentucky (63% deaths averted)
- **Research Conclusions:** The findings presented from this mathematical model provide evidence that increasing the amount time and access to opioid agonist treatment in the community and prison system can reduce drug related deaths in distinctly different geographic settings.

Suarez, E.A., Bateman, B.T., Straub, L., Hernandez, S., Jones, H.E., Gray, K.J., Connery, H.S., Davis, J.M., Lester, B., Terplan, M., Zhu, Y., Vine, S.M., Mogun, H., & Huybrechts, K.F. (2024). First Trimester Use of Buprenorphine or Methadone and the Risk of Congenital. Journal of Internal Medicine. Doi:[10.1001/jamainternmed.2023.6986](https://doi.org/10.1001/jamainternmed.2023.6986).

This cohort study compared the risk of congenital malformations in the first trimester when exposed to buprenorphine and methadone. Study data was based upon Medicaid beneficiaries in the United States from 2000 to 2018 which included 13,360 pregnancies in the first trimester. Of the 13,360 pregnancies, 9,514 were exposed to buprenorphine and 3,846 were exposed to methadone. Buprenorphine and methadone treatment groups were likely to be White (88.6% vs 77.4%), have been treated with medications for opioid use disorder before pregnancy (76.9% vs 78.8%), have an average age of 28 years, live in a metropolitan area (79.8% vs 91.9%).

- The risk of any major congenital malformation was 50.9 per 1000 pregnancies in the buprenorphine group and 60.6 per 1000 pregnancies in the methadone group.
- The risk of cardiac malformation, ventricular septal defect, oral clefts, and clubfoot for infants were lower amongst buprenorphine pregnancies compared to methadone pregnancies.

- **Research Conclusions:** In this cohort study of pregnancies exposed to medications for opioid disorder during the first trimester, buprenorphine was found to produce a lower risk of malformations in infancy compared to methadone.

Suarez, E.A., Huybrechts, K.F., Straub, L., Hernandez-Diaz, S., Jones, H.E., Connery, H.S., Davis, J.M., Gray, K.J., Lester, B., Terplan, M., Mougoun, H., Bateman, B.T. (2022). Buprenorphine versus Methadone for Opioid Use Disorder in Pregnancy. The New England Journal of Medicine. 387(22), 2033-2044. doi: 10.1056/NEJMoa22-3318.

This cohort study of pregnant women investigated the neonatal and maternal outcomes comparing the use of buprenorphine with methadone during pregnancy. The study investigated 2,548,372 pregnancies that occurred in the United States between 2000 and 2018. 10,704 women were treated with buprenorphine and 4,387 women were treated with methadone in early pregnancy (first 19 weeks of pregnancy). In late pregnancy, 11,272 pregnant women were treated with buprenorphine and 5,506 pregnant women were treated with methadone during late pregnancy (20 weeks through the day before delivery). 9,976 pregnant women received buprenorphine and 4,587 pregnant women received methadone within 30 days of delivery.

- Neonatal abstinence syndrome occurred in 52% of infants who were exposed to buprenorphine in 30 days before delivery compared to 69.2% who were exposed to methadone.
- Preterm birth occurred in 14.4% of infants who were exposed to buprenorphine and in 24.9% infants who were exposed to methadone in early pregnancy.
- Delivery by cesarian section occurred in 33.6% of pregnant women who received buprenorphine and 33.1% of pregnant women who received methadone during early pregnancy.
- Serious maternal complications were observed in 3.3% of pregnant women exposed to buprenorphine and 3.5% of pregnant women exposed to methadone in early pregnancy.
- The above results were consistent during late pregnancy as well.
- **Research Conclusions:** Results of the study found that buprenorphine is associated with a lower risk of neonatal outcomes compared to methadone during early and late pregnancy. While examining adverse maternal outcomes, buprenorphine and methadone provide similar risks.

Sugarman, O.K., Bachhuber, M.A., Wennerstrom, A., Bruno, T., Springgate, B.F. (2020) Interventions for incarcerated adults with opioid use disorder in the United States: A systematic review with a focus on social determinants of health. Plos One. 15(1). <https://doi.org/10.1371/journal.pone.0227968>.

This systemic review of existing peer reviewed literature described interventions for opioid use disorder used by the criminal justice system, social determinants of health and supports to overcome them, and commonalities between interventions with significant outcomes. Literature used in this review was published within the past 5 years, conducted in the United States, were focused on intervention for opioid use disorder, and had adults 19 years or older with involvement in the criminal justice system as study participants. Of the 13 articles

reviewed, 6 interventions occurred in prisons, 4 in jails, 2 in transitional clinics, and 1 in a civil commitment facility.

- The effectiveness and long-term impact of methadone, buprenorphine, and extended release naltrexone treatments on non-fatal overdose mortality, post release opioid use, and seeking and maintaining treatment post incarceration was associated with early initiation during incarceration and consistent treatment during incarceration.
- Scheduling assistance, transportation, financial assistance for first treatment appointment, and resources for employment and housing post incarceration were the most beneficial social determinants related supports.
- **Research Conclusions:** The findings of this review suggest that medication treatments such as buprenorphine, methadone, and extended release naltrexone should be administered and maintained during incarceration for the best results in post release outcomes. To address social determinants of health providing more individual level supports can improve the continuation of treatment in the community post release.

Sullivan, M., Bisaga, A., Pavlicova, M., Carpenter, K., Choi, J., Mishlen, K. ...& Nunes, E.(2018). A Randomized Trial Comparing Extended-Release Injectable Suspension and Oral Naltrexone, Both Combined with Behavioral Therapy, for the Treatment of Opioid Use Disorder, *American journal of Psychiatry*, 176 (2),
<https://doi.org/10.1176/appi.ajp.2018.17070732>

Swanson, J. (2016). Mental illness, release from prison, and social context. *Journal of the American Medical Association*, 316(17), 1771–1772.
<https://doi.org/10.1001/jama.2016.12434>

This study analyzed data on characteristics, treatment patterns, and criminal offending outcomes in the population of released prisoners in Sweden (N=22,275) between 2005 and 2010 with follow-up through 2013.

- Swanson speculates that social conditions have influence on the benefit that released prisoners with psychiatric disorders receive from using medications—conditions including income equality and social safety networks.
- Rates of violent reoffending were significantly lower during periods when antipsychotics, psychostimulants, and drugs for addiction were dispensed, compared with periods in which they were not.
- Swanson argues post-incarceration psychiatric interventions in the United States have been unsuccessful because they assume that criminal behavior among people with mental illness is simply a consequence of not receiving treatment, and individual-level specialized treatment continues to lead to poor reentry outcomes for employment and housing.
- **Research Conclusions:** In Sweden, the social environment necessary for successful rehabilitation after release from prison is already established in society, and when people with mental illnesses commit violent crimes, perhaps the underlying cause is

more often primarily related to brain disorders— treatable with medication—rather than social-environmental factors.

Tanum, L., Solli, K. K., Latif, Z., Benth, J. Š., Opheim, A., Sharma-Haase, K., Krajci, P., & Kunøe, N. (2017). Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: A randomized clinical noninferiority trial. *JAMA Psychiatry*, 74(12), 1197–1205.

<https://doi.org/10.1001/jamapsychiatry.2017.3206>.

A 12-week, multicenter, outpatient, open-label randomized clinical trial was conducted at 5 urban addiction clinics in Norway between November 1, 2012, and December 23, 2015; the last follow-up was performed on October 23, 2015. A total of 232 adult opioid-dependent (per DSM-IV criteria) individuals were recruited from outpatient addiction clinics and detoxification units and assessed for eligibility. Randomization to either daily oral flexible dose buprenorphine/naloxone, 4 to 24 mg/d, or extended release naltrexone hydrochloride, 380 mg, administered intramuscularly every fourth week for 12 weeks.

- Retention in the extended-release naltrexone group was noninferior to the buprenorphine/naloxone group (difference, -0.1 ; with 95% CI, -0.2 to 0.1 ; $P = .04$), with mean (SD) time of 69.3 (25.9) and 63.7 (29.9) days, correspondingly ($P = .33$, log-rank test). Treatment with extended release naltrexone showed noninferiority to buprenorphine/naloxone on group proportion of total number of opioid-negative urine drug tests (mean [SD], 0.9 [0.3] and 0.8 [0.4], respectively, difference, 0.1 with 95% CI, -0.04 to 0.2 ; $P < .001$) and use of heroin (mean difference, -3.2 with 95% CI, -4.9 to -1.5 ; $P < .001$) and other illicit opioids (mean difference, -2.7 with 95% CI, -4.6 to -0.9 ; $P < .001$).
- Superiority analysis showed significantly lower use of heroin and other illicit opioids in the extended-release naltrexone group. No significant differences were found between the treatment groups regarding most other illicit substance use.
- **Research Conclusions:** Extended-release naltrexone was as effective as buprenorphine/naloxone in maintaining short term abstinence from heroin and other illicit substances and should be considered as a treatment option for opioid-dependent individuals.

Terasaki, D., Smith, C., & Calcaterra, S.L. (2019). Transitioning Hospitalized Patients with Opioid Use Disorder from Methadone to Buprenorphine without a Period of Opioid Abstinence Using a Micro dosing Protocol. *Pharmacotherapy: The journal of Human Pharmacology and Drug Therapy*, 39(10), 1023-1029.

<https://doi.org/10.1002/phar.2313>.

This case study of sought to demonstrate how a micro dosing protocol to transition patients from methadone to buprenorphine can be effectively implemented in a U.S hospital. In January of 2019 three hospitalized adults with opioid use disorder were given low dose buprenorphine while receiving a full dose of methadone for one week. Throughout the week, the dose of buprenorphine was increased based upon clinical judgement. On the last day of the micro dosing, methadone was abruptly discontinued.

- All three patients were successfully transition from methadone to buprenorphine with minimal symptoms of opioid withdrawal.

- One patient relapsed and was lost to treatment, while the other two patients remained.
- **Research Conclusions:** Research findings show that micro dosing of buprenorphine can effectively be used to transition patients from methadone to buprenorphine in a hospital setting. However additional research may be needed to learn more about the long-term treatment retention when successfully transitioned.

Thomas, C. P., Fullerton, C. A., Kim, M., Montejano, L., Lyman, D. R., Dougherty, R. H., Daniels, A. S., Ghose, S. S., & Delphin-Rittmon, M. E. (2014). Medication-assisted treatment with buprenorphine: Assessing the evidence. *Psychiatric Services*, 65(2), 158–170. <https://doi.org/10.1176/appi.ps.201300256>.

This review includes meta-analyses, systematic reviews, and individual studies of buprenorphine maintenance treatment (BMT) from 1995 through 2012. Databases surveyed were PubMed, PsycINFO, Applied Social Sciences Index and Abstracts, Sociological Abstracts, Social Services Abstracts, and Published International Literature on Traumatic Stress. Researchers chose from three levels of evidence (high, moderate, and low) based on benchmarks for the number of studies and quality of their methodology.

- Sixteen adequately designed randomized controlled trials of BMT indicated a high level of evidence for its positive impact on treatment retention and illicit opioid use.
- When the medication was dosed adequately, both BMT and methadone maintenance treatment showed similar reduction in illicit opioid use, but BMT was associated with less risk of adverse events. However, the review suggests better treatment retention with MMT.
- BMT was associated with improved maternal and fetal outcomes in pregnancy, compared with no medication-assisted treatment.
- Rates of neonatal abstinence syndrome were similar for mothers treated with BMT and MMT during pregnancy, but symptoms were less severe for infants whose mothers were treated with BMT.
- **Research Conclusions:** BMT is associated with improved outcomes compared with placebo for individuals and pregnant women with opioid use disorders.

Towers, C., Katz, E., Weitz, B., & Visconti, K. (2019) Use of naltrexone in treating opioid use disorder in pregnancy. *American Journal of Obstetrics & Gynecology*. Doi:<https://doi.org/10.1016/j.ajog.2019.07.037>.

This study evaluated the obstetric and newborn outcomes and the maternal/fetal effects that the use of naltrexone can cause in pregnant women with opioid use disorder. A total of 230 participants were selected in the study and were placed in a group that took naltrexone (n=121) and a group that took methadone or buprenorphine (n=109) to compare outcomes. There were no significant demographic differences amongst the participants.

- The rate of neonatal abstinence syndrome in neonates at >34 weeks gestation was significantly lower in the naltrexone medication treatment group (8.4% vs 75.2%).
- 87 of the 121 patients who used naltrexone up to delivery, had no neonates experience symptoms of neonatal abstinence syndrome.

- No cases of spontaneous abortion or stillbirth occurred in either group.
- No maternal relapses occurred in the naltrexone participant group.
- In 64 participants in the naltrexone group at >24 weeks gestation, no changes were seen in the fetal heart monitor with drug initiation
- The incidence of birth anomalies was no different between the two groups
- **Research Conclusions:** Study data demonstrates that pregnant women who choose to completely detoxify off opioid drugs during gestation have a viable treatment option in naltrexone. The drug is well tolerated by both mother and fetus, newborn infants do not experience symptoms of neonatal abstinence syndrome if naltrexone is maintained to delivery.

Trivedi, M.H., Walker, R., Ling, W., Cruz, A. D., Sharma, G., Carmody, T., Ghitza, U.E., Wahle, A., Kim, M., Shores-Wilson, K., Sparenborg, S., Coffin, P., Schmitz, J., Wiest, K., Bart, G., Sonne, S.C., Wakhlu, S., Rush, A.J., Nunes, E.V., & Shoptaw, S. Bupropion and Naltrexone in Methamphetamine Use Disorder. *The New England Journal of Medicine*. 384. 140-153. doi: 10.1056/NEJMoa2020214.

This randomized double-blind trial evaluated the efficacy and safety of extended-release injectable naltrexone (380mg every 3 weeks) plus oral extended-release bupropion (450mg per day) in adults with moderate or severe methamphetamine use disorder. The study was conducted at eight sites from May 23, 2017, to July 25, 2019, in two six-week stages. During the first six weeks participants were randomly selected to receive naltrexone and bupropion (n=109) or a placebo (n=294). During the final six weeks, participants in the placebo group who did not have at least three negative urine screens for methamphetamines were rerandomized to receive the intervention medication (n=114) or the placebo (n=111). Participants eligible for the study were 18–65-year old's who wanted to quit or reduce methamphetamine use. The study sample was 68.7% male, 71.2% white, 38.7% employed, and an average age of 41 years.

- During the first stage, adherence to naltrexone-bupropion was 75.1% and 83.5% in the placebo group. During stage two, adherence to naltrexone-bupropion was 77.4% and 82.0% in the placebo group.
- At the end of stage one 16.5% of participants in the naltrexone-bupropion group and 3.4% of participants from the placebo group had three or more negative urine screens for methamphetamine. At the end of stage two, 11.4% of the naltrexone-bupropion participants and 1.8% of the placebo group had three or more negative urine screens.
- Adverse events occurred in 8 participants in the naltrexone-bupropion group and 9 in the placebo group.
- **Research Conclusions:** Study findings show that patients taking the placebo had higher adherence rates than patients taking the naltrexone and bupropion. However, Naltrexone and bupropion did outperform the placebo group in negative urine screens throughout the study.

Tsui, J.I., Leroux, B.G., Radick, A.C., Schramm, Z.A., Blalock, K., Labelle, C., Heerema, M., Klein, J.W., Merrill, J.O., Saxon, A.J., Samet, J.H., & Kim, T.W. (2021). Video directly observed therapy for patients receiving office-based buprenorphine- A pilot randomized controlled trial. *Drug and Alcohol Dependence*. 227. <https://doi.org/10.1016/j.drugalcdep.2021.108917>.

This pilot study evaluated treatment outcomes from a video application on a smartphone for directly observed therapy for patients initiating buprenorphine. Between January 2019 and May 2020, 78 adult patients with opioid use disorder were randomly assigned to receive directly observed therapy or standard care at two clinics in Seattle Washington and Boston Massachusetts. Participant demographics include: 80% unemployed, 40% homeless, 37% nonwhite, and 26% women. The standard care group received take home buprenorphine with clinic visits at their healthcare providers discretion. The directly observed therapy group submitted one video a day of themselves taking their buprenorphine that was viewed by their health care professional. Reminders were sent to patients if they forgot to submit their video. The directly observed therapy group also went into the clinic at the discretion of their health care provider. Outcomes were observed through weekly urine drug tests for illicit opioids and treatment engagement by week 12 of the study.

- Directly observed therapy participants uploaded videos 31% of the time by week 12.
- The average percentage of weekly negative opioid urine drug tests were 50% for directly observed therapy participants and 64% for the standard care participants.
- At week 12, 69% of directly observed therapy participants were still engaged in treatment vs 82% in the standard care group.
- There was no significant difference in the results of drug screens and patient participation from week 12 to week 24.
- **Research Conclusions:** Study findings show that directly observed therapy does not improve illicit opioid use and treatment engagement. Study outcomes were greatly limited by the low usage rate of the directly observed therapy video application.

Tsui, J.I., Mayfield, J., Speaker, E.C., Yakup, S., Ries, R., Funai,...& Merrill J.O. (2020). Association between methamphetamine use and retention among patients with opioid use disorders treated with buprenorphine. *Journal of Substance Abuse Treatment*, 109, 80-85, doi:<https://doi.org/10.1016/j.jsat.2019.10.005>.

This study examined the relationship between patients who use methamphetamine and their retention in treatment for opioid use. Data was collected from 799 patients who received buprenorphine treatment at the Washington State Medication Assisted Treatment-Prescription Drug and Opioid Addiction Clinic from November 2015-April 2018. The patients were asked about their substance use in the past 30 days at baseline, 6 months, and at program discharge.

- Of the 799 patients used in the sample, 237 (30%) patients reported methamphetamine use in the past 30 days.
- 156 (66%) patients reported 1-10 days of methamphetamine use, 46 (19%) reported 11-20 days of methamphetamine use, and 35 (15%) reported 21-30 days of methamphetamine use.

- Patients who used methamphetamine were twice as likely to not complete buprenorphine treatment compared to patients that did not take methamphetamine.
- The use of methamphetamine use at baseline was reduced by 15% at discharge among the patients who remained in treatment.
- **Research Conclusions:** Patients who use methamphetamines are less likely to retain buprenorphine treatment compared to patients who do not. Though patients who remain in treatment and continue to use methamphetamine are likely to decrease their methamphetamine use over time.

Vail, W., Faro, E., Watnick, D., Giftos, J., and Fox, A.D. (2021). Does incarceration influence patients' goals for opioid use disorder treatment? A qualitative study of buprenorphine treatment in jail. Drug Alcohol Dependence, 22. <https://doi.org/10.1016/j.drugalcdep.2021>.

This study was based upon semi structured interviews of incarcerated individuals in order to understand their view of buprenorphine treatment and to identify factors that led to the continuation of treatment post release. From November 2018 through May 2019, study authors interviewed 22 incarcerated men who were within one year of their release and were currently receiving buprenorphine treatment in a New York City jail system that provided initiation or continuation of buprenorphine treatment for individuals with opioid use disorder. Interviews were conducted in a private space in the jail medical clinic where correctional officers were able to have visual contact of individuals but could not hear the individuals' responses to their interview. The interview covered history of drug use, history of substance use disorder treatment, experiences, attitudes, and motivations for buprenorphine treatment in jail, past barriers to treatment, and expectations regarding treatment continuation post release.

Study participants were all men with a mean age of 44 years. 59% were Hispanic, 81% had Medicaid insurance, 68% had a high school diploma or equivalency, on average had been arrested 13 times, and 81% had used heroin as their primary substance.

- 14 incarcerated individuals planned on continuing to take buprenorphine regularly, engage in medical care, and abstain from opioid use, 7 incarcerated individuals planned to take buprenorphine on an as needed basis, and one incarcerated individual had intention to not continue buprenorphine treatment upon release.
- Incarcerated individuals who planned to continue buprenorphine treatment upon release often identified strong social supports and structured programs to address substance use post release as helpful factors to continue treatment and abstain from substance use. Additionally, these individuals viewed substance use as a source of shame which motivated them to seek treatment.
- Incarcerated individuals who planned to take buprenorphine treatment as needed predicted they would buy buprenorphine from the streets upon release, intended to avoid a return to the criminal justice system, had a desire to decrease but not stop illicit opioid use, and would self-manage symptoms of withdrawal with buprenorphine. This group of individuals tended to have a high number of prior arrests and had participated in gangs.

- The one individual who planned to not continue buprenorphine treatment, planned to taper off buprenorphine immediately upon release so that he could return to using heroin. This individual primarily used methamphetamine but reported to jail staff that he primarily used heroin, to receive buprenorphine from the doctors at the jail to get a euphoric effect from the medication.
- Common themes across all participants included use of illicit buprenorphine use due to social barriers to access opioid use disorder treatment such as unstable housing and the parole system infractions which often were counter productive towards opioid use disorder treatment goals.
- **Research Conclusions:** The structured interviews amongst incarcerated male individuals in a New York city jail system identified three attitudes about buprenorphine treatment which included a desire to continue treatment post release, to take buprenorphine on an as needed basis, and to discontinue buprenorphine treatment entirely. Despite having differing plans on buprenorphine treatment post release, individuals cited having psychosocial issues and the probation system itself as barriers that effected their access to treatment.

Varisco, T., Shen, C., & Thornton, D. (2020) Chronic prescription opioid use predicts stabilization on buprenorphine for the treatment of opioid use disorder. Journal of Substance Abuse Treatment. <https://doi.org/10.1016/j.jsat.2020.10873>

This study examined the odds of successful stabilization of buprenorphine among patients with prescription opioid use compared to those with no prescription opioid use prior to treatment. Patients with prior prescription opioid use were further divided into groups of chronic prescription opioid use and acute prescription opioid use. Chronic prescription opioid use was defined as having been prescribed opioids for a period of 90 out of 120 days, ending no sooner than 90 days prior to the start of treatment. Acute prescription opioid use was defined as having an opioid prescription within 90 days prior to the start of treatment. To be considered stabilized on buprenorphine patients had to fill two prescriptions with no more than a 6-day gap in therapy.

- Of the 6756 patients eligible to participate, 44.1% of the patients used prescription opioids 90 days prior treatment. Of the prescription opioid users, 62% of the sample met criteria for acute prescription opioid use and 37.8% for chronic opioid use.
- Patients with prescription opioid use prior to buprenorphine treatment were more likely to be older and have insurance compared to patients with no prescription opioid use.
- Patients of both groups were significantly more likely to be successfully stabilized with pharmacotherapy.
- Patients with chronic prescription opioid use were significantly more likely than those with acute prescription opioid use to be successfully stabilized.
- **Research Conclusions:** Findings suggest that patients with chronic prescription opioid use may be more likely than nonprescription opioid users to be successfully stabilized on buprenorphine with pharmacotherapy. Extending access to buprenorphine may significantly impact opioid related morbidity and mortality.

Varshneya, N.B., Thakrar, A.P., Hobelmann, J.G., Dunn, K.E., & Huhn, A.S. (2021). Evidence of Buprenorphine- precipitated Withdrawal in Persons Who Use Fentanyl. Journal of Addiction Medicine. doi: 10.1097/ADM.0000000000000922

This study investigated if buprenorphine causes withdrawal symptoms among people who use fentanyl. 1,679 opioid dependent patients who were entering treatment from one of the 49 study approved treatment facilities were given a self-report survey. The survey asked patients to report on their use of fentanyl before treatment, whether they used buprenorphine or methadone after using fentanyl, length of time between using buprenorphine or methadone after fentanyl use, and whether buprenorphine or methadone alleviated or worsened withdrawal symptoms. Study participants were primarily male (70.6%), White (80.4%), mean age of 30.77 years, and 43.9% tested positive for fentanyl at treatment admission.

- 36.5% of participants used buprenorphine within 24 hours after fentanyl use experienced severe withdrawal symptoms compared to 15% of participants who used methadone.
- 38.4% of participants reported that buprenorphine alleviated withdrawal symptoms compared to 44.3% who used methadone.
- Compared to methadone, using buprenorphine within 24 hours and between 24-48 hours after fentanyl use significantly increased the odds of a participants experiencing severe withdrawal symptoms.
- **Research Conclusions:** Study findings show that buprenorphine use within 48 hours of fentanyl use is likely to cause severe withdrawal symptoms. Methadone causes less severe withdrawal symptoms and should be considered as a medication after fentanyl use.

Velasquez, M. Flannery, M., Badolato, R., Vittitow, A., McDonald, R., Tofighi, B.,...& Lee, J. (2019). Percetipns of extended- release naltrexone, methadone, and buprenorphine treatments following release from jail. Addiction Science Clinical Practice. 14(37), doi:10.1186/s13722-019-0166-0.

This study conducted semi structured, face to face, audio taped interviews of 33 former inmates with opioid use disorder whom were recruited from the Extended-Release Naltrexone treatment at a jail reentry study (n=29) and the Bellevue Hospital Center primary care addiction medicine clinic in New York City (n=4). The goal of the interviews was to determine the participants attitudes towards extended release naltrexone, methadone, and buprenorphine treatments, and perceived barriers and facilitators of clinical outcomes during jail to community reentry. 28 of the 33 participants identified themselves as male. In the sample, 15 participants were African American, 12 Hispanic, 4 Caucasian, and 2 were classified as other. 11 participants used extended releases naltrexone, 9 used methadone, 4 used buprenorphine, and 9 used no medication.

- Following release from jail, half the patients receiving extended release naltrexone admitted to using a small amount of heroin within the first 4 weeks of release to see if the medication truly worked or they forgot that they were taking the medication. All participants who used heroin noted the extended releases naltrexone's effectiveness in preventing a high.

- Most participants agreed that extended release naltrexone lessened and nullified cravings, and most were generally satisfied.
- Initial perceptions of methadone were viewed negatively due to past treatment experiences and misinformation.
- Many participants described methadone treatment as intrusive and interfered with other responsibilities. Most participants did not adhere to methadone treatment.
- All the buprenorphine users were satisfied with it as a treatment and intended to continue treatment with it.
- Access to OBOT programs upon community reentry was difficult for some participants due to long waitlists, lack of insurance coverage, and poor clinical care after their intake in their treatment clinic.
- Participants expressed having their basic needs met first upon reentry before addressing treatment needs was most important in their recovery. Homelessness and unemployment were the primary barrier to maintain abstinence and adhering to prescribed medication.
- **Research Conclusions:** Extended release naltrexone treatment during jail to community reentry was viewed to be the most useful post-release relapse prevention option. Other agonist treatments were beneficial but had some drawbacks. Developing better information delivery of and access to medications to treat opioid use disorder in jails with post incarceration treatment plans in the community is crucial to post-release success.

Wakeman, S.E., Larochelle, M.R., Ameli, O., Chaisson, C.E., McPheeters, J.T., Crown, W.H...& Sanghavi, D.M. (2020). Comparative Effectiveness of Different Treatment Pathways for Opioid Use Disorder. JAMA. 3(2), doi:10.1001/jamanetworkopen.2019.20622.

This retrospective study evaluated the effectiveness of pharmacological and nonpharmacological treatment options for opioid use disorder. Data was obtained from medical, behavioral health, and pharmacy claims on individuals 16 years or older with opioid use disorder and commercial or Medicare Advantage coverage from October 3, 2014 to December 31, 2017. Cohorts were created based upon the type of treatment that was used: no treatment, inpatient detoxification or residential services, intensive behavioral health, buprenorphine or methadone, naltrexone, and non-intensive behavioral health.

- A total of 40,885 individuals were identified for the study. The average demographics of the study were 47 years old, 54.2% male, and 74.2% white.
- The most common form of treatment was non-intensive behavioral health (24,258 individuals [59.3%]), followed by inpatient detoxification or residential services (6,455[15.8%]), and buprenorphine or methadone (963[2.4%]).
- Not receiving any treatment (2,116[5.2%]) was more common than naltrexone 9,963[2.4%]) and intensive behavioral health (1,970[4.8%]).

- During the 3-month follow up, 707 individuals (1.7%) experienced an overdose, and 773 individuals (1.9%) had a serious opioid related acute care use episode.
- During the 3 and 12 month-follow-ups, buprenorphine or methadone was associated with a reduced risk of overdose.
- Apart from buprenorphine or methadone, all treatment groups were more likely to have a posttreatment admission to inpatient detoxification.
- At the end of 12 months, 1198(3.6%) individuals who did not use any medication had overdosed, 105 (6.4%) individuals who used buprenorphine or methadone for 1-30 days had overdosed, 101 (3.4%) individuals who used buprenorphine for 31-180 days had overdosed, and 28 (1.1%) individuals who used buprenorphine or methadone for more than 180 days had an overdosed.
- **Research Conclusions:** Treatment with buprenorphine or methadone was associated with the lowest chances on overdose and need for inpatient treatment compared to nonpharmacological treatment. Despite the effectiveness of buprenorphine or methadone, they were not the most used treatment option. Greater access to buprenorphine or methadone treatment may need to be provided.

Walker, R., Logan, T. K., Chipley, Q. T., & Miller, J. (2018). Characteristics and experiences of buprenorphine-naloxone use among polysubstance users. *The American Journal of Drug and Alcohol Abuse*, 44(6), 595–603.
<https://doi.org/10.1080/00952990.2018.1461876>.

This study examined the use, characteristics of users, and experiences of buprenorphine/naloxone (bup-nx) users among polysubstance users entering drug-free recovery programs. This study used secondary data on 896 opioid or opiate user individuals (53.4% male) collected by drug-free, self-help-based residential recovery centers during intake. Three groups of opioid users were created including one group with no bup-nx use, one with lifetime but no recent bup-nx use, and one with recent (past 6 month) use.

- Most (93 to 97%) did not receive their bup-nx solely through prescriptions.
- One-quarter of users said bup-nx helped them with their substance use while 75% of bup-nx users reported that it either had no effect (36.5%) or a negative effect on their drug problems (39%).
- Two-fifths of the recent bup-nx use group indicated bup-nx made their drug use worse compared to about one-third of the lifetime bup-nx use group.
- Of those who obtained their bup-nx solely through a prescription, over 90% reported relief from withdrawal.
- Over 80% of those who obtained bup-nx through illicit means reported using bup-nx until their preferred drug could be obtained and used it for its euphoriant effect.
- 10% of the recent bup-nx use group reported overdosing with bup-nx and other drugs.
- About 27.0% reported cost as a reason for stopping the use of bup-nx.
- More than 80% reported diverting bup-nx.

- **Research Conclusions:** This study suggests an emerging population of individuals with bup-nx use who are decidedly polysubstance users with extensive drug use histories—not just a clear opioid dependence pattern. Consistent with this pattern, more of the recent bup-nx users reported taking other drugs even while on bup-nx in order to get high. One other interpretation of this study’s findings might be that opioid users with extensive polysubstance use might have more severe substance use disorder (SUD) symptoms, calling for a different level of interventions, pointing toward a need for more services than just medical harm reduction services.

Wartko, P.D., Bobb, J.F., Bourdreau, D.M., Matthews, A.G., McCormack, J., Lee, A.K., Qiu, H., Yu, O., Hyun, N., Idu, A.E., Campbell, C.I., Saxon, A.J., Liu, D.S., Altschuler, A., Samet, J.H., Labell, C.T., Zare-Mehrjerdi, M., Stotts, A.L., Braciszewski, J.M., Murphy, M.T... Burganowski, R.P. (2023). Nurse Care Management for Opioid Use Disorder Treatment: The PROUD Cluster Randomized Clinical Trial. JAMA Internal Medicine. doi:10.1001/jamainternmed.2023.5701.

This randomized clinical trial study investigated whether the implementation of a Massachusetts model of providing nurse management care for opioid use disorder in primary care practices increases opioid use disorder treatment with buprenorphine or extended-release injectable naltrexone. The model used for this study was the Primary Care Opioid Use Disorders (PROUD) Treatment model which was conducted in health care systems in New York, Florida, Michigan, Texas, and Washington. The PROUD Treatment model included salary for a full-time opioid use disorder nurse care manager, training and technical assistance for nurse care managers, and three or more primary care clinicians who agreed to prescribe buprenorphine. Two primary care systems within the same health network of each state were randomly chosen to follow the PROUD Treatment model or to provide usual care. Patients were included in the study if they were between 16 to 90 years of age and visited the study clinic for up to 3 years before study randomization or 2 years after randomization. 130,623 patients were identified for the study. PROUD Treatment model site participants were mostly female (59.7%) and an average age of 48.6 years, while the usual care sites were mostly female (63%) and had an average age of 47.2 years.

- PROUD Treatment clinics provided 8.2 more patient years of opioid use disorder treatment per 10,000 primary care patients compared to the usual care clinics.
- Two of the study primary care sites and new patients or newly treated patients after randomization saw the most benefits from the PROUD Treatment model.
- Successful implementation of the PROUD Treatment model included broad commitment from health care system leaders and primary care teams, full financial coverage for opioid use disorder treatment, and straightforward pathways for patients to access nurse care managers.
- The uses of acute care services did not differ between PROUD Treatment model and usual care sites.
- **Research Conclusions:** Primary care sites that used the PROUD model increased the number of patients that were treated for opioid use disorder, however only two sites and new patients experienced significant benefits from the model.

Watts, B.V., Gottlieb, D.J., Riblet, N.B., Gui, J., & Shiner, B. (2022). Association of Medication Treatment for Opioid Use Disorder With Suicide Mortality. The American Journal of Psychiatry. <https://doi.org/10.1176/appi.ajp.2021.21070700>

This retrospective cohort study described the effects of medications for opioid use disorder on suicide mortality amongst veterans. Between 2003 to 2017, study authors examined suicide mortality, external causes of mortality, and all-cause mortality of over 60,000 US veterans for five years following initiation of a medication for opioid use disorder. 50% of veterans were treated with buprenorphine, 25% were treated with methadone, and 25% were treated with naltrexone. The study sample were primarily men (92.8%) with an average age of 46.5 years old.

- Buprenorphine reduced suicide mortality by 65%. Methadone was only associated with a reduced risk of suicide mortality. Naltrexone reduced all-cause mortality but was not as effective as buprenorphine and methadone.
- During times in which veterans used MOUD, the rates of suicide mortality, external mortality, and all-cause mortality were significantly lower compared to times in which veterans were off their medication.
- The demographics that were associated with a high risk for suicide mortality amongst the study population were White race and having three or more psychiatric conditions.
- **Research Conclusions:** Among veterans, medication for opioid use disorder was associated with a lowered risk of suicide mortality or all cause mortality. Buprenorphine and methadone were identified as effective medications to reduce suicide mortality, but buprenorphine was found to be more effective. Naltrexone can reduce all-cause mortality among veterans, but it is not as effective as buprenorphine and methadone.

Weintraub, E., Seneviratne, C., Anane, J., Coble, K., Magidson, J., Kattakuzhy, S., Greenblatt, A., Welsh, C., Pappas, A., Ross, T.L., & Belcher, A.M. (2021). Mobile Telemedicine for Buprenorphine Treatment in Rural Populations with Opioid Use Disorder. Journal of American Medical Association. 4(8). doi: 10.1001/jamanetworkopen.2021.18487.

This study presented the outcomes from a telemedicine mobile unit that was designed to improve medication for opioid use disorder among individuals living in rural areas. Between February 2019 to June 2020, study staff traveled to rural areas of the eastern shore of Maryland in a recreational vehicle equipped with medical, videoconferencing, and data collection devices. The mobile unit was staffed with a nurse, substance use counselor, and a peer recovery specialist. Patients received electronic buprenorphine prescriptions that were sent to their local pharmacy after their initial visit and follow up teleconferences with a physician. 118 patients utilized the telemedicine mobile unit, and 94 patients were seen at follow up visits. Patients were on average 36 years old, 62.7% were male, and 75.5% identified as white, and 93.5% of patients tested positive for opioids at baseline.

- Retention rates were 77.6% at 7 days, 72.3% at 30 days, 63.8% at 60 days, and 58.5% at 90 days.
- Buprenorphine use at enrollment was significantly associated with longer treatment retention. Age, sex, and race were not significantly associated with retention.

- Opioid use was reduced by 32.8% at 3 months when compared to patients' usage at baseline.
- Compared to brick-and-mortar treatment locations, the telemedicine mobile unit saved patients a mean of 6.52 travel miles and 10 minutes of driving.
- **Research Conclusions:** Study findings show that retention of a mobile telemedicine unit for rural individuals decreased over time, but prior buprenorphine use was positively associated with patients continuing treatment. The telemedicine mobile unit saved patients driving mileage and time compared to going to a traditional treatment setting.

Weiss, R. D., Potter, J. S., Fiellin, D. A., Byrne, M., Connery, H. S., Dickinson, W., Gardin, J., Griffin, M. L., Gourevitch, M. N., Haller, D. L., Hasson, A. L., Huang, Z., Jacobs, P., Kosinski, A. S., Lindblad, R., McCance-Katz, E. F., Provost, S. E., Selzer, J., Somoza, E. C., . . . & Ling, W. (2011). Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: A 2-phase randomized controlled trial. *Archives of General Psychiatry*, 68(12), 1238–1246. <https://doi.org/10.1001/archgenpsychiatry.2011.121>.

This study (Prescription Opioid Addiction Treatment Study, POATS) evaluated the efficacy of brief and extended buprenorphine/naloxone treatment, with different counseling intensities, for patients dependent on prescription opioids. The design was a multisite, randomized clinical trial using a 2-phase adaptive treatment research design. Brief treatment (phase 1) included 2-week buprenorphine/naloxone stabilization, 2-week taper, and 8-week post medication follow-up. Patients with successful opioid use outcomes exited the study; unsuccessful patients entered phase 2: extended (12-week) buprenorphine/naloxone treatment, 4-week taper, and 8-week post medication follow-up. A total of 653 treatment-seeking outpatients dependent on prescription opioids were in the study. In both phases, patients were randomized to standard medical management (SMM) or SMM plus opioid dependence counseling. All received buprenorphine/naloxone. Measures predefined “successful outcome” in each phase were composite measures indicating minimal or no opioid use based on urine test–confirmed self-reports.

- During phase 1, only 6.6% (43 of 653) of patients had successful outcomes, with no difference between SMM and SMM plus opioid dependence counseling.
- During phase 2, 49.2% (177 of 360) attained successful outcomes with the extended buprenorphine/naloxone treatment (12 weeks), with no difference found between counseling conditions. However, success rates 8 weeks after completing the buprenorphine/naloxone taper (phase 2, week 24) dropped to 8.6% (31 of 360), again with no counseling difference found.
- Counseling did not improve outcomes overall, but among heroin users (who attended the counseling), they had significantly better outcomes (odds ratio 3.7) when assigned to SMM and opioid drug counseling (individual manual-based counseling delivered by a trained substance use disorder or mental health professional).
- Older patients, those who had never used heroin or had initially used opioids for pain rather than to get high, and those seeking treatment for the first time were all more likely to do better.

- Surprisingly, those who had major depressive disorder had nearly twice the odds of achieving a successful outcome. Those using opioid analgesics via a route of administration for which it was not intended (e.g., snorting, crushing, chewing) was a particularly poor prognostic sign.
- Abstaining from opioids in week one did not predict later abstinence (weeks 9–12) and continuing to abstain in weeks 2, 3 and 4 only marginally improved positive predictive value. In contrast, opioid use in the first week (while patients receiving buprenorphine) had a negative predictive value of 80% and if used in week 2, the predictive value rose to 94%.
- **Research Conclusions:** Prescription opioid-dependent patients are most likely to reduce opioid use during buprenorphine/naloxone treatment. If tapered off buprenorphine/naloxone, even after 12 weeks of treatment, the likelihood of an unsuccessful outcome is high, even in patients receiving counseling in addition to standard medical management.

Weiss, R. D., Potter, J. S., Griffin, M. L., Provost, S. E., Fitzmaurice, G. D., McDermott, K. A., Srisarajivakul, E. N., Dodd, D. R., Dreifuss, J. A., McHugh, K. R., & Carroll, K. M. (2015). Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study. *Drug and Alcohol Dependence*, 150, 112–119. <https://doi.org/10.1016/j.drugalcdep.2015.02.030>.

This is a follow-up to POATS, a multi-site randomized controlled trial consisting of brief treatment (2 weeks of buprenorphine/naloxone) followed by a 2-week taper and 8 weeks of follow-up treatment and an extended treatment phase of study of 12 weeks of medication and then 8 weeks of follow-up for those who did not achieve abstinence in the first phase (see preceding summary). The follow-up study consisted of interviews of 375 POATS participants at 18, 30 and 42 months following initial randomization. The follow-up sample was more likely to be female (44% vs. 35%).

- At 42 months, 32% of the participants reported having abstained from opioids in the previous month and were not receiving agonist treatment; 29% had abstained while receiving agonist therapy; 31% were using opioids and not receiving agonist therapy; 8% were using opioid and receiving agonist therapies.
- Two-thirds of the patients continued to participate in some form of treatment during the follow-up period. One-third reporting receiving buprenorphine at each follow-up period with a smaller number attended self-help groups.
- Opioid dependence declined from 16% at 18 months to 12% at 30 months to 8% at 42 months with no compensatory increase in use of other substances. Note: Since the follow-up study included only 52% of the main-trial participants, these rates may not reflect the total sample if participants doing well were more likely included in the follow-up.
- Consistent with results from the main treatment trial, engagement in agonist therapy was significantly associated with abstinence by the end of follow-up at 42 months with 80% of participants on opioid agonist therapy (OAT) reporting abstinence from other opioids in the past month compared to half of those not on OAT. Those randomized to receive

counseling did not better than those not assigned, with the exception of those with a history of heroin use (who went to the sessions assigned).

- By 42 months, early treatment success was not predictive of initial treatment success. The only predictor was the use of heroin before study entry. Those who had used heroin had more than three times greater odds of being opioid dependent at 42 months than those who had never used heroin.
- 10% reported intravenous heroin injection at least five times in the prior year after the study began who had never used it before, all had injected heroin by month 30.
- **Research Conclusions:** Despite poor initial results of short-term buprenorphine treatment, over 3 and 1/2 years, most of the prescription pain patients were no longer opioid dependent (although 42% of the initial sample was lost to follow-up and may have done worse). Successful outcomes from the initial trial were not found to be predictors of abstinence at 42 months follow-up. However, those who failed, using opioids while on buprenorphine, portended a poor long-term prognosis. Opioid addiction treatment with buprenorphine increased at 18 months and then remained steady. Counseling did not improve outcomes generally but the standard medical management provided in this study included educational components, encouraged 12-step meetings and/or lifestyle changes, and discussed pain.
- **Note:** The study excluded heroin users immediately before study (4 times in past 30 days excluded) or long-term heroin addiction.

White N., Ali, R., Larance, B., Zador, D., Mattick, R. P., & Degenhardt, L. (2016). The extramedical use and diversion of opioid substitution medications and other medications in prison settings in Australia following the introduction of buprenorphine-naloxone film. *Drug and Alcohol Review*, 35(1), 76–82. <https://doi.org/10.1111/dar.12317>.

This study examined the use of non-prescribed and prescribed opioid substitution medications in the prison environment, the extent of non-adherent drug practices, diversion practices, and the impact of buprenorphine/naloxone film in the prison system. This study used interviews from 541 opioid substitution treatment participants 18 years and above but was narrowed down to 60 participants due to their reported incarceration in 12 months prior to the interview.

- 83% of participants reported that they received opioid substitution treatment while they were incarcerated.
- Two thirds of participants received methadone treatment, one third received buprenorphine, 2 participants received more than one form of opioid substance treatment, and 10 participants took non-prescribed medication.
- 44% of the participants who received medication during their incarceration also took non-prescribed medications (morphine, oxycodone, and benzodiazepines).
- 25% of the participants reported that they removed all or part of their supervised dose of medication during their incarceration. 75% reported that removed the medication for the purpose of selling or to supply others.

- 34% of the participants reported that at one point they felt pressured to give their prescribed medication to someone else.
- The introduction of buprenorphine/naloxone film has brought issues into the prison system from it being snuck out of supervised sites by various methods to being snuck into the prison hidden underneath stamps or placed on orange envelopes. Buprenorphine/naloxone film is reportedly much easier to hide than methadone.
- **Research Conclusions:** Despite prisons being a controlled and regulated environment there is a substantial level of sharing and diversion of medication amongst inmates. BNX-F presents many challenges due to its difficulty to monitor and hide in prisons.

Whitley, P., Dawson, E., Passik, S., Gordon, A.J., Stein, B.D. (2023). Polydrug use among patients on methadone medication treatment: Evidence from urine drug testing to inform patient safety. *Addiction*. <https://doi.org/10.1111/add.16180>.

This retrospective cohort study examined the trends and persistent use of illicit substance use within the first year of treatment with medications for opioid use. Study data relied upon urine samples of 16,386 patients with opioid use disorder who received medication for opioid use disorder in Alaska, Arizona, Florida, Illinois, Kentucky, Minnesota, New Mexico, Ohio, Virginia, and Washington from January 1, 2017, through December 31, 2021. The patients involved in the study were primarily male (50.7%), Medicaid recipients (77%), median age of 38 years, and 75% of urine samples came from Arizona, Kentucky, and Ohio.

- After one year of methadone treatment, there was a 22% reduction in the likelihood of a positive tests for fentanyl, 49% reduction in heroin, and cocaine methamphetamine use did not significantly decrease.
- **Research Conclusions:** Study findings appear to show that one year of methadone treatment is effective in reducing the illicit use fentanyl and heroin, however methamphetamine and cocaine use appear to be unaffected.

Wiest, D., Truchil, A., Yang, Q. (2023). Evaluating the Camden County Correctional Facility's Medications for opioid Use Disorder Program. Retrieved December 6, 2023, from <https://www.camdencounty.com/wp-content/uploads/2023/10/moud-evaluation-report-v3.pdf>

This report presents the findings of an evaluation of the Camden County Correctional Facility's medication for opioid use disorder (MOUD) program from 2019 through 2020. The Camden County Correctional Facility provided incarcerated individuals naltrexone, Suboxone, methadone, Sublocade, and gave incarcerated individuals already on a medication for opioid use disorder in the community the opportunity to continue their treatment while incarcerated through the MOUD program. Additionally, the MOUD program provided incarcerated individuals medication coordination to the community upon the individuals release from jail. This report was based on a sample of 1,225 incarcerated individuals, of which most were male (76%), White (55.6%), had an education greater than or equal to high school (70.9%), unemployed (79.8%), an average age of 36.7 years, and were incarcerated for a non-violent offense (81.3%). The findings of this study is based upon a subset of 462 incarcerated individuals who participated in the jail MOUD program and compared them to a group of 842 incarcerated individuals with opioid use disorder who did not participate in the MOUD program.

- 10% of incarcerated individuals in the jail MOUD program and 14.5% individuals not in the program had an overdose within 180 days of their release. Overdoses increased for incarcerated individuals in the MOUD program to 12.8% and 18.2% of incarcerated individuals not in the MOUD program 365 days after their release.
- No significant findings were able to be determined if the jail MOUD program had any impact on rearrests and reincarcerations.
- The study found that 37% of Black incarcerated individuals may have been eligible to participate in the jail MOUD program, however only 26.7% of black incarcerated individuals made up the program. 44.4% of White incarcerated individuals were eligible for the program, however White incarcerated individuals made up 55.6% of the program.
- **Research Conclusions:** The results of this examination of the Camdon County Correctional Facility's medication for opioid use disorder program show that incarcerated individuals who participated in the program experienced fewer overdoses post release compared to individuals who did not participate in the program. The examination of the jail's medication for opioid use disorder program appeared to show that there was a racial imbalance of between Black and White individuals who may have benefited from the program and those who were accepted. The findings of the study around the racial imbalance of the program were unable to determine the cause of this imbalance, so additional investigation of this imbalance is needed.

Williams, A.R., Aronowitz, S.V., Rowe, C., Gallagher, R., Behar, E., Bisage, A. (2022). Telehealth for opioid use disorder: retention as a function of demographics and rurality. The American Journal of Drug and Alcohol Abuse, 49(20), 260-265. <https://doi.org/10.1080/00952990.2023.2180382>.

This cohort study investigated the demographic characteristics that may affect telehealth buprenorphine treatment retention amongst individuals with opioid use disorder. Study authors analyzed a sample of 1,378 patients who used a telehealth platform between April 1, 2020, through September 30, 2021, in Pennsylvania and New York. Treatment retention data was analyzed 180 and 365 days in treatment.

- Treatment retention at 180 days was 56.4% and was 48.3% at 365 days.
- No association was found between sex, race/ethnicity, state, or rurality in relation to retention.
- The only significant relationship observed were patients between the ages of 30-50 years older had significantly greater odds of treatment retention at 180 days compared to patients 30 years and below.
- **Research Conclusions:** Study findings appear to show that telehealth retention is not impacted by geographic location, rurality, or race or gender. However, findings suggest that age may play a factor in retention, with patients under the age of 30 probably benefiting from a more intensive form of treatment to increase retention.

Williams, A.R., Krawczyk, N., Hu, M., Harpel, L., Aydinoglo, N., Cerda, M., Rotrosen, J., & Nunes, E.V. (2023). Retention and critical outcomes among new methadone

maintenance patients following extended take-home reforms: a retrospective observational cohort study. The Lancet, 28. <https://doi.org/10.1016/j.lana.2023.100636>.

This retrospective observational cohort study compared retention in treatment, opioid use, and adverse events among patients who were newly admitted into methadone maintenance treatment between a pre COVID (2019) cohort and a post COVID (2020) cohort. Patients received treatment from nine opioid treatment programs in nine different states were observed six months after their entry into treatment. The nine sites participating in the study were required to have been in operation since at least January 1, 2018, and had changed their methadone take home procedures in accordance with the SAMHSA's guidelines in response to the COVID-19 pandemic. Patients enrolled in the study had to have been enrolled into treat between April 15 and October 14, 2020 (post COVID cohort) or March 15 and September 14, 2019 (pre COVID cohort). Patients who initiated methadone for detoxification were excluded from the study. In total 821 patients were enrolled in the study, of which 386 patients were part of the pre-COVID cohort, and 435 patients were in the Post COVID cohort. The Pre COVID cohort were mostly men (61.1%), White (70.5%), non-Hispanic (70.7%), insured by Medicaid (64.5%), unemployed (36%), had criminal justice involvement (68.6%), had secured housing (58%), and an average age of 39.6 years. The Post COVID group were mostly men (58.9%), White (77.2%), non-Hispanic (71.7%), insured by Medicaid (66.7%), had secured housing (58.9%), unemployed (37.2%), had criminal justice involvement (68.3%), and an average age of 38.8 years.

- There was no significant difference between the pre and post COVID cohorts when examining treatment retention and adverse events.
- The study found higher rates of opioid use among patients post COVID compared to pre COVID (64.8% vs 51.1%)
- The study did not find any significant differences among patient demographics and program characteristics when examining treatment adherence, opioid use, and adverse events.
- **Research Conclusions:** The results of this retrospective observational study appear to show that among methadone maintenance programs for newly enrolled patients pre and post covid have not caused any significant changes in treatment retention and adverse events. Despite SAMHSA providing guidelines to increase methadone take homes, opioid use among the post COVID cohort significantly increased compared to the pre COVID cohort.

Williams, A.R., Mauro, C.M., Feng, T., Wilson, A., Cruz, A., Olfson, M., Crystal, S., Samples, H., Chiodo, L. (2022). Performance Measurement for Opioid Use Disorder Medication Treatment and Care Retention. The American Journal of Psychiatry. <https://doi.org/10.1176/appi.ajp.202220456>.

This multisite study investigated how the Health Effectiveness and Data Information Set (HEDIS) engagement measure effects treatment retention for individuals with opioid use disorder has on 6-month treatment retention. The HEDIS engagement measure utilizes professional encounters as a measure of success and requires two outpatient visits or other professional services within 34 days of the start of treatment. Patients were provided best practice addiction treatment with their level of care increased as needed to help to maintain clinical stability. The study identified 19,487 patients who were initiating a new episode of buprenorphine care between January 1, 2011, and March 31, 2017, at buprenorphine clinics across eight states. Majority of patients were male (57.5%), non- Hispanic White, and an

average age of 35.7 years. Patient data throughout the length of the study was collected through the clinic's electronic health record. Patients were considered to have discontinued treatment if there was a treatment gap of 60 days or more. Of the 19,487 patients identified for the study, 16,063 (82.4%) successfully met the HEDIS engagement measure and 3,424 (17.6%) did not.

- Among patients who met the engagement standard, 47% of patients remained in treatment for a minimum of 6 months compared to 2.9% who did not meet the engagement measure. The retention rate decreased further as time passed 33% at 12 months and 22% at 24 months.
- Odds of 6-month retention were higher among women, adults aged 50-64 years, and patients who tested positive for buprenorphine at the start of the study.
- Patients who tested positive for cocaine and had hepatitis C at the start of the study were least likely to retain treatment at six months.
- HIV was not significantly associated with treatment retention.
- **Research Conclusions:** HEDIS engagement was associated with patients retaining treatment for six months compared to those not engaged in HEDIS. However, less than half retained treatment by six months and that was reduced to a third at one year.

Williams, A.R., Mauro, C.M., Feng, T., Wilson, A., Cruz, A., Olfson, M., Crystal, S., Samples, H., & Chiodo, L. (2022). Non-prescribed buprenorphine preceding treatment intake and clinical outcomes for opioid use disorder. Doi: <https://doi.org/10.1016/j.jsat.2022.108770>.

This observational retrospective study examined the use of non-prescribed buprenorphine prior to treatment intake and its effects on clinical outcomes. Data were obtained from a random sample of 1,000 electronic health records from newly admitted patients with opioid use disorder at office based opioid treatment programs nationwide. Use of non-prescribed buprenorphine was identified through drug testing at intake.

- Those who tested positive for buprenorphine at intake were less likely to discontinue treatment compared to those who tested negative for buprenorphine at intake.
- The risk of discontinuation did not significantly differ between prescribed buprenorphine or non-prescribed buprenorphine at intake.
- Opioid use was low amongst patients who tested for positive buprenorphine positive at intake and throughout the early months of treatment but became opioid usage became similar with those who tested negative for buprenorphine after seven months of treatment.
- **Research Conclusions:** Research findings show that nonprescribed and prescribed buprenorphine use was associated with a low risk of discontinuation and low opioid use within the first few months of treatment. These findings suggest that buprenorphine use prior to treatment may be an indicator that patients are ready for treatment and will stay in treatment.

Williams, A.R., Rowe, C., Gallagher, R., Aronowitz, S.V., Diamond-Reivich, J., Bisage, A. (2023). Urine Drug Screening in a Telehealth Setting for the Treatment of Opioid Use Disorder. JAMA Health Forum, 4(7), doi: 10.1001/jamahealthforum.2023.2247.

This observational cohort study investigated whether urine drug testing can be utilized along with a telehealth based opioid treatment platform. The study examined individuals with opioid use disorder who were treated through Ophelia, a virtual telehealth based opioid treatment platform that operates within 14 states. Patients received their care through the application with no in person visits necessary. Patients were sent two 16 panel urine drug screen kits and provided self-administered samples offline provided at follow up visits, additional urine drug screen kits were sent to patients. Urine screen results were inspected by clinicians and discussed with patients in real time over video in the app. In network patients were mainly Medicaid beneficiaries and were able to use insurance to pay for the service, while out of network or uninsured patients paid \$195 per month. Patients were prescribed buprenorphine at intake, seen on a weekly basis during the stabilization period, and once stabilization was reached patients were seen on a biweekly or monthly schedule. Patients were eligible for the study if they were English speaking adults and had a diagnosis of opioid use disorder. Patients were deemed ineligible for the study if they required a higher level of care, had physical dependency on higher doses of sedative hypnotics, had severe alcohol use that required detoxification, or were enrolled in a methadone program with a dose greater than 80mg per day. The study sample included 3,395 patients who completed an intake between January 1, 2021, through June 6, 2022, received their first buprenorphine prescription within seven days of their intake, and retained treatment for 30 days or more. Patients were mostly male (54%), non-Hispanic White (82%), lived in urban areas (80%), paid for their intake visit out of pocket (74%), and had an average age of 38.2 years.

- 2,494 (73%) patients tested negative for opioids (73%), 288 (8.5%) patients tested positive for opioids, and 613 (18%) did not complete a urine screen within the first 30 days of treatment.
- Younger patients, nonwhite patients, patients living in urban settings, and patients who paid out of pocket were less likely to provide a urine drug screen within the first 30 days of treatment.
- Of the 1,754 patients who were retained for 180 days and with a baseline and follow up urine drug screen, there was a 1.5% increase in the positivity rate for buprenorphine and a positivity decrease for opioids (1.3%), cocaine (1.2%), and benzodiazepines (2.2%).
- **Research Conclusions:** The findings of the study show that most patients who used a telehealth-based app for opioid use disorder treatment were likely to complete a urine drug screen within the first 30 days treatment. The positivity rates for opioids and other illicit drugs decreased while buprenorphine positivity increased over time as patients continued to retain treatment through the app. These findings appear to suggest that the use of drug testing with a telehealth platform that does not require in person visits is a feasible way to conduct treatment.

Williams, A.R., Samples, H., Crystal, S., & Olfson, M. (2020). Acute Care, Prescription Opioid Use, and Overdose Following Discontinuation of Long-Term Buprenorphine Treatment for Opioid Use Disorder. The American Journal of Psychiatry. 177(2), 117-134. doi: <https://doi.org/10.1176/appi.ajp.2019.19060612>.

This retrospective longitudinal study compared adverse health outcomes among patients who discontinued buprenorphine and patients who successfully retained buprenorphine

beyond six months. The study sample included 8,996 patients who maintained Medicaid enrollment for at least six months after buprenorphine discontinuation and were between 18-64 years old. Patients were organized into cohorts of 6-9 months, 9-12 months, 12-15 months, and 15-18 months based upon the length of buprenorphine use. Majority of patients were women (61%), white (91.5%), and were between 25-44 years old (76.4%).

- There were no significant demographic characteristics that were associated with long term buprenorphine use except nonwhite participants were less likely to retain buprenorphine for 15-18 months.
- Compared with the 6–9-month group, the 15–18-month cohort had significantly lower rates of emergency department visits (41.2% vs 48.6%), inpatient hospitalizations (11.3% vs 13.9%). Similar patterns occurred for the 9-12 month and 12–15-month cohorts but they did not reach the same level of significance as the 15–18-month cohort.
- Across all cohorts 5% of participants experienced at least one overdose.
- **Research Conclusions:** While adverse events, emergency department visits and overdose events were common among patients, retaining buprenorphine beyond 15 months yielded the best treatment outcomes when compared to the other cohorts.

Wish, E.D., Kaptchuk, T.J. (2023). Placebo With Methadone in Treatment of Opioid Use Disorder. A Randomized Clinical Trial. JAMA Network Open. 6(4).

Doi:10.1001/jamanetworkopen.2023.7099.

This study was an open label single blind randomized clinical trial that investigated the effects of adding a pharmacological conditioned open label placebo pill has on 90-day methadone treatment program. The study examined the placebo pills effects on retention, drug use, withdrawal, craving, quality of life, and sleep. The idea behind using a placebo pill in conjunction with a methadone dose was for the therapeutic effects of methadone would be conferred to the placebo pill, thus making the body think the placebo was an increased dose of methadone. This 12-week study recruited 131 patients with moderate to severe opioid use disorder. All study patients were seeking opioid use disorder treatment from an urban, community based, opioid treatment program. Of the 131 study patients, most were men (64%), Black or African American (63.4%), and had a mean age of 45.9 years. 77 patients were randomly assigned to receive the condition open label placebo pill with methadone, while 54 patients received methadone only. Patients provided data at baseline and 2,4-,8-, and 12-weeks after baseline.

- 77.9% of the patients who received the conditioned open label placebo pill remained in treatment for 90 days compared to 61.1% of the methadone only patients.
- Patients who received the conditioned open label placebo reported having improved sleep quality compared to the methadone only patients.
- For all other outcomes including methadone dose, no significant differences were found between the two treatment groups.
- **Research Conclusions:** The findings of this study show that a conditioned open label placebo pill does not have much of an effect on 90-day methadone treatment apart from treatment retention and quality of sleep.

Witkiewitz, K., Litten, R.Z., & Leggio, L. (2019). Advances in the science and treatment of alcohol use disorder. *Science Advances*, 5(9). Doi:10.1126/sciadv.aax4043.

This study provides an overview of the current scientific understanding alcohol use disorder and acceptable clinical techniques that can be used to help treat it.

- A-2 agonists (clonidine) and beta blockers (atenolol) can be used with benzodiazepines to control alcohol withdrawal when benzodiazepines are not enough. A-2 agonists and beta blockers should not be used by themselves to treat alcohol withdrawal.
- Disulfiram paired with alcohol causes adverse reactions such as vomiting and nausea which is considered helpful control alcohol use.
- •Acamprosate can promote abstinence and prevent relapse in already detoxified individuals. The most common side effect of acamprosates is diarrhea. Naltrexone reduces cravings for alcohol and is most effective in reducing heavy drinking. Common side effects of naltrexone include nausea, headache, dizziness, and sleep problems. Naltrexone should be used with caution among individuals with acute liver disease and should not be used by individuals with acute hepatitis or liver failure.
- Topiramate is a medication that can be used while individuals are still drinking alcohol. Topiramate is best used as to initiate abstinence and should be used at the beginning of treatment. Topiramate is not approved by the FDA but is a recommended treatment in the US Department of Veterans Affairs.
- Behavioral treatments with the greatest evidence of efficacy to treat alcohol use disorder include motivational interviewing, contingency management, cognitive behavioral treatment, 12 step facilitation.
- **Research Conclusions:** Reducing alcohol use or beginning alcohol abstinence can be achieved through several pharmacological means. The increasing knowledge of how alcohol use disorder works within the mind and body have produced an increasing number of behavioral health treatments that may be beneficial as well.

Xu, K.Y., Mintz, C.M., Presnall, N., Bierut, L.J., & Grucza, R.A. (2022). Comparative Effectiveness Associated With Buprenorphine and Naltrexone in Opioid Use Disorder and Cooccurring Polysubstance Use. *Journal of American Medical Association*, 5(5). Doi: 10.1001/jamanetworkopen.2022.11363.

This observational study compared the distribution of buprenorphine and naltrexone among individuals with opioid use disorder to individuals with cooccurring substance use disorder. Study authors collected insurance claims data from 2011 to 2016 among individuals aged 12 to 64 years old with opioid use disorder as their primary diagnosis. The sample of participants consisted of 179,280 individuals who were primarily men (50.3%), White (83.6%), had psychosocial treatment with medication during their first treatment episode (57.4%), and average age of 33.2 years. Individuals who had a history of methadone treatment were excluded from the study because study authors believed that the close supervision and frequent testing associated with methadone would obscure study results.

- 46,488 individuals with a cooccurring substance use disorder, 33,449 (70.4%) did not receive a medication for opioid use disorder with psychosocial treatment, whereas of 131,792 individuals without a cooccurring substance use disorder, 39,481 (52.7%) received psychosocial treatment without a medication for opioid use disorder.

- The presence of a cooccurring substance use disorder was associated with a increased likelihood of initiating extended release naltrexone and oral naltrexone upon entering opioid use disorder treatment.
- Buprenorphine was associated with lower odds of hospitalization and emergency department visits for drug related poisoning among individuals with and without cooccurring substance use disorder.
- Extended-release naltrexone lowered the odds of hospitalization and emergency department visits for drug related poisonings among individuals with cooccurring substance use disorder only. Oral naltrexone was not associated with these protective benefits.
- **Research Conclusions:** The findings of this comparative study show that most individual with cooccurring substance use disorder do not receive medication for opioid use disorder with their treatment. Of the individuals with cooccurring substance use disorder who receive medication for opioid use disorder, many are receiving naltrexone despite buprenorphine providing better prevention from drug related events.

Xu, K.Y., Presnall, N., Mintz, C.M., Borodovsky, J.T., Bhat, N.R., Bierut, L.J., & Gruzca, R.A. (2021). Association of Opioid Use Disorder Treatment With Alcohol-Related Acute Events. JAMA Network. 4(2). doi:10.1001/jamanetworkopen.2021.0061.

This case-controlled cohort study evaluated how buprenorphine, methadone, and naltrexone impact emergency and inpatient admissions for alcohol related events (falls, injuries, and poisonings). Data were obtained from the MarketScan database of 12,335 individuals from January 1, 2006 to December 21, 2016. Participants were 12 to 64 years old, had prescription drug coverage, a diagnosis of opioid use disorder, at least one opioid use claim, and continuous insurance enrollment. Majority of the participants were male (55.9%), had private insurance (69.6%), and an average age of 33.1 years. 6,299 (47.2%) participants received buprenorphine, 667 (5.0%) participants received methadone, 1096 (8.2%) participants received extended-release naltrexone, and 3236 (24.3%) participants received oral naltrexone.

- Among agonist medications, methadone (66%) was associated with the largest reduction in alcohol related acute events followed by buprenorphine (43%).
- Among antagonist medications, extended-release naltrexone was associated with a 37% reduction in alcohol related acute events followed by oral naltrexone which was associated with a 16% reduction.
- **Research Conclusions:** Findings of this study suggest that opioid use medications are helpful in decreasing the need for hospital admissions for alcohol related events among people with opioid use disorder. Agonist medications such as methadone and buprenorphine appear to be most effective opioid use medications to reduce alcohol related events.

Zaaijer, E.R., Dijk, L., Bruin, K., Goudriaan, A.E., Lammers, L.A., Koeter, M.W., Brink, W., Booij, J. (2015). Effect of extended-release naltrexone on striatal dopamine transporter availability, depression, and anhedonia in heroin dependent patients. Psychopharmacology, 232(14), 2597-2607. Doi: 10.1007/s00213-015-3891-4.

This study investigated changes in striatal dopamine transporter (DAT) availability and symptoms of depression and anhedonia before and during extended-release naltrexone treatment. Twelve detoxified heroin dependent patients (11 were male) from addiction treatment centers in the Netherlands were matched by age, gender, and body mass index to a group of eleven healthy individuals who did not have a diagnosis of substance dependence. The heroin dependent study patients underwent a FP-CIT single photon emission computed tomography (SPECT) scan that was performed just before the extended-release naltrexone injection and two weeks after the injection to measure DAT. The nonsubstance dependent participants only received one SPECT scan at baseline. All study participants had to have negative urine screens for opioids, cocaine, and amphetamines on the day of the scans. Four heroin dependent patients tested positive for substance use (cocaine and opioids), while one individual from the non-substance dependent group tested positive for opioid use. Thus, these participants were not included in the final analysis. Data on depressive disorder and anhedonia symptoms were gathered from self-report surveys before each scan.

- There were no significant changes in stratal DAT among the two groups.
- Depression scores were significantly higher among heroin dependent participants than individuals without substance use at baseline, however two weeks after the extended-release naltrexone injection the depression score for heroin dependent individuals were significantly lower than individuals who did not have substance dependence.
- There were no significant differences between the two groups for anhedonia.
- **Research Conclusions:** Study findings suggest that extended-release naltrexone treatment can lower depression symptoms, however it does not appear to have much of an effect on anhedonia symptoms or DAT availability.

Zaller, N., McKenzie, M., Friedmann, P.D., Green, T.C., McGowan, S., Rich, J.D. (2013). Initiation of buprenorphine during incarceration and retention in treatment upon release. 45(2), 222-226. <https://doi.org/10.1016/j.jsat.2013.02.005>.

This open label study compared initiating buprenorphine/naloxone prior to and post release from incarceration and linking individuals to community treatment providers upon release. The study sample included 44 male and female prisoners diagnosed with opioid dependence from the Rhode Island Department of Corrections. The sample were mostly male (84%), White (68%), never married (68%), average of 37.3 years, and incarcerated for an average of 49.3 months. 32 of the 44 participants started buprenorphine/naloxone treatment post release and 12 participants started buprenorphine/naloxone treatment during their incarceration. Study participants were followed up six months later in the community post release.

- Of the 32 participants who were referred to buprenorphine/naloxone treatment post release, 25 participants were linked to care in the community, the average length of time till the first appointment was 9.2 days. Seven participants attended the initial appointment only and 11 participants remained in care for the entire 6 months. The average length of treatment was 13.2 weeks.
- Of the 12 participants who started buprenorphine/naloxone treatment during incarceration, 11 participants were linked to care in the community to continue treatment. The average number of days till the first appointment was 3.9 days. 10 participants

remained in care for 6 months post release. The average length of treatment in the community were 20.3 weeks.

- Of the 12 participants who started buprenorphine/naloxone while incarcerated, zero participants reported an overdose at follow up compared to 3 participants from those who started buprenorphine/naloxone after incarceration.
- None of the participants who started buprenorphine/naloxone during incarceration reported any opioid or drug injection use at the six month follow up. Six participants who started buprenorphine/naloxone post incarceration reported heroin use and seven participants reported drug injection use at the six month follow up.
- Six participants were rearrested, with all six having had started buprenorphine/naloxone post incarceration. Participants who were rearrested spent an average of four nights in jail.
- **Research Conclusions:** Study findings appear to show that individuals who had started buprenorphine/naloxone were more likely to be linked community treatment post release from prison, have a short wait time till their first appointment, and stay in treatment longer than individuals who began to take buprenorphine naloxone after their release. Additionally providing buprenorphine/naloxone prior to release led to a decrease in risk behaviors and reduced drug use and rearrests.

Zhang, P., Tossone, K., Ashmead, R., Bickert, T., Bailey, E., Doogan, N.J., Mack, A., Schmidt, S., & Bonny, A.E. (2022). Examining differences in retention on medication for opioid use disorder: An analysis of Ohio Medicaid Data. *Journal of Substance Abuse Treatment*. 136. <https://doi.org/10.1016/j.jsat.2021.108686>.

This study investigated the association between medications for opioid use disorder type effected treatment retention and whether the addition behavioral health therapy increased retention. Study data included 81,752 Medicaid claims of Ohio individuals who were prescribed with methadone, buprenorphine, and naltrexone. The insurance claims data was used to examined to see the length of time between starting and stopping the medication during treatment.

- Compared to methadone, buprenorphine was associated with a high risk of discontinuation, however after one year of treatment the difference between the two medications were similar.
- Compared to methadone and buprenorphine, naltrexone was associated with a high risk of discontinuation at initiation and increased over one year.
- Independent of medication for opioid use disorder type, behavioral health therapy with medication for opioid use disorder was associated with a low risk of discontinuation amongst the entire sample, however adolescents/young adults and pregnant women were the most vulnerable to discontinuing.
- **Research Conclusions:** Study findings shows that methadone and buprenorphine are effective in lowering the odds of discontinuing treatment whereas naltrexone use leads to a high risk of discontinuation. Combining behavioral health treatment with medications for opioid use disorder can increase retention but is ineffective amongst young people and pregnant women.