

RESIDENTIAL SUBSTANCE ABUSE TREATMENT (RSAT)

Training and Technical Assistance

Recent Medication-Assisted Treatment Studies Relevant to Corrections



Advocates for
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INTRODUCTION

The following studies address various aspects of medication-assisted treatment relevant to corrections and serving individuals before and after release. The research has been classified by primary opioid medications studied, although many 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 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. That is followed by a full citation so that readers may access the full study. The summary begins with a very brief description of the study, including its 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) Current MAT Use in Community Treatment Facilities Through 2015

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

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

This report updates the trends in the use of methadone and buprenorphine and adds to those trends by including the use of extended-release, injectable naltrexone in the treatment of opioid use disorder in substance abuse treatment facilities. This report includes data from 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.

- Clients receiving treatment with methadone accounted for approximately 21 to 25 percent of all substance abuse treatment clients each year.
- 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.

2) Naltrexone Studies

Two-thirds of parolees/probationers remained on Injectable Naltrexone for at least three months, less likely to be re-incarcerated

Coviello, D. M., Cornish, J. W., Lynch, K. G., Boney, T. Y., Clark, C. A., Lee, J. D., ... & Schwartz, R. 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.

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 Penn site were retained at least 4 months and 64% were retained at least 3 months across all 5 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., 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.

The purpose of this study was to compare 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.

- 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 no better than those receiving psychosocial treatment alone, but better than those receiving buprenorphine/naloxone.

Crits-Christoph P, Markell HM, Gibbons MB, Gallop R, Lundy C, Stringer M, et al. (November 2016). A naturalistic evaluation of extended-release naltrexone in clinical practice in Missouri. *Journal of Substance Abuse Treatment*, 70:50–7.

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).

- 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, prolonged retention, but did not significantly reduce relapse or rearrest

Dugosh, KL, Festinger DS. (2017). *Ohio Addiction Treatment Program Evaluation Final Report*. Treatment Research Institute.

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 non-random 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 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 an 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 EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. (April 30, 2011). Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Lancet* 377(9776):1506–13.

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 one-year open-label extension.
- Research Conclusion: Vivitrol met FDA criteria to be approved for the treatment of opioid use disorder in addition to alcohol use disorder which it was approved for years earlier.

Injectable Naltrexone use associated with improved HIV viral suppression among persons released from prison or jail

Springer, S. A. Di Paola, A., Azar, MM., 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.

This first ever study examined whether inmates released on injectable naltrexone were more likely to maintain or improve their HIV viral load suppression. 93 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%), 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 more likely to result in continued injections than if not begun until after release and also 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.A., 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.

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.
- 100% of the prerelease injection group received the first injection in prison while only 67% received their first injection in the comparison group. 78% in the prerelease injection group went on to receive more than the initial injection while only 17% did in the comparison group.
- Only 22% of the prerelease 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 more effective to reduce relapse among offenders, no overdoses (0/153) compared to comparison group (7/155)

Lee, J.D., Friedmann P.D., Kinlock T.W., Nunes, E.V., et al. (2016). Extended-release naltrexone to prevent opioid relapse in criminal justice offenders. *New England Journal of Medicine* 374, 1232-42.

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 DL, Milchak W, Gastfriend DR, Herschman PL, Bixler EO, Velott DL, et al. (April 2015). Effects of injectable extended-release naltrexone (XR-NTX) for opioid dependence on residential rehabilitation outcomes and early follow-up. *American Journal of Addiction* 24(3):265–70.

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 out-patient treatment, but residential patients proved reluctant to receive it.

Pre-release Injectable Naltrexone associated with higher retention post release, subsequent overdose deaths occurred 2.5 months or more after the last injection.

Lincoln T, Johnson BD, 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.

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 it 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*, 1-8.

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 US Food and Drug Administration Adverse Event Reporting System Case narratives to identify overdose deaths amongst 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 more likely to receive more injections of Naltrexone and, in turn, more injections associated with lower relapse rates.

Saxon AJ, Akerman SC, Liu CC, et al. (2018). Extended-release naltrexone (XR-NTX) for opioid use disorder in clinical practice: Vivitrol's Cost and Treatment Outcomes Registry *Addiction*. doi: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 US 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 6-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 1, 2, or 3 injections, the 6-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., et. al. (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*, 2019; DOI: 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 and assessed them 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.

- 46 people in the implant group remained on ART regimen compared to 32 in the oral drug group.
- 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.
- 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 it Naltrexone orally.

3) Methadone Studies

Methadone and counseling together found 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. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/26808307>

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.
 - 5 studies¹ demonstrated greater treatment attendance and 2 studies² demonstrated lower treatment dropout rates
 - 5 studies³ demonstrated decreased opioid use among MMT clients receiving psychosocial treatment.

¹ 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; Hser, Y. I., Li, J., Jiang, H., Zhang, R., Du, J., Zhang, C., Zhang, B., Evans, E., WU, F., Chang, Y.J. & Peng, C. (2011). Effects of a randomized contingency management intervention on opiate abstinence and retention in methadone maintenance treatment in China. *Addiction*, 106(10), 1801-1809; 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; 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; 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.

² (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; 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.

³ 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; Chawarski, M. C., Zhou, W., & Schottenfeld, R. S. (2011). Behavioral drug and HIV risk reduction counseling (BDRC) in MMT programs in Wuhan, China: a pilot randomized clinical trial. *Drug and alcohol dependence*, 115(3), 237-239; Hser, Y. I., Li, J., Jiang, H., Zhang, R., Du, J., Zhang, C., Zhang, B., Evans, E., WU, F., Chang, Y.J. & Peng, C. (2011). Effects of a randomized contingency management intervention on opiate abstinence and retention in methadone maintenance treatment in China. *Addiction*, 106(10), 1801-1809; 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; 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.

- 7 studies revealed significant effects of psychosocial interventions on secondary outcomes including HIV risk,⁴ psychosocial functioning⁵, adherence to psychiatric medications⁶ alcohol use,⁷ and fear of detoxification⁸
- Research conclusion: Results of the studies generally support the use of psychosocial interventions [such as Contingency Management and Cognitive Based 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 non-prescribed Benzodiazepines do.

Dellabella, H. (2019, January 22). Benzodiazepines, if Prescribed, May Not Affect Methadone Treatment Retention. Retrieved from <https://www.clinicalpainadvisor.com/opioid-addiction/use-of-prescribed-benzodiazepine-may-not-affect-retention-of-methadone-treatment/article/828548/>

The study included patients from 52 opioid use disorder outpatient clinics who were initiating Methadone Maintenance Treatment (MMT) 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. A total of 3,692 participants initiating methadone-assisted treatment for the first time made up the study. 76% had no benzodiazepine prescription and <30% screening positive for benzodiazepine, 13% had a benzodiazepine prescriptions but had negative UDS, 6% did not have a benzodiazepine prescription but had positive UDS, and 6% had a benzodiazepine prescription and had positive UDS.

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

Rapid Methadone detox in jail discourages post-release Methadone Maintenance.

⁴Chawarski, M. C., Zhou, W., & Schottenfeld, R. S. (2011). Behavioral drug and HIV risk reduction counseling (BDRC) in MMT programs in Wuhan, China: a pilot randomized clinical trial. *Drug and alcohol dependence*, 115(3), 237-239

⁵Hesse, 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; Gerra, G., Saenz, E., Busse, A., Maremmanni, 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.

⁶Kidorf, 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.

⁷Gruber, 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.

⁸Stotts, 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.

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. <http://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 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 associated with reduced enrollment post-release.

Rich JD, McKenzie M, Larney S, Wong JB, 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. *Lancet*, 386, 350–9.

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 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 to 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 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), e1002625. Retrieved from <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.

4) Buprenorphine Studies

Buprenorphine alone effective for at least interim periods.

Sigmon SC, Ochalek T, Meyer A, et al. (2016). Interim buprenorphine vs waiting list for opioid dependence. *New England Journal of Medicine* 375, 2504–2505. Retrieved from <https://www.nejm.org/doi/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 wide among polydrug abusers on Medicaid, not used as intended for maintenance.

Walker, R., TK Logan, Quintin T. Chipley & Jaime Miller (2018) Characteristics and experiences of buprenorphine-naloxone use among polysubstance users, *The American Journal of Drug and Alcohol Abuse*, DOI: 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 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, not well connected to treatment.

Gordon AJ, Lo-Cignanic WH, Cochran G, et al. (2015). Patterns and quality of buprenorphine opioid agonist treatment in a large Medicaid program. *J Addict Med*, 9, 470-477.

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 opioid use disorder (OUD) filling prescriptions for buprenorphine increased from 9.8% to 25.2% from 2007 to 2012. Increases varied by age, sex, and race.

- 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 common, 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), 175-80.

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 used as 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.

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, 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 decreased users securing other opioid prescriptions.

Benham, B., & JH Bloomberg School of Public Health. (2017, February 23). Many Patients Receive Prescription Opioids During Medication-Assisted Treatment for Opioid Addiction. Retrieved from <https://www.jhsph.edu/news/news-releases/2017/many-patients-receive-prescription-opioids-during-medication-assisted-treatment-for-opioid-addiction.html>

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 between one to six months. It did not look at the use of heroin and non-prescribe opioids.

- Most of the study subjects discontinued using buprenorphine within three 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 not associated with better outcomes.

Gordon MS, Kilock TW, Robert RP, et al. (2017). A randomized clinical trial of buprenorphine for prisoners: Findings at 12-months post-release. *Drug and Alcohol Dependence*, 172, 34-42.

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 (In-Prison 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 twelve 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-months 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*.

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 = 4928; 28.4%) and most discontinued before 180 days (N = 11,189; 64.6%).
- Risk factors for discontinuation included: a lower initial buprenorphine dose (≤ 4 mg); male sex; younger age, minority race/ethnicity, 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 substance use disorders.

Buprenorphine found 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), e1-e6.

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 3 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 (ie, 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 (ie, 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 upon 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, 74.e11-74.e17. Retrieved from <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 cognitive behavioral therapy.
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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., ... & Hasson, A. L. (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.

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 ration 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 effective over time, not effective if limited to short periods

Weiss, R. D., Potter, J. S., Griffin, M. L., Provost, S. E., Fitzmaurice, G. M., McDermott, K. A., . . . Carroll, K. M. (2015). Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study. *Drug Alcohol Depend*, 150, 112-119. doi: 10.1016/j.drugalcdep.2015.02.03

This is a follow up to POATS, a multi-site randomized controlled trial consisting of brief treatment (2 weeks of buprenorphine/naloxone) followed by two 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 5 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.

Injectable buprenorphine at various doses linked to significantly greater abstinence than placebo

Haight, B. R., Learned, S. M., Laffont, C. M., Fudala, P. J., Zhao, Y., Garofalo, A. S., ... & Andersen, J. L. (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.

This randomized, double-blind, placebo-controlled, phase 3 trial was done at 36 treatment centers in the USA. 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 counselling. 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 six [6%] participants in the placebo group), constipation (16 [8%] vs 19 [9%] vs 0), nausea (16 [8%] vs 18 [9%] vs five [5%]), and injection-site pruritis (19 [9%] vs 13 [6%] vs four [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 compared to daily film

Lofwall, M. R., Walsh, S. L., Nunes, E. V., Bailey, G. L., Sigmon, S. C., Kampman, K. M., & Oosman, 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.

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 2 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.

5) Comparisons of the Opioid Medications

Vivitrol found not to be inferior to Buprenorphine

Tanum, L., Solli, K. K., Latif, Z., Benth, J. Š., Opheim, A., Sharma-Haase, K., & ... 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. doi: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., and Kunoe, N. (2018) Effectiveness, safety and feasibility of extended-release naltrexone for opioid dependence: a 9-month follow-up to a 3-month randomized trial. *Addiction*, 113: 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 chose 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, out-patient 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 same effects on symptoms of anxiety and depression as Buprenorphine/Naloxone, but insomnia score significantly lower.

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.

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 1 of these 2 drugs. The study was conducted at outpatient addiction clinics in 5 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 2 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.*

The purpose of this study was to compare 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 HM, Gibbons MB, Gallop R, Lundy C, Stringer M, et al. (November 2016). A naturalistic evaluation of extended-release naltrexone in clinical practice in Missouri. *Journal of Substance Abuse Treatment, 70:50–7.*

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 Economical Review. (2018). Extended-Release Opioid Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder: Effectiveness and Value. Evidence Report.

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 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.

Daily Buprenorphine more cost effective than Injectable Naltrexone

Staff, A. I. (2018, December 18). Daily medication appears more cost-effective than monthly injections for opioid use disorder | ACP Internist Weekly. Retrieved from

<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 RP, Butler T, Degenhardt L (2015). A longitudinal comparison of retention in buprenorphine and methadone treatment for opioid dependence in New South Wales, Australia. *Addiction*. 2015 Apr;110(4):646-55. doi: 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 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.*

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.

Injectable Naltrexone more cost effective than Methadone or Buprenorphine.

Jackson H, Mandell K, Johnson K, et al. (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.*

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 E., 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 one day.

Methadone and Buprenorphine require higher doses to be effective; higher retention 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, 79-87.*

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 9 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 found ineffective because participants did not continue injections after the first.

Larochelle, M.R., Bernson, D., Land, T., Stopka, T.J., Wang, N., Xuan, Z., Bagley, S.M., Liebschutz, J.M., Walley, A.Y. (2018). Medication for Opioid Use Disorder After Nonfatal Opioid Overdose and Association With Mortality: A Cohort Study. *Annals of Internal Medicine. doi: 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 on-going 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

Maria Paz Garcia-Portilla, Maria Teresa Bobes-Bascaran, Maria Teresa Bascaran, Pilar Alejandra Saiz, and Julio Bobes (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.

This review compared multiple methadone with 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, 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.

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 and Injected Naltrexone same retention once begun, harder to begin Vivitrol

Lee, J.D., Nunes, E.V., Novo, P., Bachrach, K., Bailey, G.L., Bhatt, S., Stablein, D., Subramaniam, G., & Rotrosen, J. (2018). Comparative Effectiveness of Extended Release Naltrexone Versus Buprenorphine-Naloxone for Opioid Relapse Prevention (X:BOT): a multicentre, open-label, randomized controlled trial. *The Lancet 391*(10118), 309-318.

This study compared randomly assigned to Buprenorphine/Naloxone (n=287) and Injectable Naltrexone (n=283) for 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 percent of those who started on it relapsed over the course of the 24-week study, compared with 56 percent 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 associated with reduced accidental overdoses, Buprenorphine associated with reduced arrests and accidental overdoses; Methadone associated 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, *American Journal of Psychiatry*. Retrieved from [10.1176/appi.ajp.2018.17101112](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, but Buprenorphine associated with less risk of adverse events, but better treatment retention with Methadone.

Thomas, C. P., Fullerton, C. A., Kim, M., Montejano, L., Lyman, D. R., Dougherty, R. H., & Delphin-Rittmon, M. E. (2014). Medication-assisted treatment with buprenorphine: assessing the evidence. *Psychiatric Services*, 65(2), 158-170.

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 safer than Methadone, but treatment duration shorter in buprenorphine, so they come out the same

Hickman, M., Steer, C., Tilling, K., Lim, A. G., Marsden, J., Millar, T., ... & 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.

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 compared, methadone all cause and overdose death rates higher than buprenorphine

Sordo Luis, Barrio Gregorio, Bravo Maria J, Indave B Iciar, Degenhardt Louisa, Wiessing Lucas et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies *BMJ* 2017; 357 :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 1000 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 1000 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.

6) Miscellaneous Studies

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

Olfson M, Wall M, Wang S, Crystal S, Blanco C. (2017). Service Use Preceding Opioid-Related Fatality. *American Journal of Psychiatry*, 175(6), 638-544.

This study investigates over 13,000 overdose deaths between 2001 and 2007 of those in the Medicaid program that 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 these deaths 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, 1771–2.

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, 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 US 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 effective for justice-involved population

Coviello DM, Zanis DA, Wesnoski SA, Palman N, Gur A, Lynch KG, McKay JR. (2013). Does mandating offenders to treatment improve completion rates? *Journal of Substance Abuse Treatment*, 44, 417–425.

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 six-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.

Legality of denying MAT questioned

Center, L. A. (2011). Legality of denying access to medication assisted treatment in the criminal justice system. Legal Action Center, 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 United States 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 (“Title II”) 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 Rehabilitation Act 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 United States 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

Enos A. Gary (2017) Cost Analysis backs immediate access to agonist treatment for opioid dependence, Behavioral Healthcare Executive, Krebs, E. (2017). Annals of Internal Medicine.

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 associated with decline in post-release overdose deaths

Green, Traci & Clarke, Jennifer & Brinkley-Rubinstein, Lauren & Marshall, Brandon & Alexander-Scott, Nicole & Boss, Rebecca & D. Rich, Josiah. (2018). Postincarceration Fatal Overdoses After Implementing Medications for Addiction Treatment in a Statewide Correctional System. JAMA Psychiatry, 75(4), 405-407

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 percent) who died of an overdose in the first six months of 2016 were recently incarcerated compared with 9 of 157 (5.7 percent) in the same period in 2017, a 60.5 percent 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 no better than daily.

Institute for Clinical and Economical Review. (2018). Extended-Release Opioid Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder: Effectiveness and Value. Evidence Report.

This study compared the effectiveness of newer, extended-release treatments for MAT i.e. looking at what's effective out of all of these (two buprenorphine injections, one buprenorphine implant, and naltrexone injection) 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 Probuophine (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.

Mobile technology platform increases MAT retention

Schuman-Olivier, Z., Borodovsky, J. T., Steinkamp, J., Munir, Q., Butler, K., Greene, M. A., & 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(1), 21.

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 min, 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.

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*. Retrieved April 3, 2019 from 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 those taking it orally.
- 46 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.

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.* doi:10.1111/add.12266

This randomized controlled trial compared the effectiveness of 4 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 1 of 4 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. Primary outcome was opioid use, measured as a proportion of opioid-negative urine results over the number of tests possible. Secondary outcomes include 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 opiates users seeking treatment.

Release prisoners on agonist medication less likely to die and more likely to attend treatment in month following release.

Marsden, J., Stillwell, G., Jones, H., Metcalfe, C., Hickman, M., Cooper, A., & ... Shaw, J. (n.d). 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.*

This United Kingdom-based study investigated if receiving Suboxone or Methadone before release increases or decreases risk of death after release. The study 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
- 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.