

# RESIDENTIAL SUBSTANCE ABUSE TREATMENT (RSAT)

Training and Technical Assistance

## Recent Medication-Assisted Treatment Studies Relevant to Corrections



Advocates for  
Human Potential, Inc.

*This project was supported by grant No. 2016-MU-BX-K021 awarded by the Bureau of Justice Assistance. The Bureau of Justice Assistance is a component of the Office of Justice Programs, which also includes the Bureau of Justice Statistics, the National Institute of Justice, the Office of Juvenile Justice and Delinquency Prevention, the SMART Office, and the Office for Victims of Crime. Point of view or opinions in this document are those of the author and do not represent the official position or policies of the United States Department of Justice.*

Table of Contents

---

INTRODUCTION .....	3
1) MAT Use and Related Issues .....	4
2) Naltrexone Studies .....	16
3) Methadone Studies .....	25
4) Buprenorphine Studies.....	32
5) Comparisons of the Opioid Medications.....	56
6) Methamphetamine Studies.....	78
7) Alcohol Use Disorder Studies .....	80
8) Miscellaneous Studies .....	83
9) Withdrawal Management .....	100

## INTRODUCTION

---

The following studies address various aspects of medication-assisted treatment (MAT) relevant to corrections and serving individuals before and after release. The research has been classified by primary opioid medications studied, although many studies address overlapping issues. As can be seen, some contradict others. The problem is that much of the research deals with specific populations, for example, individuals who became addicted to pain medication and exclusively remain on opioids compared to polydrug users, or studies confined to clinical compared to correctional populations, and so on.

In each study summary, we headline what we believe to be a primary finding of the study most relevant to corrections. This is followed by a full citation so readers may access the full study. The summary begins with a very brief description, including the study's basic methodology. This is followed by bulleted specific findings, again most relevant to corrections.

**Note:** In all cases where percentages are used to differentiate results among samples, the differences were found to be statistically significant unless specifically noted otherwise.

## 1) MAT Use and Related Issues

---

### **Financial incentives sped up hospitals plans to provide access to opioid treatment but access to buprenorphine was often not initiated.**

**Kilaru, A.S., Lubitz, S.F., Davis, J., Ericksen, W., Siegel, S., Kelley, D., Perrone, J., Meisel, Z.F. (2021). A State Financial Incentive Policy to Improve Emergency Department Treatment for Opioid Use Disorder: A Qualitative Study. *Psychiatric Services*. <https://doi.org/10.1176/appi.ps.202000501>**

This qualitative study examined the decisions of hospitals to participate in the Opioid Hospital Quality Improvement Program (O-HQIP), a voluntary financial incentive program designed to increase engagement in addiction treatment for Medicaid patients with opioid use disorder in Pennsylvania. Hospitals enrolled in the program received financial compensation if they initiated buprenorphine treatment during emergency department visits, assisted patients to get outpatient treatment, provided referrals to treatment for pregnant patients, and inpatient initiation of methadone or buprenorphine. Twenty semi structured interviews were conducted with the leaders of hospitals and health systems to find out how they made their decisions to address opioid treatment at their hospitals.

- Most hospitals had plans of adopting treatment practices that were part of the Opioid Hospital Quality Improvement Program but the financial incentives from the program sped up those plans and made hospitals prioritize access to opioid treatment.
- Smaller and independent hospitals with a low number of opioid use disorder patients could not justify all the requirements of the Opioid Hospital Quality Improvement even with a financial incentive.
- Some hospitals did not initiate buprenorphine treatment because they believed it to be too difficult and time consuming to implement.
- Research Conclusions: A financial incentive program encouraged hospitals and health systems to make changes to support treatment for opioid use disorder at a faster pace than normal. However, some hospitals experienced challenges in making changes even with the prospect of financial compensation, specifically attempting to initiate buprenorphine was a type of treatment that hospitals chose to not implement.

### **Nurse practitioner ability to prescribe buprenorphine increased access to the medication in rural/frontier areas in Oregon.**

**Klein, T.A., Geddes, J., Hartung, D. (2020). The Geographic Impact of Buprenorphine Expansion to Nurse Practitioner Prescribers in Oregon. *The Journal of Rural Health*. <https://doi.org/10.1111/jrh.12538>**

This study examined the geographic impact that the Comprehensive Addiction and Recovery Act (CARA) had on the distribution of medication to treat opioid use disorder in Oregon. CARA expanded nurse practitioner's role to be able to prescribe buprenorphine. 420,765 buprenorphine prescriptions written

by waived physicians and nurse practitioners in the Oregon Prescription Drug monitoring database from January 1, 2016 to December 31<sup>st</sup>, 2018 were analyzed.

- Prior to the CARA, there were 150 prescriptions per month for buprenorphine. After CARA implementation, there were 88 additional buprenorphine prescriptions per month.
- After CARA implementation, rural areas had an absolute increase of 368 prescriptions.
- Nurse practitioner prescribing of buprenorphine increased buprenorphine prescriptions in both urban (.44% per month) and rural (.78% per month) environments.
- Nurse practitioners provided 36% of all buprenorphine prescriptions in very rural/frontier areas of Oregon by the end of 2018.
- Research Conclusions: Changes in the law that granted nurse practitioners the ability to prescribe medication for opioid use disorder, increased access to medication throughout Oregon, especially rural areas where there is little access to buprenorphine waived physicians.

**For-profit and nonprofit opioid treatment programs were the only programs that experienced an increase in medication availability as a result of Medicaid expansion.**

**Abraham, A.J., Yarbrough, C.R., Harris, S.J., Adams, G.B., Andrews, C.M. (2020). Medicaid Expansion and Availability of Opioid Medications in the Specialty Substance Use Disorder Treatment System. Psychiatric Services. <https://doi.org/10.1176/appi.ps.202000049>**

This retrospective study examined the effects of Medicaid expansion on the availability of opioid use disorder medication in treatment programs across the United States. The National Survey of Substance Abuse Treatment Services from 2002-2017 supplied Medicaid medication data on opioid treatment programs (publicly owned, private for profit, and private nonprofit) and non-opioid treatment programs.

- The effects of Medicaid expansion on opioid disorder medication were only observed in private nonprofit and private for-profit opioid treatment programs. For profit and nonprofit opioid treatment programs accounted for less than 10% of treatment programs.
- Medicaid expansion was associated with a 135.1% increase for injectable naltrexone for nonprofit programs and 57.5% increase for profit programs.
- Medicaid expansion provided a 64.4% increase in nonprofit opioid treatment programs offering buprenorphine.
- Research Conclusions: Nonprofit and for-profit opioid treatment programs experienced significant increases in the availability of medication for opioid disorder due to Medicaid expansion. However, for-profit and nonprofit opioid treatment programs make up a small percentage of treatment programs in the United States, which suggests that there are great disparities in the accessibility to opioid medication for Medicaid enrollees.

**Methadone accounts for 25% of OTP treatment, with buprenorphine way up and most naltrexone outside OTPs.**

**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](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.
- 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.

### **Washington State reports 58% of persons enrolled in MAT are from correctional facilities**

**Washington State Opioid Response, Opioid Treatment Network. (2019, October 16). *Monthly summary report*. <https://www.hca.wa.gov/assets/program/sor-otn-monthlyreport-october.pdf>**

Between January 2019 and September 2019, the “cumulative enrollment events” for medication-assisted treatment were 578 from medical facilities, 750 from community agencies and 1,763 from correctional agencies reported by the state’s Opioid Treatment Networks. Opioid Treatment Networks (OTN) were developed to increase the identification of opioid use disorders (OUD) in emergency departments, jails, and community agencies (syringe service programs, shelters, or fire departments). OTNs initiate medication treatment for OUD (MOUD) with identified individuals and make referrals to community providers for ongoing care. OTNs can offer all FDA-approved MOUDs (buprenorphine, methadone, and naltrexone).

- Of the five jail programs with MAT, two only offered buprenorphine, three also offered naltrexone, and one also offered methadone.

- The total number of clients provided MAT in the five jails was 1,584 during this period. Of these clients, 946 were discharged during this period, with 179 re-enrolling during this period.
- Research conclusions: Corrections is generating more enrollment in MAT than all other non-correctional agencies in the state. Jail retention rates are a little under 50% excluding those who re-enroll during the period reported. The retention rate reported by the largest state community agency (with 612 clients) was higher at a little under two-thirds.

### **Peer influence is the most common reason why people to start and stop taking opioid medication**

**Randall-Kosich, O., Andraka-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.

### **Adolescents are not being provided MAT for opioid use disorder.**

**Feder, K., Krawczyk, N., & Saloner, B. (2017). Medication-assisted treatment for adolescents in specialty treatment for opioid use disorder. *Journal of Adolescent Health*, 60(6), 747–750, <https://doi.org/10.1016/j.jadohealth.2016.12.023>**

This study examined teenagers' access to MAT treatment. Data from a public database of funded treatment programs in the United States that provided specialty treatment for heroin and opioid use with a focus on adolescents and adults who received MAT was used to make conclusions.

- 2.4% of adolescents in treatment for heroin received MAT vs. 26.3% of adults.
- 0.4% of adolescents in treatment for prescription opioids received MAT treatment vs. 12% of adults.
- Research conclusions: Changes and expansions of Medicaid and Children's Health Insurance Program (CHIP) coverage for MAT may help to improve adolescents' access to MAT.

### **No prior authorization for opioid medications cuts hospital costs, lowers mortality, and increases medication usage**

**Parish, W., Mark, T. (2019). Economic and Health Effects of Removing Prior Authorization from Medications to Treat Opioid Use Disorders under New York State Medicaid. The Legal Action Center. [https://www.scribd.com/document/438556266/RTIRreport-RemovingPriorAuth#fullscreen&from\\_embed](https://www.scribd.com/document/438556266/RTIRreport-RemovingPriorAuth#fullscreen&from_embed)**

This study estimate the cost and health effects that may occur when prior authorization requirements are removed from medications that are used to treat opioid use disorder. Data from the 2018 Centers for Medicare and Medicaid Service Stated Drug Utilization Database of New York was applied to calculate estimations of the cost and mortality impact of buprenorphine medication without preauthorization.

- In 2018 Medicaid in New York spent \$64.4 million on buprenorphine for opioid users. Medicaid also spent \$215.2 million on opioid related health care events, with 195 million of those dollars spent on inpatient admissions.
- It was estimated that that without prior authorization on buprenorphine products in New York there would be a 20% increase in the number of people using buprenorphine.
- Greater access to buprenorphine would lead to an estimated 42% decrease in both hospitalizations and emergency room visits, resulting in an estimated 51.9-million-dollar savings per year in hospital and emergency room costs.
- Removing prior authorizations could result in an estimated 80% decrease in mortality which would roughly be equivalent to the saving of 586 lives from opioid use disorder related deaths in New York.
- Research Conclusions: The removal of prior authorization on medications to treat opioid use disorder increases the access that people have to opioid treatment medications which results in lower mortality rates and less hospital and emergency room visits.



## Most hospitalized OUD patients' referrals to post-acute medical care facilities are rejected because of their OAT treatment or substance use despite Ant-Discrimination Settlement

**Kimmel, S.D., Rosenmoss, S., Bearnot, B., Larochele, M., Walley, A.Y. (2020). Rejection of Patients with Opioid Use Disorder Referred for Post-acute Medical Care Before and after Anti-discrimination Settlement in Massachusetts. Journal of Addiction Medicine. doi:10.1097/ADM.0000000000000693**

This study examined the frequency in which medical inpatients with opioid use disorder are referred to post-acute medical care facilities and are rejected due to substance uses or treatment with OAT. Additionally, the frequency of rejections was examined after the US Attorney's anti-discrimination settlement in May 2018 to see if there was a change in the number of rejections. Data was obtained from electronic referrals from Boston Medical Center and were compared to referrals from private Massachusetts post-acute medical care facilities in 2018. Referrals included in this study consisted of individuals 18 years or older, hospitalized with opioid use disorder, and received at least one electronic referral to a private post-acute care medical facility in Massachusetts. Referrals to state funded post-acute care and respite care for homeless individuals were not included.

- There were 219 hospitalization cases with opioid use disorder that received at least 1 referral for post-acute medical care. These cases included individuals that were 54.3% white, 92.2% English speaking, 87.7% received opioid agonist therapy in the hospital, and 53.4% insured by Medicaid.
- Of the 219 hospitalization cases, 63.9% were discharged to post-acute medical care facilities, 17.8% were discharged home without services, 9.1% were discharged home with services, 7.3% left the hospital against medical advice, and 1.8% died during hospitalization.
- The 219 hospitalization cases resulted in 1,648 referrals to 285 facilities (an average of 7.5 referrals per case). 81.8% (1348) of the referrals were rejected. 105 referrals identified OAT as the reason for rejecting the referral and 98 referrals identified substance use as the reason for rejection.
- There was no statistically significant change in the proportion of referrals that were rejected following the US Attorney settlement in May 2018.

Research conclusions: A large percentage of patients with opioid use disorder or being treated with OAT are being rejected from receiving post-acute medical care. Additional efforts are needed to address the barriers that prevent acceptance.

## Medication for opioid use disorder during incarceration with retainment after post release saves more live than just offering medication during incarceration

**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.

### **MAT use in jails and prisons provide the best long-term outcomes for incarcerated adults post release.**

**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.

### **12 out of 15 Appalachian Kentucky pharmacies report either limiting or refusing to dispense buprenorphine**

**Cooper, H., Cloud, D.H., Freeman, P.R., Fadanelli, M., Green, T., Van Meter, C., Beane, S., Ibragimov, U., Young, A.M. (2020). Buprenorphine dispensing in an epicenter of the U.S. opioid epidemic: A case study of the rural risk environment in Appalachian Kentucky. International Journal of Drug Policy. <https://doi.org/10.1016/j.drugpo.2020.102701>**

This case study examined the buprenorphine dispensing practices of 12 rural Appalachian Kentucky counties. 15 pharmacies (14 pharmacists responded) were selected to participate in one on one semi structured interviews. The dispensing practices and the influences on their dispensing practices were collected through the interviews.

- 12 out of 15 pharmacies reported that they limited dispensing of buprenorphine by refusing to serve new patients, only dispensing to known patients or prescribers, or refused to dispense buprenorphine altogether.
- Pharmacies were concerned about exceeding the Drug Enforcement Administration cap on dispensing opioids. Pharmacists are afraid to stock and/or reluctant to increase the amount of buprenorphine they order to avoid raising red flags with the DEA.
- Pharmacists were distrustful of aggressive and fraudulent marketing strategies by pharmaceutical companies that promote opioid medications
- Pharmacists were distrustful of physicians because they felt their over prescription of buprenorphine undermined their trust in buprenorphine.
- Pharmacists felt that they were influenced by the war on drugs perception of people who use drugs
- Research Conclusions: Pharmacists increasing their willingness and ability to obtain/dispense buprenorphine would benefit from policy changes to how buprenorphine is monitored, marketed, and prescribed.

### **15-24 year old's are least likely to use and continue buprenorphine treatment, but otherwise use expanding greatly**

**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**

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, 25-34-year old's, 35-44 year old's, 45-54 year old's,

and 55-80 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.
- 35-44-year old's rate of buprenorphine use increased the most out of all age groups from 2.41 to 8.34 per1000 persons.
- 15-24 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 15-80-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.

### **Family Physicians are more likely to prescribe buprenorphine when working with a mental health professional**

**Peterson, L.E., Morgan, Z.J., Borders, T.F. (2020). Practice Predictors of Buprenorphine Prescribing by Family Physicians. *Journal of American Board of Family Medicine*, 33(1), 118-123, doi: <https://doi.org/10.3122/jabfm.2020.01.190235>**

From 2017 to 2018 family physicians submitted information about their practice features and characteristics, practice location, individual characteristics, and county level mental health service associated with their practice through a questionnaire on the American Board of Family Medicine Certification Registration questionnaire. The questions that the physicians answered were used to investigate how family physician and practice characteristics impacted the prescription of buprenorphine. The response rate was 100% due to the questionnaire being required for physicians to keep or begin their certification with the American Board of Family Medicine. To reduce the sample size, family physicians that did not answer the questions about buprenorphine practices, were not linked to a US county, or had noncontinuity practices were excluded. This took the sample size from 18,762 family physicians to 2,726 family physicians.

- Of the 2,726 family physicians only 161 (5.9%) of them prescribed buprenorphine

- Family physicians in Federally qualified health centers (15.6%) and academic health centers (10.2%) had the highest rates of prescribing buprenorphine.
- Family physicians that had a mental health professional prescribed buprenorphine at a nearly double the rate (8.7% vs 4.4%) than those without a mental health professional.
- Rural family physicians in both solo and large practices had a lower higher prescribing rates than urban settings (36.6% vs 24.6%). Rural solo practices had the highest prescribing rate at 17.1%
- There were no significant personal characteristics that were associated with buprenorphine
- Research Conclusions: The number of family physicians that prescribe buprenorphine is a small amount but practice settings that support having a mental health professional are helpful in providing greater access to buprenorphine treatment.

### **Treatment facilities that accept Medicare coverage are becoming more difficult to access.**

**Harris, S.J., Abraham, A.J., Andrews, C.M., Yarbrough, C.R. (2020). Gaps In Access To Opioid Use Disorder Treatment For Medicare Beneficiaries, Behavioral Health Care. 39(2), 233-237, doi: 10.1377/hlthaff.2019.00309**

This study analyzed the accessibility of opioid use disorder treatment for people with Medicare coverage in the United States. Data was obtained from the National survey of substance abuse treatment services and the Medicare geographic variation public use files from 2007-2016.

- 13.8% of specialty treatment programs in 2016 accepted Medicare and offered buprenorphine or injectable naltrexone treatment for opioid use disorder.
- Specialty treatment programs that only offered buprenorphine services and excluded extended treatment the percentage of services dropped from 13.8% to 12.8%.
- Nearly two thirds of programs that accept Medicare and offer medication for opioid use disorder are found in urban areas.
- Medicare coverage and evidence-based treatment was less likely to available in private for profit and nonprofit treatment programs than in government run programs.
- Research Conclusions: The accessibility of MAT treatment with Medicare coverage is increasingly difficult. This lack of accessibility is impacting those who are seeking a specific type of opioid use treatment and those who live in rural environments. Greater access to services and medical professionals who can prescribe opioid use medications are needed.

### **Methadone is least utilized medication in Ohio rehab facilities**

**Pfleger, P. (2020, February). Only Half of Ohio's Rehab Centers Offer this Proven Opioid Addiction Treatment. WOUB Public Media. <https://woub.org/2020/02/18/only-half-of-ohios-rehab-centers-offer-this-proven-opioid-addiction-treatment/>**

This news article discussed the lack of medication assisted treatment services offered in Ohio rehab centers. Data on medication assisted treatment in the state of Ohio was obtained from the Substance Abuse and Mental Health Services Administration from 2018.

- Of the 450 rehab facilities in Ohio only about 250 of the facilities offer any type of MAT.
- Naltrexone followed by buprenorphine are the most utilized treatment in Ohio with about 200 facilities each.
- Methadone is the least utilized treatment with under 50 facilities using the treatment method.
- Research Conclusions: MAT services are still underutilized in the state of Ohio. Potential barrier or attitudes about specific medications may impact the underutilization of certain medications.

### **Retention of OAT lowers an individual's risk of mortality from opioids and fentanyl**

**Pearce, L.A., Min, J.E., Piske, M., Zhou, H., Homayra, 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 1<sup>st</sup> 1996 to September 30<sup>th</sup> 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.

### **Privately insured opioid use disorder patients taking buprenorphine received inconsistent treatment from practitioners**

**Mark, T.L., Hinde, J.M., Zarkin, G.A., Parish, W., Kluckman, M. (2020). Adherence to buprenorphine treatment guideline among individuals with an opioid use disorder who have private insurance. Journal of Substance Abuse Treatment, 116, <https://doi.org/10.1016/j.jsat.2020.108062>**

This longitudinal study examined how closely practitioners followed buprenorphine best practice guidelines among privately insured opioid use disorder patients prescribed with buprenorphine. Data was obtained from the 2012-2017 Health Care Cost Institute commercial claims database on patients commercially insured with no Medicaid or Medicare coverage, 18-64 years old, opioid use disorder diagnosis, filled at least one prescription buprenorphine or buprenorphine naloxone, and continuously enrolled for 3 months prior and 6 months after buprenorphine or buprenorphine induction. The insurance claims data was used to determine the number of patients tested for hepatitis B, hepatitis C, HIV, and liver function; number of urine drug screens; number of outpatient visits; and the number of patients that filled buprenorphine prescriptions for at least 6 months.

- Of the 38,517 patients claims analyzed, 4.7% of patients were tested for hepatitis B, 6.5% were tested for hepatitis C, and 29.3% were tested for HIV, and 8% were tested for liver function
- 33% of patients received urine drug screens
- 76% of patients had at least one outpatient visit for opioid use disorder. The average number of outpatient visits was 7.38.
- After the initial prescription, 47.5% of patients stayed on buprenorphine for at least 6 months.
- Research Conclusions: Research findings suggest that there are inconsistent practicing behaviors by practitioners in following the best practice guidelines for treating patients taking buprenorphine

## 2) Naltrexone Studies

---

### Two-thirds of parolees/probationers remained on injectable naltrexone for at least 3 months and were less likely to be re-incarcerated

Coviello, D. M., Cornish, J. W., Lynch, K. G., Boney, T. Y., Clark, C. A., Lee, J. D., Friedmann, P. D., Nunes, E. V., Kinlock, T. W., Gordon, M. S., Schwartz, R. P., Nuwayser, E. S., & O'Brien, C. P. (2012). A multisite pilot study of extended-release injectable naltrexone treatment for previously opioid-dependent parolees and probationers. *Substance Abuse*, 33(1), 48–59.

<https://doi.org/10.1080/08897077.2011.609438>

This is a feasibility study conducted to pilot test the ability of five sites to recruit, treat, and retain opioid-dependent offenders in a trial of extended-release injectable naltrexone (XR-NTX). The participants, 61 previously opioid-dependent individuals under legal supervision in the community, received up to 6 monthly injections of Depotrex brand naltrexone and completed a 6-month follow-up interview.

- Six-month outcomes showed that those who completed treatment had significantly fewer opioid-positive urines and were less likely to have been incarcerated than those who had not completed treatment.
- Nearly 60% of the participants at the Pennsylvania site were retained at least 4 months and 64% were retained at least 3 months across all five sites.
- Research conclusions: The findings indicate that XR-NTX holds promise as a feasible, effective treatment option for opioid-dependent offenders.

### Injectable naltrexone resulted in longer treatment duration than psychosocial only and resulted in more likely abstinence than buprenorphine and treatment only.

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

**Patients receiving injectable naltrexone stayed in community-based treatment longer, but their composite scores for abstinence, employment, arrests and self-help meeting attendance were no better than those receiving psychosocial treatment alone; they were better than those receiving buprenorphine/naloxone.**

**Crits-Christoph, P., Markell, H. M., Connolly Gibbons, M. B., Gallop, R., Lundy, C., Stringer, M., & Gastfriend, D. R. (2016). A naturalistic evaluation of extended-release naltrexone in clinical practice in Missouri. *Journal of Substance Abuse Treatment, 70*, 50–57.**

<https://doi.org/10.1016/j.jsat.2016.07.014>

- Data were analyzed from Missouri patients with OUD (N=8,996) who were admitted and discharged during 2010–2011. A composite outcome was created by summing four binary measures (abstinence, employment, arrests, and self-help meeting attendance).
- Patients receiving Vivitrol stayed in treatment longer but did not show more benefit on composite outcomes than those receiving psychosocial treatment alone.
- Exploratory analyses suggested that patients receiving Vivitrol had better composite outcomes compared with those receiving oral naltrexone and buprenorphine/naloxone.
- Research conclusions: These hypothesis-generating findings need to be further investigated in randomized clinical trials.

**Injectable naltrexone proved valuable for drug courts in terms of health cost savings and prolonged retention but did not significantly reduce relapse or rearrest.**

**Dugosh, K. L., & Festinger, D. S. (2017). *Ohio Addiction Treatment Program evaluation final report*. Treatment Research Institute.**

<https://mha.ohio.gov/Portals/0/assets/ResearchersAndMedia/Data%20and%20Reports/Reports/ATP-Evaluation-Report.pdf>

This is an evaluation of Ohio drug courts examining the 6-month outcomes of 595 drug court participants of at least 6 months in the courts and their involvement with MAT.

- The drug courts providing access to MAT (89% limited to injectable naltrexone, Vivitrol, only) did not significantly reduce relapse (based on urinalysis results) or rearrest compared to a nonrandom group of other drug court participants who did not take Vivitrol.
- The MAT group was significantly more likely to stay in the drug court program and had health savings of \$4,384 on average (probably the result of less use of emergency room services for overdoses).
- Those receiving MAT spent more on substance use disorder treatment but spent less on health care services. Although clients receiving MAT spent \$606 more on substance use disorder treatment over the course of the program compared to those who did not receive MAT, they

spent on average \$4,384 less on Medicaid health expenditures during this time, probably resulting from less use of emergency room costs for overdoses.

- Research conclusion: Findings provide statistically significant support for the value of incorporating MAT into the drug court model.

### **FDA approved injectable naltrexone for opioid use disorder treatment based on Russian randomized, placebo-controlled, double blind trial.**

**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 conclusion: 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.

### **Injectable naltrexone use is associated with improved HIV viral suppression among persons released from prison or jail.**

**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 conclusion: Injectable naltrexone improves or maintains VS after release to the community for incarcerated people living with HIV with OUD.

**Injectable naltrexone begun in prison is more likely to result in continued injections than if not begun until after release and results in better treatment retention as well as opioid receptor blockade during first two weeks post-release with highest risk for overdose death.**

**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 conclusion: The initiation of Vivitrol begun pre-release might be an effective approach to reduce relapse, but these findings require confirmation in a larger trial.

**Injectable naltrexone, compared to non-MAT treatment, is more effective in reducing relapse among offenders, with no overdoses (0/153) compared to comparison group (7/155).**

**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 conclusion: 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.

### **Injectable naltrexone during inpatient treatment improves retention and aftercare participation.**

**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 conclusion: 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.

### **Pre-release injectable naltrexone is associated with higher retention post-release; subsequent overdose deaths occurred 2.5 months or more after the last injection.**

**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 conclusion: 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.

### **Individuals receiving injectable naltrexone for opioid use disorder treatment are not dying trying to overcome its blocking effects.**

**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 conclusion: 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.

### **Those employed with private insurance and better mental health are more likely to receive more injections of naltrexone; in turn, more injections are associated with lower relapse rates.**

**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 conclusion: 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.

### **Naltrexone implants did better than oral naltrexone for HIV treatment and abstinence.**

**Krupitsky, E., Blokhina, E., Zvartau, E., Verbitskaya, E., Lioznov, D., Yaroslavtseva, 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 conclusion: 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.

### **Naltrexone implants did better than oral naltrexone for HIV treatment and abstinence.**

**University of Pennsylvania School of Medicine. (2019, March 21). *Naltrexone implant helps HIV patients with opioid dependence prevent relapse: Slow-release drug also helped improved HIV outcomes compared to oral form of drug.* ScienceDaily.**

<https://www.sciencedaily.com/releases/2019/03/190321130327.htm>

This Russian phase 3 study was a double-blind, double-dummy trial with 200 people seeking treatment for HIV and opioid dependence. 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 implant every 12 weeks along with daily placebo oral naltrexone (100 people), or oral naltrexone 50 mg/day along with a placebo implant (100 people). All were offered biweekly drug counseling and treated with antiretroviral therapies.

- Naltrexone implants placed under the skin proved more effective at helping HIV-positive patients with an opioid addiction reduce relapse and have better HIV-related outcomes compared to taking it orally.
- Forty-six people in the implant group remained on ART compared to 32 in the oral drug group, and 66 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).

### **Greater quality of life improvement and lesser opioid cravings for opioid dependent health care workers who use extended release naltrexone**

**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.



### 3) Methadone Studies

---

#### **Methadone and counseling together are found to be effective.**

**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<sup>1</sup> demonstrated greater treatment attendance and two studies<sup>2</sup> demonstrated lower treatment dropout rates.
- Five studies<sup>3</sup> demonstrated decreased opioid use among MMT clients receiving psychosocial treatment.

---

<sup>1</sup> Hesse, M., & Pedersen, M. U. (2008). Easy-access services in low-threshold opiate agonist maintenance. *International Journal of Mental Health and Addiction, 6*(3), 316–324. <https://doi.org/10.1007/s11469-007-9084-6>; Hser, Y. I., Li, J., Jiang, H., Zhang, R., Du, J., Zhang, C., Zhang, B., Evans, E., Wu, F., Chang, Y. J., Peng, C., Huang, D., Stitzer, M. L., Roll, J., & Zhao, M. (2011). Effects of a randomized contingency management intervention on opiate abstinence and retention in methadone maintenance treatment in China. *Addiction, 106*(10), 1801–1809. <https://doi.org/10.1111/j.1360-0443.2011.03490.x>; Chen, W., Hong, Y., Zou, X., McLaughlin, M. M., Xia, Y., & Ling, L. (2013). Effectiveness of prize-based contingency management in a methadone maintenance program in China. *Drug and Alcohol Dependence, 133*(1), 270–274. <https://doi.org/10.1016/j.drugalcdep.2013.05.028>; Gu, J., Lau, J. T., Xu, H., Zhong, Y., Hao, Y., Zhao, Y., Fan, L., & Ling, W. (2013). A randomized controlled trial to evaluate the relative efficacy of the addition of a psycho-social intervention to standard-of-care services in reducing attrition and improving attendance among first-time users of methadone maintenance treatment in China. *AIDS and Behavior, 17*(6), 2002–2010. <https://doi.org/10.1007/s10461-012-0393-9>; Kidorf, M., Brooner, R. K., Gandotra, N., Antoine, D., King, V. L., Peirce, J., & Ghazarian, S. (2013). Reinforcing integrated psychiatric service attendance in an opioid-agonist program: A randomized and controlled trial. *Drug and Alcohol Dependence, 133*(1), 30–36. <https://doi.org/10.1016/j.drugalcdep.2013.06.005>

<sup>2</sup> Gerra, G., Saenz, E., Busse, A., Maremmani, I., Ciccocioppo, R., Zaimovic, A., Gerra, M. L., Amore, M., Manfredini, M., Donnini, C., & Somaini, L. (2011). Supervised daily consumption, contingent take-home incentive and non-contingent take-home in methadone maintenance. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 35*(2), 483–489. <https://doi.org/10.1016/j.pnpb.2010.12.002>; Gu, J., Lau, J. T., Xu, H., Zhong, Y., Hao, Y., Zhao, Y., Fan, L., & Ling, W. (2013). A randomized controlled trial to evaluate the relative efficacy of the addition of a psycho-social intervention to standard-of-care services in reducing attrition and improving attendance among first-time users of methadone maintenance treatment in China. *AIDS and Behavior, 17*(6), 2002–2010. <https://doi.org/10.1007/s10461-012-0393-9>

<sup>3</sup> Gruber, V. A., Delucchi, K. L., Kielstein, A., & Batki, S. L. (2008). A randomized trial of 6-month methadone maintenance with standard or minimal counseling versus 21-day methadone detoxification. *Drug and Alcohol Dependence, 94*(1–3), 199–206. <https://doi.org/10.1016/j.drugalcdep.2007.11.021>; Chawarski, M. C., Zhou, W., & Schottenfeld, R. S. (2011). Behavioral drug and HIV risk reduction counseling (BDRS) in MMT programs in Wuhan, China: A pilot randomized clinical trial. *Drug and Alcohol Dependence, 115*(3), 237–239. <https://doi.org/10.1016/j.drugalcdep.2010.09.024>; Hser, Y. I., Li, J., Jiang, H., Zhang, R., Du, J., Zhang, C., Zhang, B., Evans, E., Wu, F., Chang, Y. J., Peng, C., Huang, D., Stitzer, M. L., Roll, J., & Zhao, M. (2011). Effects of a randomized contingency management intervention on opiate abstinence and retention in methadone maintenance treatment in China. *Addiction, 106*(10), 1801–1809. <https://doi.org/10.1111/j.1360-0443.2011.03490.x>; Chen, W., Hong, Y., Zou, X., McLaughlin, M. M., Xia, Y., & Ling, L. (2013). Effectiveness of prize-based contingency management in a methadone maintenance program in China. *Drug and Alcohol Dependence, 133*(1), 270–274. <https://doi.org/10.1016/j.drugalcdep.2013.05.028>; Marsch, L. A., Guarino, H., Acosta, M., Aponte-Melendez, Y., Cleland, C., Grabinski, M., Brady, R., & Edwards, J. (2014). Web-based behavioral treatment for substance use disorders as a partial replacement of standard methadone maintenance treatment. *Journal of Substance Abuse Treatment, 46*(1), 43–51. <https://doi.org/10.1016/j.jsat.2013.08.012>

- Seven studies revealed significant effects of psychosocial interventions on secondary outcomes including HIV risk,<sup>4</sup> psychosocial functioning,<sup>5</sup> adherence to psychiatric medications,<sup>6</sup> alcohol use,<sup>7</sup> and fear of detoxification.<sup>8</sup>
- Research conclusion: 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.

### Prescribed benzodiazepines do not interfere with methadone maintenance, but nonprescribed benzodiazepines do.

Dellabella, H. (2019, January 25). *Benzodiazepines, if prescribed, may not affect methadone treatment retention*. Psychiatry Advisor.

<https://www.psychiatryadvisor.com/home/topics/addiction/benzodiazepines-if-prescribed-may-not-affect-methadone-treatment-retention/>

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.

---

<sup>4</sup> Chawarski, M. C., Zhou, W., & Schottenfeld, R. S. (2011). Behavioral drug and HIV risk reduction counseling (BDR) in MMT programs in Wuhan, China: A pilot randomized clinical trial. *Drug and Alcohol Dependence*, 115(3), 237–239. <https://doi.org/10.1016/j.drugalcdep.2010.09.024>

<sup>5</sup> Hesse, M., & Pedersen, M. U. (2008). Easy-access services in low-threshold opiate agonist maintenance. *International Journal of Mental Health and Addiction*, 6(3), 316–324. <https://doi.org/10.1007/s11469-007-9084-6>; Gerra, G., Saenz, E., Busse, A., Maremmani, I., Ciccocioppo, R., Zaimovic, A., Gerra, M. L., Amore, M., Manfredini, M., Donnini, C., & Somaini, L. (2011). Supervised daily consumption, contingent take-home incentive and non-contingent take-home in methadone maintenance. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 35(2), 483–489. <https://doi.org/10.1016/j.pnpbp.2010.12.002>

<sup>6</sup> Kidorf, M., Brooner, R. K., Gandotra, N., Antoine, D., King, V. L., Peirce, J., & Ghazarian, S. (2013). Reinforcing integrated psychiatric service attendance in an opioid-agonist program: A randomized and controlled trial. *Drug and Alcohol Dependence*, 133(1), 30–36. <https://doi.org/10.1016/j.drugalcdep.2013.06.005>

<sup>7</sup> Gruber, V. A., Delucchi, K. L., Kielstein, A., & Batki, S. L. (2008). A randomized trial of 6-month methadone maintenance with standard or minimal counseling versus 21-day methadone detoxification. *Drug and Alcohol Dependence*, 94(1–3), 199–206. <https://doi.org/10.1016/j.drugalcdep.2007.11.021>

<sup>8</sup> Stotts, A. L., Green, C., Masuda, A., Grabowski, J., Wilson, K., Northrup, T. F., Moeller, F.G., & Schmitz, J. M. (2012). A stage I pilot study of acceptance and commitment therapy for methadone detoxification. *Drug and Alcohol Dependence*, 125(3), 215–222. <https://doi.org/10.1016/j.drugalcdep.2012.02.015>

- 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 conclusion: The use of the prescribed benzodiazepine may not affect retention of MMT.

### **Rapid methadone detox in jail discourages post-release 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 MMT 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 conclusion: 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.

### **Forced detox from methadone in prison is associated with reduced enrollment post-release.**

**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 conclusion: 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.

### **Methadone is associated with reduced mortality.**

**Russolillo, A., Moniruzzaman, A., & Somers, J. M. (2018). Methadone maintenance treatment and mortality in people with criminal convictions: A population-based retrospective cohort study from Canada. *PLOS Medicine*, 15(7), Article e1002625. <https://doi.org/10.1371/journal.pmed.1002625>**

This study examines the risk of all-cause and cause-specific death among 14,530 people with criminal convictions who had been prescribed methadone between 1998 and 2015. By using population-level data in British Columbia, Canada, it investigates the association between mortality rates and adherence to MMT. The median numbers of methadone medicated and nonmedicated periods in years were 2.0 and 3.2; the median follow-up period was 6.9 years.

- The overall all-cause mortality rate was 11.2 per 1,000 person-years (PYs)
- Death due to infectious diseases was 5 times lower for those on methadone.
- Death due to overdose fatalities was 3 times lower for those on methadone.
- Research conclusion: Adherence to methadone was associated with significantly lower rates of death.

### **MMT programs for inmates during and after incarceration improve behavior and reduce recidivism.**

**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.

### **Long drive times to methadone clinics exist in rural counties.**

**Joudrey, P. J., Edelman, E. J., & Wang, E. A. (2019). Drive times to opioid treatment programs in urban and rural counties in 5 US states. *JAMA*, 322(13), 1310–1312.**

<https://doi.org/10.1001/jama.2019.12562>

This study examines the drive times for people to get to certified opioid treatment programs in counties in rural and urban areas across Indiana, Kentucky, Ohio, Virginia, and West Virginia. These data were then compared to the drive time to federally qualified health centers that could potentially be methadone prescribing centers. Drive times to dialysis centers were also recorded to compare the driving distance for methadone treatment vs. kidney treatment.

- The mean drive to a methadone clinic was 37 minutes, compared to 16 minutes to a federally qualified health center and 15 minutes to a dialysis center.
- The longest drive time to a methadone clinic in a rural area was 2 hours.
- The shortest drive time to a methadone clinic in an urban area was 8 minutes.
- Research conclusions: Methadone is poorly accessible in rural communities. Policy change to support methadone being provided at federally qualified health centers, construction of new methadone clinics, or the integration of methadone into primary care could increase rural communities access to methadone treatment.

### **Methadone opioid treatment programs (OTP) have many barriers that prevent them from also administering buprenorphine and naltrexone.**

**Jones, C.M., Byrd, D.J., Clarke, T.J., Campbell, T.B., Ohuoha, C., McCance-Katz, E.F. (2019). Characteristics and current clinical practices of opioid treatment programs in the United States. Drug and Alcohol Dependence, doi:10.1916/j.drugalcdep.2019.107616**

A 46-question survey was sent to opioid treatment programs in the United States to assess opioid treatment programs current operations, types of medication used, behavioral health related services, HIV and viral hepatitis education, marketing and outreach strategies, and support services. The survey was sent to 1,605 opioid treatment programs and received 497 (31%) responses.

- 60.8% of the programs that responded were standalone facilities followed by 15.5% affiliated with a health system or hospital, and 14.3% were a community health center or federally qualified health center.
- Medicaid was accepted by 75.1% of opioid treatment programs, 24.8% accepted Medicare, 53.3% accepted private insurance, 80.5% accepted cash, and 8.5% were cash only.
- 95.8% of programs used methadone, 61.8% used buprenorphine, 43.9% used naltrexone, and 32.4% used all three medications.
- 27.5% of programs did not dispense or administer buprenorphine because of lack of patient demand, insurance reimbursement (19.8%). With naltrexone, there were clinical logistical concerns with naltrexone induction (11.4%), comfort with medication compared with methadone (10.5%), insurance prior authorization or other requirements (9.2%), profitability compared to methadone (3.5%), other concerns (37.7%).
- The average number of patients receiving methadone was 383, 51 for buprenorphine, and 6 for extended release naltrexone.
- 77.3% of OTP's reported at least one barrier to accepting additional patients. The most common barriers were physical constraints of the OTP (26.2%), insurance reimbursement or requirements (26.2%), insufficient behavioral health provider staff (21.3%), and lack of patient demand (20.3%)
- Research Conclusions: Effort is still needed to be increase the availability of having buprenorphine, naltrexone, as well as methadone at opioid treatment programs.

**Low mortality rate of patients in a 12-month methadone management treatment after being exposed to fentanyl.**

**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.



## 4) Buprenorphine Studies

---

### **Incentivized adherence and abstinence monitoring promotes opioid abstinence but has problems with retaining people through treatment.**

**Elarabi, H.F., Shawky, M., Mustafa, N., Radwan, D., Elaraheed, A., Ali, A.Y., Osman, M., Kashmar, A., Kathiri, H.A., Gawad, T., Koder, 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 were required to attend the clinic for five days and were given a seven day take home supply if they attend 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 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.

### Higher use of non-prescribed buprenorphine in the past six months lowers the odds of an opioid related overdose.

**Carlson, R.G., Daniulaityte, R., Silverstein, S.M., Nahhas, R.W., Martins, S.S. (2020). Unintentional drug overdose: Is more frequent use of non-prescribed buprenorphine associated with lower risk of overdose?. International Journal of Drug Policy. 79. <https://doi.org/10.1016/j.drugpo.2020.102722>**

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.

### **Buprenorphine plus naloxone improved viral suppression among HIV opioid use disorder patients but has poor treatment retention and more adverse events than methadone maintenance.**

**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.

### **Nasal administration of buprenorphine with alcohol consumption causes fatal respiratory depression of central nervous system.**

**Ferrant, O., Papin, F., Clin, B., Lacroix, C., Saussereau, 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.

### **Alaska Natives and American Indians with a young age and co-occurring substance use are more likely to discontinue buprenorphine/naloxone treatment.**

**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.

### **Emergency department buprenorphine use is on the rise, particularly in the Northeast and metropolitan areas.**

**Rhee, T.G., D’Onofrio, G., Fiellin, D.A. (2020) Trends in the Use of Buprenorphine in US Emergency Departments, 2002-2017. *JAMA Network Open*, 3(10).**

<http://jamanetwork.com/article.aspx?doi=10.1001/jamanetworkopen.2020.21209>

This cross-sectional study examined the trends of buprenorphine use in emergency departments in the United States from 2002 through 2017. Emergency department visit data was provided by the National Ambulatory Medical Care Survey. Only emergency department visits where buprenorphine was dispensed was included in the analysis. A limitation of this study was that the study authors assumed that all buprenorphine prescriptions were for opioid use disorder.

- Patients who received buprenorphine were more likely to be male (49.1%), non-white Hispanic (66.3%), and live in an urban area (92.7%).
- The use of buprenorphine increased from 12.3 per 100,000 emergency department visits in 2002-2003 to 42.8 per 100,000 emergency department visits in 2016-2017.
- The use of buprenorphine increased among individuals aged 19 to 44 years old (from 10.4 to 38.4 per 100,000 emergency department visits).
- Buprenorphine use increased over time in the Northeast (from 0.0 to 8.2 per 100,000 emergency department visits) and metropolitan areas (12.2 to 42.8 per 100,000 emergency department).
- Research Conclusions: This study was unable to determine if emergency room buprenorphine was used to treat patients with opioid use disorder. Despite not knowing what emergency department buprenorphine was used to treat, study findings have provided evidence that buprenorphine use in emergency departments is on the rise, particularly in the Northeast and metropolitan areas.

### **Buprenorphine alone is effective for at least interim periods.**

**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 conclusion: Results suggest that interim buprenorphine dosing could reduce drug-related risks when comprehensive treatment is not available.

### **Buprenorphine abuse is widespread among polydrug abusers on Medicaid and not used as intended for maintenance.**

**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 conclusion: 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.

### **Use of buprenorphine is varied and not well connected to treatment.**

**Gordon, A. J., Lo-Ciganic, W. H., Cochran, G., Gellad, W. F., Cathers, T., Kelley, D., & Donohue, J. M. (2015). Patterns and quality of buprenorphine opioid agonist treatment in a large Medicaid program. *Journal of Addiction Medicine*, 9(6), 470–477. <https://doi.org/10.1097/ADM.000000000000164>**

This study investigates predictors of buprenorphine treatment, patterns of care, and quality of care in a large state Medicaid program by using data from Pennsylvania Medicaid from 2007 to 2012. Enrollees with OUD filling prescriptions for buprenorphine increased from 9.8% to 25.2% from 2007 to 2012. Increases varied by age, sex, and rate.

- Between 26.2% and 32.0% of enrollees using buprenorphine had no diagnosis of OUD, depending on the year.
- Only 60.1% of enrollees with buprenorphine use received at least one urine drug screen; only 41.0% had behavioral health counseling services.
- Between 34.7% and 38.0% had other opioid and benzodiazepine claims. The mean daily doses of buprenorphine decreased over time.
- There was wide variation in likelihood of buprenorphine use among those with OUD based upon age, sex and race.
- Research conclusion: The quality of care received seemed to be generally poor.

### Use of diverted buprenorphine is common, and it is often used for therapeutic purposes.

**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 conclusion: 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.

### **Buprenorphine is used as a substitute for other drugs, particularly heroin.**

**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 conclusion: 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.

### **Buprenorphine use for 3 months did not decrease instance of users securing other opioid prescriptions.**

**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 conclusion: 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.

### **Starting buprenorphine in prison increases retention post-release, but buprenorphine is not associated with better outcomes.**

**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 conclusion: 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.

### **Buprenorphine retention characteristics listed, although most stopped taking medication within 180 days.**

**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>**



This study analyzed insurance claims from the 2013–2015 MarketScan multi-state Medicaid database. The sample included adults 18–64 years old with an opioid use disorder diagnosis in the 6 months before initiating buprenorphine treatment.

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 ( $\leq 4$  mg), male sex, younger age, minority race/ethnicity, capitated insurance, comorbid substance use disorder (alcohol, non-opioid drugs), hepatitis, opioid overdose history in the 6-month baseline period, any in-patient care in the 6-month baseline period.
- Research conclusion: For Medicaid beneficiaries with OUD treated with buprenorphine, there is a need to implement treatment models that more effectively address barriers to treatment retention. These barriers are particularly challenging for minorities, younger individuals, and those with additional SUDs.

### **Buprenorphine is found to be more effective than non-buprenorphine treatment.**

**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](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 conclusion: This study supports the use of buprenorphine with and without induction to decrease inpatient use and to lower medical, health, and pharmacy costs.

### **CBT did not improve on buprenorphine MAT alone.**

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 conclusion: 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.

### **Buprenorphine taper and 12-week follow up did not result in continued abstinence when buprenorphine was then discontinued.**

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 conclusion: 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.

### **Buprenorphine treatment is effective over time but not effective if limited to short periods.**

**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 conclusion: 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.

### **Buprenorphine is a viable medication treatment for adolescent opioid users.**

**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.

### **Injectable buprenorphine at various doses is linked to significantly greater abstinence than placebo.**

**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 conclusion: 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.

### Long-acting buprenorphine injections are compared to daily film.

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 conclusion: 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.

### **Methamphetamine use is frequently observed amongst patients in opioid use treatment.**

**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 Conclusion: 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.

### **Benzodiazepines are helpful but come with some risk in treating opioid use disorder**

**Park, T., Larochele, 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.

### **The SAMHSA registry of doctors waived to prescribe buprenorphine is inaccurate.**

**Flavin, L., Malowney, M., Patel, N.A., Alpert, M.D., Cheng, E., Noy, G...Boyd J.W. (2020). Availability of Buprenorphine Treatment in the 10 States with the Highest Drug Overdose Death Rates in the United States. Journal of Psychiatric Practice, 26(1),17-22, doi:10.1097/PRA.000000000000437**

This study assessed the accuracy of the Substance Abuse and Mental Health Services Administration database for patients who are trying to seek buprenorphine treatment providers. 10 states with the highest overdose death rates (West Virginia, New Hampshire, Kentucky, Ohio, Rhode Island, Pennsylvania, Massachusetts, New Mexico, Utah, and Tennessee) were selected for the study. The sites in these states were each called to determine if the data that are listed in the database were correct, including appointment availability, if the site accepts insurance, wait time till first appointment, and out of pocket costs.

- Of the 505 providers that were called, 310 (61.4%) providers phone numbers were listed correctly. 137 (27.1%) of the providers listed were wrong numbers or were no longer in service.
- 131 (25.9%) of the 505 providers did not prescribe buprenorphine, while 195 (38.6%) did prescribe it.
- Of the sites that provided buprenorphine, 131 providers accepted private insurance, while 37 providers did not.
- 105 providers accepted Medicaid while 54 providers did not.
- 71 of the 505 providers had appointments available in less than 7 days. Providers in New Hampshire, New Mexico, and West Virginia had no appointments available. 69 providers had a wait time of more than 7 days with an average length of 25 days.
- 39 providers had out of pocket costs associated with their site. Out of pocket costs ranged from \$90-600, and the average cost of an initial visit was \$231.



- Research Conclusions: The SAMHSA buprenorphine treatment database has limited useful for patients with outdated contact information, a small number of available appointments, and limited access to buprenorphine.

### **Large single doses of buprenorphine help lower suicidal ideation in patients with major depression and opioid dependence**

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

### **12-month injections of extended releases buprenorphine increase quality of life and treatment satisfaction for moderate to severe opioid use disorder patients.**

**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 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.

### **Extended release buprenorphine is associated with higher rates of abstinence and quality of life improvements.**

**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.cct2018.11.015>**

**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.

### **The longer patients stick with their buprenorphine treatment the more stable their health becomes after discontinuation.**

**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.

### **Emerging adults with opioid use disorder respond favorably to interim buprenorphine treatment with technology-assisted monitoring.**

**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.

### **Illicit use of buprenorphine use prior to incarceration associated with more polydrug abuse, high risk behavior and more prior drug treatment**

**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 12,007 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 findings suggest increased medical care for inmates and an increase in community-based providers or outreach teams to help those in rural areas.

### **Buprenorphine retention characteristics listed, although most stopped taking medication within 180 days, long term retention improved health.**

**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 ( $\leq 4$  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.

### **Chronic prescription opioid use before buprenorphine treatment is an indicator of successful stabilization throughout 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.

## 5) Comparisons of the Opioid Medications

---

### Methadone and buprenorphine are both effective in reducing heroin and alcohol cravings.

**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



### **Vivitrol is found not to be inferior to buprenorphine.**

**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.
- 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.

### **Patients who switch to injectable naltrexone from buprenorphine after 24 weeks have similar year-long retention and abstinence. Half of the groups completed treatment after one year.**

**Solli, K. K., Latif, Z., Opheim, A., Krajci, P., Sharma-Haase, K., Benth, J. Š., Tanum, L., & Kunøe, 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 conclusion: 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.

### **Injectable naltrexone had the same effects on symptoms of anxiety and depression as buprenorphine/naloxone, but insomnia score was significantly lower.**

**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 conclusion: 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.

### **Injectable naltrexone proved more effective for criminal justice population than oral naltrexone, buprenorphine/naloxone, or psychosocial treatment alone.**

**Crits-Christoph, P., Lundy, C., Stringer, M., 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 compared 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 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.

- Patients receiving XR-NTX had longer durations of care (compared to oral naltrexone and psychosocial treatment only) and were more likely to become abstinent (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 conclusion: XR-NTX has demonstrated its effectiveness in the real world and with criminal justice populations.

### **Patients receiving injectable naltrexone stayed in community-based treatment longer and their composite scores for abstinence, employment, arrests and self-help meeting attendance was better than those receiving buprenorphine/naloxone.**

**Crits-Christoph, P., Markell, H. M., Connolly Gibbons, M. B., Gallop, R., Lundy, C., Stringer, M., & Gastfriend, D. R. (2016). A naturalistic evaluation of extended-release naltrexone in clinical practice in Missouri. *Journal of Substance Abuse Treatment, 70*, 50–57. <https://doi.org/10.1016/j.jsat.2016.07.014>**

Data were analyzed from Missouri patients with opioid use disorder (N=8,996) who were admitted and discharged during 2010–2011. A composite outcome was created by summing four binary measures (abstinence, employment, arrests, and self-help meeting attendance). Propensity scoring was used derived from 18 intake variables to compare groups using injectable naltrexone, psychosocial treatment alone, and buprenorphine/naloxone.

- Those with injectable naltrexone had superior composite scores than those with oral naltrexone for opioid treatment (as well as for alcohol treatment).

- The group that received injectable naltrexone stayed in treatment longer vs. psychosocial treatment only.
- Those receiving buprenorphine/naloxone remained in treatment longer than those receiving injected naltrexone.
- Research conclusion: Both buprenorphine/naloxone and injectable naltrexone kept patients in treatment longer than psychosocial treatment alone, but those on buprenorphine/naloxone stayed in treatment longer than those on injected naltrexone.

### **Extended-release naltrexone and buprenorphine differed only marginally with generic daily buprenorphine/naloxone, but at much higher costs.**

**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-review.org/wp-content/uploads/2018/04/ICER\\_MAT\\_Evidence\\_Report\\_102518-1.pdf](https://icer-review.org/wp-content/uploads/2018/04/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 conclusion: 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.

### **Buprenorphine is more cost-effective than extended-release naltrexone.**

**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 conclusion: Buprenorphine/naloxone is typically preferred as a first-line treatment when both options are clinically appropriate.

### **Daily buprenorphine is more cost-effective than injectable naltrexone.**

**ACP Internist. (2018, December 18). *Daily medication appears more cost-effective than monthly injections for opioid use disorder*. ACP Internist Weekly. <https://acpinternist.org/weekly/archives/2018/12/18/1.htm>**

Researchers performed a cost-effectiveness analysis alongside a previous randomized clinical trial that compared a 24-week intervention with buprenorphine/naloxone or injectable naltrexone plus 12 weeks of observation. The trial was conducted with adults with opioid use disorder in eight inpatient or residential treatment programs, and the primary outcome was opioid relapse-free survival. The randomized clinical trial involved 570 patients with an average age of 34 years. Most were male and white and had public insurance. Limitations of the analysis included relatively short follow-up, a substantial amount of missing data, and the lack of information on patients' out-of-pocket costs and costs for social services.

- In the base-case analysis, when the health care sector perspective and a willingness-to-pay threshold of \$100,000 per QALY were used, buprenorphine/naloxone was more likely to be preferable to injectable naltrexone at 24 and 36 weeks.
- Over 24 weeks, injectable naltrexone cost an average of \$5,317 more than buprenorphine/naloxone, primarily because the former was more expensive and required a longer detoxification period.
- Research conclusion: Buprenorphine/naloxone should usually be preferred over injectable naltrexone for first-line treatment in cases where both options are clinically appropriate, where patients must undergo detoxification to initiate the latter therapy.

### Higher retention found for methadone over buprenorphine.

**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 conclusion: 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.

### Both methadone and buprenorphine maintenance therapies are more effective and cost-effective than no-medication therapy.

**Connock, M., Juarez-Garcia, A., Jowett, S., Frew, E., Liu, Z., Taylor, R. J., Fry-Smith, A., Day, E., Lintzeris, N., Roberts, T., Burls, A., & Taylor, R. S. (2007). Methadone and buprenorphine for the management of opioid dependence: A systematic review and economic evaluation. *Health Technology Assessment, 11*(9), 1–171. <https://doi.org/10.3310/hta11090>**

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 conclusion: 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.

**Both naltrexone and buprenorphine were effective for those who took them, but greater retention was achieved with buprenorphine, with more overdose deaths in the buprenorphine group.**

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 conclusion: 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.

**Injectable naltrexone is more cost-effective than methadone or buprenorphine.**



**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>

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 et al., 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 conclusion: 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.

### **Methadone and buprenorphine require higher doses to be effective; higher retention achieved with methadone, but less opioid use with buprenorphine.**

**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 conclusion: 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.

**Agonist medication reduced all-cause and overdose deaths following opioid overdoses, while injectable naltrexone was found to be ineffective because participants did not continue injections after the first.**

**Laroche, 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.

### **Most, but not all studies find methadone rated better than buprenorphine.**

**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 conclusion: 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.

### **Inmates continued buprenorphine more than methadone.**

**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 conclusion: After initiating opioid agonist treatment in jail, continuing buprenorphine maintenance in the community appears to be more acceptable to offenders than continuing methadone maintenance.

### **Buprenorphine is more challenging than methadone to administer safely in prison.**

**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 conclusion: 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.

### **Buprenorphine and injected naltrexone have the same retention once begun, while it is harder to begin Vivitrol.**

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.
- Research conclusion: 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.

### **Naltrexone is associated with reduced accidental overdoses, buprenorphine with reduced arrests and accidental overdoses, and methadone with reduced suicides and arrest reduction but increased accidental overdoses.**

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 conclusion: Medications currently used to treat alcohol and opioid use disorders also appear to reduce suicidality and crime during treatment.

**When dosed adequately, both agonist medications showed similar reduction in illicit opioid use; buprenorphine was associated with less risk of adverse events, but there was better treatment retention with methadone.**

**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 conclusion: BMT is associated with improved outcomes compared with placebo for individuals and pregnant women with opioid use disorders.

**Buprenorphine is safer than methadone, but treatment duration is shorter in buprenorphine, so they come out the same.**

**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.
- 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.

### **During and after agonist medication treatment overdose death rates are compared, with methadone all-cause and overdose death rates higher than those for buprenorphine.**

**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.
- 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.

### Switching from methadone treatment to buprenorphine/naloxone treatment has predictive factors that make the switch of medication difficult.

**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 conclusion: 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.

### Rates of overdose are similar among methadone, buprenorphine, and injectable naltrexone treatments.



**Kelty, E., & Hulse, G. (2017). Fatal and non-fatal opioid overdose in opioid dependent patients treated with methadone, buprenorphine or implant naltrexone. *International Journal of Drug Policy*, 46, 54–60. <https://doi.org/10.1016/j.drugpo.2017.05.039>**

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.

### **No significant difference in sleep quality between methadone or buprenorphine**

**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 diary 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.

### Extended release naltrexone provides the best outcomes for jail to community reentry for opioid users

**Velasquez, M. Flannery, M., Badolato, R., Vittitow, A., McDonald, R., Tofighi, B.,...Lee, J. (2019). Perceptions 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.

### **Extended Release naltrexone is helpful in reducing cravings in heroin and non-heroin opioid users**

**Cousins, S.J., Radfar, S.R., Crevecoeur-MacPhail, D., Ang, A., Darfler, K., Rawson, R.A. (2015). Predictors of Continued Use of Extended-Released 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 a 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

### **Naltrexone provides positive outcomes for pregnant women and their newborns.**

**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.

### **Retention of OAT lowers an individual's risk of mortality from opioids and fentanyl, death rates lower with buprenorphine than methadone**

**Pearce, L.A., Min, J.E., Piske, M., Zhou, H., Homayra, 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 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 1<sup>st</sup> 1996 to September 30<sup>th</sup> 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 death were reported in the sample. Mortality rates were highest among individual under 20 years old, HIV (positive or unknown), and with hepatitis C.
- 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: 2085; off OAT: 4237).

- 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 to 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 even with the increased prevalence of fentanyl.

### **Buprenorphine or Methadone for at least 30 days result in the least opioid related overdoses compared to non-pharmacological treatment and no treatment.**

**Wakeman, S.E., Larochele, 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 for detox compared to other treatment methods. 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.

## 6) Methamphetamine Studies

---

### Clinical trials for medications for methamphetamine use disorder found to be largely negative

**Ballester, J., Valentine, G. & Sofuoglu, M. (2016). Pharmacological treatments for methamphetamine addiction: current status and future directions, Pages 305-314 | Received 15 Aug 2016, Accepted 01 Dec 2016, Accepted author version posted online: 07 Dec 2016, Published online: 20 Dec 2016.**

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.

### Mirtazapine has poor adherence but is a helpful medication in reducing methamphetamine use

**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 condomless sex.
- 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.



## 7) Alcohol Use Disorder Studies

---

### **Naltrexone mixed with a combination of acamprosate or disulfiram decreases the likelihood of a person with alcohol use disorder going to the hospital due to alcohol related issues.**

**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.

### **Women, younger and non-White Hispanic people experienced the most changes in alcohol use during the COVID-19 pandemic.**

**Pollard, M.S., Tucker, J.S., Green, H.D. (2020). Changes in Adult Alcohol Use and Consequences During the COVID-19 Pandemic in the US. *JAMA Network*. 3(9).  
Doi:10.1001/jamanetworkopen.2020.22942**

This survey study compared individual changes in alcohol use and consumption before and during the COVID-19 pandemic. Participants surveyed for this study were members of the RAND Corporation

American Life Panel, which consists of 6,000 participants 18 years or older who spoke English or Spanish. 2,615 members of the American Life Panel between 30-80 years old were invited to participate in the baseline survey from April 29-June 9, 2019. 1,540 participants responded to the baseline survey and the follow up survey May 28-June 16, 2020. Majority of the participants were between 30-59 years old (53.6%), female (57.3%), and non-Hispanic white (71.4%). Comparisons were made between baseline and follow up surveys on number of days of any alcohol use, heavy drinking (5 or more drinks for men and 4 or more drinks for women), and average number of drinks consumed over the past 30 days. Participants also completed the 15 item Short Inventory of Problems to assess adverse consequences associated with alcohol use in the past 3 months.

- Frequency of alcohol use increased overall by 14% from baseline to follow up survey.
- From baseline to follow up, the frequency of alcohol consumption significantly increased among women by 17%, adults from 30 to 59 years of age by 19%, and non-Hispanic White individuals by 10%.
- Among women, there was a 41% increase in heavy drinking from the baseline to follow up.
- Women saw a 39% increase in the Short Inventory of Problems scale, which represents increased alcohol related problems independent of consumption level for nearly 1 in 10 women.
- Research Conclusions: Overall alcohol consumption has increased during the COVID-19 pandemic. Non-Hispanic Whites and adults 30-59 years of age experienced a significant increase in alcohol consumption. However, women have experienced the most dramatic changes in alcohol use during the pandemic, including consumption, frequency of heavy drinking, and alcohol related problems not related to consumption.

### **The rate of alcohol withdrawal hospitalizations consistently increased when compared to 2019 alcohol withdrawal hospitalizations.**

**Sharma, R.A., Subedi, K., Gbadebo, B.M., Wilson, B., Jurkowitz, C., Horton, T. (2021). Alcohol Withdrawal Rates in Hospitalized Patients During the COVID-19 Pandemic. JAMA Network Open.4(3). doi:10.1001/jamanetworkopen.2021.0422**

This retrospective cohort study investigated alcohol withdrawal rates among hospitalized patients with alcohol use disorder before COVID-19 stay at home orders, during the COVID-19 stay at home orders, and after state at home orders were lifted. The electronic health care records of patients from the Christian Care hospital in Newark, Delaware from January 1, 2018 to September 22, 2020 were analyzed and grouped according to the timepoint of their alcohol withdrawal diagnosis. Patients included in this study either presented with alcohol withdrawal at admission or had developed alcohol withdrawal during their hospital stay. 340 patients received a diagnosis of alcohol withdrawal prior to stay-at-home orders. This group of patients had 101 women (29.7%), average age of 52.3 years, 73 Black patients (21.5%), and 18 Hispanic patients (5.3%). 231 patients received a diagnosis of alcohol withdrawal during stay-at-home orders. This second group of patients had 74 women (32.0%), average age of 53.2 years, 44 Black patients (19.1%), and 12 Hispanic patients (5.2%). 502 patients received a diagnosis of alcohol withdrawal after stay-at-home orders were lifted. This third group had 156 women (30.8%), average age of 52.2 years, 114 black patients (22.5%), and 25 Hispanic patients (4.9%).

- The rate of alcohol withdrawal in hospitalized patients were consistently higher in 2020 compared to 2019 and 2018 hospitalizations.
- The largest increase in alcohol withdrawal cases between 2020 vs 2019 occurred in the last two weeks of stay-at-home orders (May 20, 2020-June 2, 2020). The second largest increase in alcohol withdrawal cases between 2019 and 2020 occurred August 26 to September 8<sup>th</sup> during statewide reopening phases.
- The rate of alcohol withdrawal increased by 34% in 2020 during the pandemic (March 25 to September 22) compared to the same period in 2019.
- Research Conclusions: Study findings show that there was an overall increase in alcohol withdrawal hospitalizations during 2020 compared to previous years with a peak increase at the end of stay-at-home orders. With states reopening plans taking effect, rates of alcohol withdrawal hospitalizations continued to increase from the rates observed in 2019 and 2018.

### **Methadone and buprenorphine provide the greatest reductions of alcohol 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 extended-release 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.

## 8) Miscellaneous Studies

---

### **Primary use of alcohol and nonmedical buprenorphine with marijuana and nonmedical opioids before incarceration is a significant factor for reuse after incarceration.**

**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.

### **Over 90% of patients and healthcare professionals surveyed found telephone counseling satisfactory.**

**Henderson, J. (2021). Early Data Show Promise in Telephone Counseling for Opioid-Use Disorder. Medpage Today. <https://www.medpagetoday.com/special-reports/exclusives/91299?vpass=1>**

In an unpublished study, CODAC Behavioral Healthcare partnered with Brown University to survey CODAC patients and healthcare providers about how they felt about telephone counseling for MAT during the COVID-19 pandemic. Surveys were given to 247 patients and 42 counselors between August and October 2020.

- Overall satisfaction between patients and healthcare professionals about telephone counseling was 92.3%.
- 70.9% of patients believed that telephone counseling helped the with substance use similarly to in person services. 16.4% of patients believed that telephone counseling helped more than in person services.

- 69.1% of patients believed that telephone counseling helped with recovery the same as in person services. 19.3% believed that telephone counseling helped more with recovery more than in person services.
- Both patients and counselors mentioned lack of privacy during sessions at home and potential for impersonal experiences. Counselors felt that telephone counseling made their workflow feel tedious.
- Research Conclusions: Most patients and healthcare professionals found telephone counseling a satisfactory experience. Some patients believed that telephone counseling was more helpful in than traditional in person services. While telephone counseling provides a great experience to patients and providers, it can make discussing confidential topics difficult and can make interactions seem impersonal.

### **Across 3 different geographic areas, opioid agonist treatment is estimated to significantly reduce mortality.**

**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.

**Substance use disorder and ADHD patients treated with ADHD medication are five times more likely to retain SUD treatment than patients just treated for SUD alone.**

**Kast, K.A., Rao, V., Wilens, T.E. (2020). Pharmacotherapy for ADHD and long-term retention in outpatient addiction treatment: a retrospective cohort study. American Academy of Addiction Psychiatry Annual Meeting & Scientific Symposium.**

The results of a retrospective study comparing treatment retention amongst diagnosed substance use disorder and ADHD patients treated with ADHD medication to non-ADHD diagnosed patients was presented at the 2020 American Academy of Addiction Psychiatry conference. Data was obtained from electronic records of 2,163 patients who attended an addiction clinic at Mass General from July 2014 to January 2020. Of the 2,163 patients, 203 patients were diagnosed with ADHD and 171 of those patients received ADHD pharmacotherapy.

- Patients who were diagnosed with ADHD were found to be more likely than non-ADHD patients to be younger (mean age 38 years old vs 45 years old), use cocaine (31% vs 12%), and have private insurance (64.4% vs 44%).
- Patients treated with ADHD pharmacotherapy within the first 90 days of substance use disorder treatment were five times more likely to remain in treatment than patients who did not receive ADHD medication.
- Research Conclusions: Patients with a comorbid diagnosis of ADHD and substance use disorder are more likely to not stay in SUD treatment if their ADHD symptoms are not treated. Providing pharmacotherapy to treat ADHD while providing substance use treatment significantly increases a patient's likelihood of remaining in SUD treatment.

**Those on agonist treatment for OUD, less likely to abuse fentanyl while in treatment if they also use cannabis than if they don't. Majority also test positive for stimulants and a little under half for methamphetamine.**

**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 as strain of cannabis, cannabis dose, cannabis use frequency, reason for cannabis use, and method of cannabis administration.

### **Complexity shrouds the answer to if benzodiazepines and opioids be used concurrently.**

**Duerr, H.A. (2020). Should Benzodiazepines and Opioids Be Used Concurrently. Psychiatric Times. <https://www.psychiatristimes.com/view/should-benzodiazepines-opioids-used-concurrently>**

This news article describes a discussion by Thomas Kosten, M.D and Carla B. Marienfeld, M.D at a Medical Crossfire at the Annual Psychiatric Times World CME Conference. Kosten and Marienfeld discussed the safety of concurrent benzodiazepine and opiate use for patients. To explain their positions on the issue Kosten examined the US FDA warnings over the past few years and Marienfeld presented a case study.

- Safety of concurrent benzodiazepine and opioid use is not clear due to the FDA's conflicting safety evaluations. In 2016 the FDA regarded opioid with buprenorphine use as a serious risk and then in 2017 the FDA did not want patients who took opioid medication to be withheld from taking benzodiazepines or other drugs that depress the central nervous system. Currently the FDA places black box warnings on benzodiazepines detailing risks and abuse of the drug.
- When prescribing benzodiazepines for patients with a history of substance use disorder, choose medications that have a slower onset of action so that they will be less likely to be abused.
- Clinical judgment, patient symptoms and functioning should be considered before prescribing benzodiazepines to reduce harm or to identify if a prescribed medication is increasing harm.
- Research Conclusions: The concurrent use of benzodiazepines and opioids does not have a clear answer. The safety precautions by the FDA have changed over the years which have added to the uncertainty of concurrent use. The safest approach to prescribe benzodiazepine and opioid medication is to use clinical judgment and regularly meeting with patients to assess their treatment needs and safety.

### **Low doses of benzodiazepines or Z-drugs while receiving buprenorphine treatment greatly lower the risk of a drug related death.**

**Xu, K.Y., Borodovsky, J.T., Presnall, N., Mintz, C.M., Hartz, S.M., Bierut, L.J., Gruzca, R.A. (2021). Association Between Benzodiazepine or Z-Drug Prescriptions and Drug- Related Poisonings Among Patients Receiving Buprenorphine Maintenance: A Case-Crossover Analysis. The American Journal of Psychiatry. <https://doi.org/10.1176/appi.ajp.2020.200081174>**



This study investigated the association of benzodiazepine and Z-drug use (drugs typically prescribed for insomnia, including eszopiclone (Lunesta), zaleplon (Sonata) and zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist) with drug related poisonings among individuals receiving buprenorphine treatment. Data were obtained from 23,036 patients between the ages of 12-64 with opioid use disorder who had buprenorphine prescriptions and had insurance claims in the IBM MarketScan databases from 2006-2016.

- Buprenorphine treatment was associated with a 40% reduction in the risk of poisoning events whereas benzodiazepine or z-drug treatment were associated with an 88% increase in the risk of poisoning.
- High doses, but not low doses of benzodiazepines or Z-drug treatment combined with buprenorphine, were associated with an increased risk of poisoning.

Research Conclusions: Research findings suggest that there is an increased risk of drug related poisoning associated with the use of benzodiazepines and Z-drug use. Individuals receiving buprenorphine treatment should receive low doses of benzodiazepines or Z-drugs due to the lowered risk of a drug related poisoning.

Most opioid overdose deaths are from opioid medications used for pain; most had prescriptions for both benzodiazepines and opioids.

**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.”

### **Crime reduction requires medication for mental illness as well as drugs.**

**Swanson, J. (2016). Mental illness, release from prison, and social context. *JAMA*, 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.
- 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.

### **Forced treatment is found to be effective for justice-involved population.**

**Coviello, D. M., Zanis, D. A., Wesnoski, S. A., Palman, N., Gur, A., Lynch, K. G., & McKay, J. R. (2013). Does mandating offenders to treatment improve completion rates? *Journal of Substance Abuse Treatment*, 44(4), 417–425. <https://doi.org/10.1016/j.jsat.2012.10.003>**

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.
- Findings reveal that stipulated treatment for offenders may be an effective way to increase treatment compliance.

### **The legality of denying MAT is questioned.**

**Legal Action Center. (2011). *Legality of denying access to medication assisted treatment in the criminal justice system*. [https://lac.org/wp-content/uploads/2014/12/MAT\\_Report\\_FINAL\\_12-1-2011.pdf](https://lac.org/wp-content/uploads/2014/12/MAT_Report_FINAL_12-1-2011.pdf)**

This report examines the prevalence of opiate addiction in the criminal justice system, its devastating consequences, and the widespread denial of access to one of its most effective forms of treatment: medication-assisted treatment (MAT). The report then analyzes the circumstances in which the denial of MAT violates federal anti-discrimination laws and the U. S. Constitution.

- Legal arguments against denying incarcerated individuals MAT include that it may be in violation of the Americans with disabilities Act (ADA) and the Rehabilitation Act (RA). Title II of the ADA prohibits discrimination by state and local governments of individuals with disabilities and was deemed to apply to prison programs in *Pennsylvania Dep't of Corrections v. Yeskey* in 1999. Court decisions have upheld that individuals who qualify for MAT also qualify as “disabled” and are protected by the ADA. Not allowing these individuals to participate in MAT while incarcerated is considered discrimination under the ADA, unless the institution can prove that allowing these individuals to participate places an undue burden on the institution or compromises the safety or health of others. This is unlikely as most argument against providing MAT in prisons are not based on legal grounds but on personal views that MAT is not effective in treating addiction. While the ADA and RA do not require correctional facilities to provide an individual’s preferred choice of treatment, they do prohibit the denial of treatment for discriminatory reasons.
- Failure to provide incarcerated individuals with appropriate medical treatment for their withdrawal symptoms from opiate addiction could violate the U. S. Constitution’s Eighth Amendment prohibition on cruel and unusual punishment (applicable to prisons) or Fourteenth Amendment Due Process Clause (applicable to jails).

### **Agonist MAT saves money if provided in lieu of detox and treatment.**

**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.

- 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.

### **RI prison and jail MAT is associated with decline in post-release overdose deaths.**

**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.
- 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.

### **Long-acting opioid medication is no better than daily.**

**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-review.org/wp-content/uploads/2018/04/ICER\\_MAT\\_Evidence\\_Report\\_102518-1.pdf](https://icer-review.org/wp-content/uploads/2018/04/ICER_MAT_Evidence_Report_102518-1.pdf)**

This study compared the effectiveness of newer, extended-release treatments for MAT (i.e., looking at what is effective out of all of these: two buprenorphine injections, one buprenorphine implant, and naltrexone injection). It evaluated studies of patients 16 years or older with OUD. For the comparison of the interventions of interest versus each other and versus transmucosal formulations of buprenorphine/naloxone, we 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 did not statistically differ in comparison to sublingual buprenorphine/naloxone. Results from the Probuphine (long-acting implants) trials showed statistically significantly greater abstinence than buprenorphine/naloxone on various measurements.
- Participants on Sublocade (injection) treatment were also more likely to be abstinent, but 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 fewer individuals began Vivitrol treatment.
- 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.

### **A mobile technology platform increases MAT retention.**

**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.
- 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.

**Therapy did not reduce opiate use when added to buprenorphine and medical management.**

**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.
- 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.

### **Released prisoners on agonist medication are less likely to die and more likely to attend treatment in the month following release.**

**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.

### **Suicidal ideation is linked to misuse of opioids and benzodiazepines.**

**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 conclusion: 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.

### **Released inmates are at substantially greater risk for overdose deaths, especially in the first 2 weeks post-release.**

**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.



### **OST treatment leads to better reduction and retention rates among adolescents.**

**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.

### **MAT medication combined with 12-step treatment leads to positive outcomes post-treatment.**

**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 conclusion: 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.

### **Benzodiazepines have a high mortality rate amongst opioid users in treatment despite treatment length**

**Macleod, J., Steer, C., Tilling, K., Cornish, R., Marsden., Millar,...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.

### **Opioid users with high drug cravings make more risky unknown decisions and are at higher risk to use again.**

**Konova, A., Lopez-Guzman, S., Urmanche, 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.

### **Fentanyl screens could help bring awareness to those at risk of an overdose.**

**Jaeger S., Fuehrlein B., Garcia Vassallo G. (2019). Rates of Fentanyl Use Among Psychiatric Emergency Room Patients at VA Connecticut Healthcare System. Poster presented at the American Academy of Addiction Psychiatry 30th annual meeting**

This study analyzed urines of patients admitted to the VA in Connecticut for a variety of substances to determine the presence of fentanyl over a 7 -month period. Data was collected from 746 patients, and examining basic demographic information, psychiatric diagnosis, suicide risk, presenting complaint, and urine drug screen.

- 461 screens revealed 66 (14.3%) of those screened were positive for fentanyl.

- The average age of those who tested positive for fentanyl was 45 years old with 62 of the patients being male and 4 were female.
- Of the participants who tested positive for fentanyl, 66.7% were also positive for opioids, 47% were also positive for cocaine, only 8% were negative for both opioids and cocaine.
- 59% of the patients who tested positive for fentanyl were in treatment because of their opioid use.
- 44 patients who screened positive for fentanyl were also identified as a high risk for suicide.
- PTSD (42.4%) and depression (36.4%) were the two most frequent comorbid disorders amongst patients that tested positive for fentanyl.
- Research Conclusions: Without routine screening of fentanyl, patients who are using it unknowingly are being missed and are at a higher risk of death by overdose and suicide. Knowledge of opioid and fentanyl use will be able to present treatment options of opioid users and provide greater preventative treatment options to those of high overdose risk.

### **Medicaid expansion reduces opioid related overdose deaths**

**Kravitz-Wirtz, N., Davis, C.S., Ponicki, W.R. (2020). Association of Medicaid Expansion with Opioid Overdose Mortality in the United States. JAMA, 3(1), doi:10.1001/jamanetworkopen.2019.19066.**

This cross-sectional study observed opioid overdose death data from 3,109 counties within 49 states and the District of Columbia (Alaska was excluded) from January 2011 to December 2017. The study compared opioid overdose deaths with counties that expanded or did not expand Medicaid coverage. Opioid overdose death data was collected from the National Vital Statistics System.

- Counties that expanded Medicaid had a 6% decreased rate of opioid overdose deaths compared to states that did not expand Medicaid eligibility
- Medicaid expansion also decreased fatal heroin overdoses by 11%, synthetic opioid deaths by 10%
- However, the expansion of Medicaid did increase methadone involved overdose deaths by 11%.
- Overall counties within states that expanded Medicaid had a 2% decrease rate in all drug related overdoses compared to no expansion states.
- Research Conclusions: Medicaid expansion is associated with reductions in opioid overdose deaths, but it does increase methadone related deaths. More attention should be given to the role that health coverage expansions play in reducing opioid overdose mortality.

### **CBT and pharmacotherapy treatment are more effective than clinical management in treating AUD/SUD**

**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.

### **Federal and State policies have not impacted heroin use in Kentucky**

**Bunting, A.M., Victor III, G., Pike, E., Staton, M., Winston, E., Pangburn, K. (2019). The Impact of Policy Changes on Heroin and Nonmedical Prescription Opioid Use among an Incarcerated Population in Kentucky, 2008-2016. Criminal Justice Policy review. 1-17. Doi:10.1177/0887403419838029**

This study analyzed the impact national and state level policies had on the trends of nonmedical prescription opioids and heroin use from 2008-2016 amongst incarcerated individuals in the state of Kentucky. Data was collected from the Criminal Justice Kentucky Treatment Outcome Study which was

conducted from July 1, 2011 to June 30, 2017. The individuals in the data set began their incarceration between 2008-2016 and had entered Kentucky corrections-based substance abuse programs between 2011-2017. Individuals could only be in the study 1 time to prevent duplicates. The policies that were examined were: (1) 2010 reformulation of OxyContin (Oxycontin became more difficult to crush, snort and inject), (2) 2012 Kentucky House Bill 1 ( mandated regulation of pain management clinics and new practice standards for prescribing and distributing prescription opioids), and (3) 2015 Kentucky Senate Bill 192 (designates sources of funding for substance use treatment and authorizes expanded access to naloxone).

- The rate of heroin use increased from 11.2 per 100 individuals in 2008 to 34.1 per 100 individuals. OxyContin reformulation in 2010, Kentucky House Bill 1 in 2012, and Kentucky Senate Bill 192 did not impact the rate of heroin use.
- The trend of injected drug use mirrored heroin use but occurred at a greater rate (31.9 per 100 individuals in 2008 to 51.58 per 100 individuals in 2016). Reformulation of oxycontin, Kentucky House Bill 1, and Kentucky Senate Bill 192 did not impact injected drug usage.
- Since 2008 the non-medical prescription opioid use rates were consistently greater than heroin usage. A significant drop (-7.41%) in nonmedical prescription opioid occurred between 2012-2013 after the introduction of Kentucky House bill 1.
- Being female, history of heroin use, identifying as white, living in a rural area, history injected drug use, and a younger age were significant indicators in the likelihood of non-medical prescription opioid use.
- Research Conclusions: The trends reported in this study suggests that attempts to reduce substance use through policy alone are not effective among the criminal justice population with the unintended consequences of switching from a highly regulated substance to another.

### **Prison based OSP improves mortality rate of OUD prisoners within the first four weeks of release**

**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.

## 9)Withdrawal Management

---

### Case studies reveal that rapid micro induction of buprenorphine/naloxone prevent withdrawal symptoms.

**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.

### **Non-opioid lofexidine effective in withdrawal management, better than clonidine**

**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 conclusion:** 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.

### **Alpha<sub>2</sub>-adrenergic agonists work well to reduce withdrawal symptoms**

**Gowing, L., Farrell, M., Ali, R., White, J.M. (2016). Alpha<sub>2</sub>-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 alpha<sub>2</sub>-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 alpha<sub>2</sub>-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 alpha<sub>2</sub>-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 alpha<sub>2</sub>-adrenergic agonist than those treated with reducing doses of methadone.
- Neither alpha<sub>2</sub>-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 alpha<sub>2</sub>-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 alpha<sub>2</sub>-adrenergic agonists.
- The most common adverse effects of alpha<sub>2</sub>-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 conclusion:** The completion rates of withdrawal treatment are similar for alpha<sub>2</sub>-adrenergic agonists and methadone. Duration of treatment was longer and there were fewer adverse effects with methadone when compared to alpha<sub>2</sub>-adrenergic agonists. Symptom severity is worse early in treatment for alpha<sub>2</sub>-adrenergic agonists whereas it peaks near the end of the taper for individuals taking reducing doses of methadone.

### Buprenorphine and methadone most effective methods of opioid detoxification

Meader N. (2010). A comparison of methadone, buprenorphine and alpha<sub>2</sub> 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 conclusion:** Both buprenorphine and methadone found superior to lofexidine or clonidine for completion of detoxification, with buprenorphine found to be superior to methadone.

