Buprenorphine MAT's Impact on Opioid Relapse

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Introduction

The Merriam-Webster dictionary defines an addict as someone exhibiting a compulsive need for a habit-forming substance (Merriam-Webster, n.d.). The compulsivity in reference is a more modern inclusion to the description of addiction. This came to be following substantial evidence highlighting biological, genetic, neurological, and environmental components resulting in dependence or a chronic inclination to do, use, or indulge in something repeatedly. This updated definition aligns with the disease model of addiction more widely recognized by scientists and researchers today. Following this evidence, over the past century, professionals have shifted towards treating addiction through the lens of the disease model. Medicine-assisted treatment (MAT) has become commonly used in addiction treatment centers around the world. MAT is described as a comprehensive approach that combines medications with behavioral therapies to treat patients (FDA, n.d.). MAT is often chosen to treat opioid use disorder due to overwhelmingly positive outcomes and its harm reduction framework. More specifically, the Substance Abuse and Mental Health Services Administration (SAMHSA) notes that MAT can not only successfully treat these disorders but can also help sustain recovery while preventing or reducing opioid overdose (Medication-assisted treatment, n.d.). In 2020, opioids were involved in 68,630 overdose deaths, which accounted for 74.8% of all drug overdose deaths (Centers for Disease Control and Prevention, 2022). Furthermore, 82.3% of opioid-involved overdose deaths involved synthetic opioids other than methadone and deaths involving primarily fentanyl continue to rise (U.S. Department of Health and Human Services, 2022). These staggering numbers represent the importance of addressing opioid dependence and introducing evidence-based treatment options such as MAT.

Opioid use disorder and dependence does not only take a toll on American lives. It was estimated that in 2017 the cost of the United States opioid epidemic was $1,021 billion, including $550 billion attributed to the cost of fatal opioid overdose (Center for Disease Control and Prevention, 2021). Opioid use is a societal issue due to its brevity. Introductions to updated treatment modalities highlight the cost-effectiveness of MAT. For example, in a comparison of implantable medication that was approved by the FDA in 2016 for the treatment of opioid use disorder, as opposed to the traditional sublingual form, society gained approximately $5,953 in benefits with a non-medical costs savings of $1,721, most attributable to lower criminal justice costs (Carter et al., 2017, p. 896; FDA, n.d.). More specifically, this modality was associated with lower costs related to treatment administration, emergency room and hospital utilization, new hepatitis C virus (HCV), and diversion (Carter et al., 2017). MAT not only proves to be the most economically smart choice, but it has shown to reduce the potential for relapse and subsequently lowering a person's risk of contracting HIV or HCV (Medication-assisted treatment, n.d.). Addressing comorbidities further increases the benefits of MAT, especially since one particular research database recorded that 35% of participants receiving MAT had chronic HCV (Reimer et al., 2020). MAT is designed to incorporate more holistic services because of the understanding that addiction is complex and unique in every scenario. A narrow focus on the substance being used may neglect important aspects and barriers to recovery, resulting in relapse.

As previously mentioned, perspectives pertaining to addiction have begun to change over the past several decades. Despite efforts by clinicians, researchers, and professionals to refute misconceptions surrounding addiction, a substantial amount of stigma remains. Previously, and still in many ways today, society has adopted a choice model perspective of addiction.

Essentially, addiction was viewed as a choice in which the individual was not exhibiting substantial will power. However, from the lens of a disease model, addiction medicine such as buprenorphine and methadone used in MAT, serve as a viable option for treating opioid dependence, and have proven their value by saving countless lives over the past half a century ("Fifty years after…", 2018).

Buprenorphine vs. Methadone

Buprenorphine was discovered in 1966 but was not approved by the FDA until nearly three decades later (Campbell & Lovell, 2012). Prior to that, Methadone emerged in the late 1940s and has since then been the dominator in addiction medicine ("Fifty year after…, 2018). A longer history seems to be the only thing continuing to propel methadone to the top. In many ways, buprenorphine would seem to be the better option for treating opioid addiction. One of its safer characteristics includes that at a certain point, taking more of the medicine will not increase the drug's effects (Whelan & Remski, 2012). Additionally, it is often associated with less analgesia and euphoria, which could account for its lack of popularity.

A common concern is that these medications simply trade one addiction in for another. SAMHSA notes that opioid dependence medications such as buprenorphine, methadone, and naltrexone are safe to use for a lifetime (Medication-assisted treatment, n.d.). These medications are partial opioid agonists that are designed to bind to the same receptors as opioids, but to activate them less strongly and thus serves as a powerful aid during withdrawal. At sufficient doses, buprenorphine can make continued opioid abuse less attractive by decreasing the pleasurable effects of other opioids (FDA, n.d.).

Individuals experiencing addiction often have a notable number of adverse childhood experiences (ACEs). Research has shown that ACEs have a significant impact on stress-levels

throughout life, and high stress-levels can increase cravings (Guille et al., 2021). In conjunction with supplementary medication such as Lofexidine to address stress-related cravings, MAT can be properly customized to maximize benefits and produce the most desirable outcomes. Mary Jeanne Kreek, one of the pioneers of Methadone, discusses how abstinence-based therapies continue to dominate society despite the majority of scientists arguing that abstinence-based treatment does not work for most opiate addicts. ("Fifty years after…, 2018). Furthermore, they emphasize that MAT medications tend to result in sustained treatment and lower relapse rates. Whether the patient's goal is abstinence or sustained recovery, opioid dependence medications prove to be a safe and viable option supported by the FDA and many major national addiction specific organizations.

An opposition to MAT neglects the empirically sound evidence, disregards the importance of combating the opioid epidemic, and exhibits a lack of urgency to save lives. Buprenorphine at any dose has been found to retain patients in recovery better than a placebo (Reimer et al., 2020). A 36-week follow-up of 428 individuals receiving MAT reported that four of the individuals not on MAT had overdose events, while only 2 receiving MAT had overdose events (Greiner et al., 2021). It becomes difficult to argue the benefits of MAT when it has the potential to cut overdose rates in half.

Predicting the factors that contribute to relapse can ultimately promote prevention and lower the risk of overdose (Chang et al., 2019). Rural populations typically face higher numbers of opioid use across the United States (Derefinko et al., 2019). Furthermore, researchers found that individuals seeking treatment for opioid dependence were more likely to be unemployed, have a high school education or less, homeless, and on parole or probation (Greiner et al., 2021). Other researchers found that amongst those abstinent from heroin, they were more likely to be

younger and were less likely to be Hispanic (Zhu et al., 2018). These disparities are systemically engrained and represent the repercussions of an outdated choice model of addiction. Some of the barriers people must overcome in order to initiate MAT and receive adequate dosing include regulations, strict rules surrounding missed doses and the use of other drugs, and the requirement of daily visits at the beginning of treatment (Biondi et al., 2022). More disturbing trends specific to women diagnosed with opioid use disorder (OUD) have emerged and subsequently increased the need for research considering gender differences and vulnerability to relapse (Guille et al., 2021). However, amongst non-fatal overdoses (NFOD) in 2016 from Maryland prescription drug monitoring data, individuals were more likely to be male and younger than 35 (Chang et al., 2019). Identifying ways to address addiction and prevent relapse across all demographics remains crucial.

Method

Criteria for Inclusion

A preliminary search was conducted through Milligan University library's database using the key words "opioid use disorder" and "medicine-assisted treatment." These parameters yielded over a thousand results, and thus the criteria for inclusion was amended. In order to narrow the search, updated key words included "buprenorphine," "relapse," "adults," and "opioid use disorder" with results narrowed to those peer-reviewed and ranging from 2012 to 2022. Since adolescent treatment for opioid use disorder varies and often is drastically different from adult MAT, the search was limited to publications pertaining to adults only. Approximately 100 results appeared and were sifted through for more accurate relevance to factors increasing relapse or characteristics congruent with treatment retention. After reviewing abstracts, 30 publications were deemed to be potentially relevant. A more in-depth examination revealed that

11 provided significant supplementary information or addressed the question at hand specifically. These 11 articles were read in depth, annotated, and included in the appendix.

Annotated Bibliography

Many of the studies included in the appendix include large databases and a few utilize data from the same clinical trial of buprenorphine-naloxone and extended-release naltrexone. Furthermore, Reimer et al. (2020) and Rudolph et al. (2022) specifically include data relevant to buprenorphine dosage and relapse. These sources report data consistent with previous literature and emphasize the need for adequate dosing. A systematic review conducted by Goel et al. (2018) highlights the lack of literature reporting relapse rates, and from my own search, it is apparent that there is still not enough data pertaining to this topic.

Table 1

Effects of Medication-Assisted Treatments for Opioid Use Disorder

References	Duration & Type of Study	Participants	Explanatory Variables	Measurable Outcomes	Findings
Greiner et al. (2021)	36-week naturalistic follow-up of X:BOT comparative effectiveness trial conducted by Lee et al. (2018)	428 (75%) of the 570 original participants; 225 of the 287 from the BUP-NX group and 203 of the 283 from the XR-NTX group	XR-NTX, BUP-NX	Relapse, opioid use, stimulant use, retainment on medication	At follow-up, fewer participants on MAT met relapse criteria (16.4% vs 38.9%), had fewer opioid use days in the past month (4.4 days vs 9.8 days), and had less stimulant use (15.2% vs 27.7%). Additionally, 47.4% reported not being on medication.
Zhu et al. (2018)	Minimum of 5-year follow up of randomization to treatment groups in a multi-site trial spanning from 2006-2009 conducted by Saxon et al. (2013)	699 adults with OUD according to the DSM-V	Methadone, BUP-NX	Abstinence from heroin, abstinence from all opioids, Addiction Severity Index (ASI)	Participants in the heroin-abstinent group were less like to have been randomized to BUP (vs. MET: 50.4% vs. 59.7%); 232 (33.2%) had achieved 5-year abstinence from heroin and 20.7% had remained abstinent from all opioids including heroin. Abstinent participants had significantly lower ASI scores and reported less severe problems in several areas of life.

References	Duration & Type of Study	Participants	Explanatory Variables	Measurable Outcomes	Findings
Reimer et al. (2020)	Analysis of real-world data set; Record collection spanning from 2011-2012	364 German adults with qualifying OUD according to the International Classification of Diseases 10th Edition	BUP prescription	Risk of relapse	They found a protective effect of higher BUP dosages was significantly associated with lower risk of relapse, 166 patients suffered from relapse, and dosage of higher than 16 mg/day was found to reduce the risk of relapse by 82% compared to less than 6 mg/day.
Chang et al. (2019)	Analysis of prescription drug monitoring data from 2015 and hospital discharge records in 2016	25, 487 Maryland BUP adult patients	BUP	Non-fatal overdose (NFOD)	Data revealed that 827 (3.24%) had one or more NFOD in 2016. Longer days of BUP supply were significantly associated with lower odds of NFOD. Individuals with NFOD, compared to those without, had shorter days of buprenorphine supply (123 vs. 173 days), were more likely to have had opioid analgesic prescription (40.02% vs 29.90%), were more likely to have any benzodiazepine prescription (31.08% vs 23.19%)

Note. X:BOT = extended-release naltrexone vs. buprenorphine for opioid treatment; XR-NTX = extended-release naltrexone; BUP-NX = buprenorphine-naloxone; BUP = buprenorphine; OUD = opioid use disorder

Table

Four sources were chosen for inclusion into the table in order to highlight the effects of medication-assisted treatments for opioid use disorder. Other sources were not included based on their lack of relevance to buprenorphine MAT and the risk of relapse specifically. They all examined the impact of buprenorphine on relapse or abstinence, and their findings complimented each other by further emphasizing the benefits of MAT. NFOD is a particularly interesting measurable outcome that highlights relapse through a different lens. Researchers found that longer days of BUP supply were significantly associated with lower odds of NFOD, which ties in well with appropriate dosing and treatment retention (Chang et al., 2019). Additionally, these four sources were published within the past 4 years, and since the use of buprenorphine to treat opioid dependence is relatively new amongst the medical community, more up-to-date literature is appropriate. Of note, Zhu et al. (2018) reported that individuals in the heroin-abstinent group were less likely to be randomized to buprenorphine. This supports a hypothesis previously describing as to why methadone remains more popular than buprenorphine despite characteristics making it the superior choice of treatment for opioid dependence.

Conclusion

When addressing what factors increase the risk of relapse amongst adults receiving buprenorphine medicine-assisted treatment for opioid use disorder, it's important to remember the complexity of addiction and the influence that environmental, biological, physiological, and systemic factors have on recovery outcomes. From a review of literature published within the past decade, it is apparent that one of the most important aspects of MAT is dosing. In general, research suggests that patients are receiving lower doses than they should be. Reimer et al. (2020) highlight that their dataset denoted 6 mg of buprenorphine as the lowest and largest

dosage group. They go on to conclude, consistent with previous studies, that higher buprenorphine dosages are a protective factor to relapse. “The maintenance dosage recommended for buprenorphine is between 12 and 24 mg, with evidence suggesting that higher doses (perhaps over a particular threshold, e.g. ≥ 16 mg, or perhaps incrementally along a continuum) are protective against dropping out of treatment and relapse” (Rudolph et al., 2022). Similarly, a longer duration of treatment proves to yield more positive treatment outcomes. Data revealed that longer days of buprenorphine supply were significantly associated with lowers odds of NFOD (Chang et al., 2019). More specifically, an additional 100 days equated to 21% lower odds of overdose. Professionals providing MAT must take into consideration not only how much they are prescribing, but over what period of time as well.

Although there is significant evidence supporting buprenorphine MAT as one of the best treatment options for opioid use disorder, patients remain highly vulnerable to treatment discontinuation and relapse (Chang et al., 2019). However, Greiner et al. (2021) found that of those who retained treatment, fewer met relapse criteria (16.4% vs 38.9%), they had fewer opioid use days in the past month (4.4 days vs 9.8 days), and they had less stimulant use (15.2% vs 27.7%). Barriers to treatment not only play a role during initiation, but also throughout maintenance. The same Massachusetts government database cited previously, reported that among the 114,971 buprenorphine treatment episodes recorded, 102,918 (90%) ended in discontinuation (Park et al., 2020). Additionally, amongst the 570 participants in the buprenorphine-naloxone and extended-release naltrexone clinical trial, almost half (47.4%) at follow-up reported not being on medication (Greiner et al., 2021). Retaining treatment tends to yield positive outcomes, so the question then becomes, what factors promote retention of MAT?

Factors shown to negatively impact treatment retention include houselessness, HIV status, cocaine use, DSM-V diagnosed depression, referral to treatment from prison/jail, employment status, and a higher dosage of medication outlined to be either more than 85 mg of methadone or 16 mg or more of buprenorphine (Bionidi et al., 2022). Other potential correlates shown to possibly be associated with opioid abstinence include treatment history and the patient's motivation for change (Zhu et al., 2018). A combination of all these factors at play is what makes it so difficult to determine what specifically promotes retention of treatment.

Many of the samples included in the literature chosen, represent real-world data and highlight significant benefits of MAT for opioid dependence. However, some of this data dates back to over five years ago. More recent data pools should be analyzed to confirm previous findings. Additionally, data sets may not accurately represent illicit opioid use, and thus, findings may lack validity. Regardless, the findings being presented should be applied to treatment practices and used to inform public policies.

Based on the available research, it is apparent that adequate and flexible dosing yields positive outcomes for patients receiving buprenorphine MAT. Furthermore, treatment alone, and ultimately sustained treatment, results in more favorable outcomes than not receiving any treatment. Despite compelling data, stigma surrounding addiction, outdated perspectives, and subsequent barriers to treatment continue to counteract efforts to address the opioid epidemic in the United States. Further research should aim to identify ways in which demographics and treatment variables impact maintaining recovery from opioid addiction.

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Appendix

What factors increase the risk of relapse amongst adults receiving buprenorphine medicine-assisted treatment for OUD?

Biondi, B. E., Vander Wyk, B., Schlossberg, E. F., Shaw, A., & Springer, S. A. (2022). Factors associated with retention on medications for opioid use disorder among a cohort of adults seeking treatment in the community. *Addiction Science & Clinical Practice*, *17*(1), 15. https://doi-org.milligan.idm.oclc.org/10.1186/s13722-022-00299-1

In order to identify factors that increase retention of medication treatment for opioid use disorder (MOUD), researchers studied a population of 118 adults diagnosed with moderate to severe OUD, according to the DSM-V, that were actively seeking methadone or buprenorphine treatment in the community. 24.8% were black/African American and 31.6% were Hispanic/Latinx which was considered a strength due to the fact minorities are typically underrepresented in medication trials for OUD. Furthermore, the 36.4% of participants that had HIV were more likely to start Buprenorphine than those without. Exposures identified with MOUD retention included houselessness, HIV status, cocaine use, DSM-V diagnosed depression, referral to treatment from prison/jail, employment status, and a high dose of MOUD (> 85 mg of methadone or >/= 16 mg of Buprenorphine). At 6 months, 53% were retained on MOUD (49% and 58% of those who started buprenorphine and methadone, respectively). Although not statistically significant ($p = 0.052$), there was a strong association between lack of housing and MOUD retention. Researchers concluded that, consistent with previous findings, adequate dosing and high pain interference at baseline led to higher odds of retention. Highlighting this unique dynamic between retention and pain interference will be appropriate in my discussion of

medication assisted treatment. Both buprenorphine and methadone have analgesic (acting to relieve pain) effects serving dual purposes for those who have prominent pain interference, and as a result of the data, researchers recommend participant collaboration on dosages, identifying patient's pain management needs, addressing housing issues, and broader policy changes. Limitations of this study include it contains a small sample and selection bias could have impacted the results.

Carter, J. A., Dammerman, R., & Frost, M. (2017). Cost-effectiveness of subdermal implantable buprenorphine versus sublingual buprenorphine to treat opioid use disorder. *Journal of Medical Economics*, 1–20. https://doi-org.milligan.idm.oclc.org/10.1080/13696998.2017.1341416

Although these results should be interpreted with caution, they draw attention to a relatively new treatment modality that shows evidence of lowering expenses from a US societal perspective. Subdermal implantable buprenorphine (BSI) was approved in 2016 as a branded product differing from the generic sublingual buprenorphine (SL-BPN) by assuming to offer the same benefits while lowering the risk of diversion, misuse, and non-adherence. OUD expenses have become a societal issue with costs being driven largely by workplace, health care, and criminal justice expenditures. They including opioid-dependent, clinically stable adults in an office-based setting. Researchers found that the BSI cohort received higher rates of complete abstinence and retention in treatment, lower total costs ($20,733 vs $25,119), more quality-adjusted-life-years (QALYs) (0.832 vs 0.801), and a longer net monetary benefit than SL-BPN. Although BSI was associated with higher acquisition and supplemental use costs, BSI had lower accompanying costs related to emergency room and hospital utilization, treatment

administration, diversion, new HCV infection, rehabilitation service utilization, and pediatric poisonings. More specifically, "…for each patient treated with BSI instead of SL-BPN, society gained $5,953 in benefits" (p. 896). In conclusion, BSI offers improved outcomes and reduced overall costs that should be taken into account when identifying possible avenues for abstinence retention.

Chang, H. Y., Krawczyk, N., Schneider, K. E., Ferris, L., Eisenberg, M., Richards, T. M., Lyons, B. C., Jackson, K., Weiner, J. P., & Saloner, B. (2019). A predictive risk model for nonfatal opioid overdose in a statewide population of buprenorphine patients. *Drug & Alcohol Dependence*, *201*, 127–133. https://doi-org.milligan.idm.oclc.org/10.1016/j.drugalcdep.2019.04.016

This study includes Maryland prescription drug monitoring data from 2015 used to identify risk factors for non-fatal overdoses among adult buprenorphine patients (N = 25,487) that were included in hospital discharge records in 2016. Researchers aimed to identify what factors could predict relapse and recognized that although buprenorphine treatment is known to curb overdose risk, patients still remain highly vulnerable to treatment discontinuation and relapse. Of the total population included, 827 individuals (3.24%) had one or more non-fatal overdose (NFOD) in 2016. They were more likely to be male and younger than 35 years old. Furthermore, individuals with a NFOD, compared to those without, had shorter days of buprenorphine supply (123 vs. 173 days), had more unique pharmacies where they obtained buprenorphine (1.83 vs 1.71), had fewer buprenorphine prescriptions paid by cash (15.11% vs 18.54%) and commercial plans (50.67% vs 58.20%), were more likely to have buprenorphine prescriptions paid by Medicaid (60.70% vs 46.95%), were more likely to have had opioid analgesic

prescription (40.02% vs 29.90%), to have had more unique opioid analgesic prescribers (1.04 vs 0.69) and pharmacies (0.83 vs 0.57), to have had opioid prescriptions paid by cash (10.52% vs 7.40%), Medicaid (18.26% vs 10.17%), and commercial plans (24.30% vs 19.90%), were more likely to have any benzodiazepine prescription (31.08% vs 23.19%), and a higher number of benzodiazepine prescriptions (2.51 vs 1.77). Also, longer days of buprenorphine supply were significantly associated with lowers odds of NFOD. Specifically, an additional 100 days lowered the odds of overdose by 21%. As previously proposed in prior research, there is a great need for individualized care and these results emphasize screening measure to predict overdose beneficial to prescribers and clinicians.

Comer, S. D., Mannelli, P., Alam, D., Douaihy, A., Nangia, N., Akerman, S. C., Zavod, A., Silverman, B. L., & Sullivan, M. A. (2020). Transition of patients with opioid use disorder from buprenorphine to extended-release naltrexone: A randomized clinical trial assessing two transition regimens. *American Journal on Addictions*, *29*(4), 313–322. https://doi-org.milligan.idm.oclc.org/10.1111/ajad.13024

This study was designed to examine the transition from buprenorphine to extended-release naltrexone amongst adults diagnosed with opioid use disorder in outpatient and residential treatment facilities. Participants were randomly assigned to either the treatment or placebo group; however, both groups were given ancillary medications such as clonidine, trazodone, and clonazepam to combat withdrawal symptoms because it was deemed to be unethical to withhold this support. Furthermore, research indicates that buprenorphine discontinuation without pharmacological support is associated with a heightened risk of relapse. Researchers stated in their concluding

statements, “The combination of a fixed-dose ancillary regimen (including clonidine, clonazepam, and trazodone), a 7-day transition period, and psychoeducational counseling represented a well-tolerated approach to the management of opioid withdrawal symptoms, leading to XR-NTX induction in a hybrid inpatient/outpatient setting.” Additionally, positive outcomes were more common amongst those on BUP doses less than 8 mg/d at the time of protocol initiation. More specifically, participants in placebo groups prescribed less than 8 mg of buprenorphine had a 95% success rate of induction as compared to those on 8 mg who only had a 63% success rate. There were few limitations to this study, and overall, these findings will prove to be influential amongst my own research.

Derefinko, K. J., Salgado García, F. I., Talley, K. M., Bursac, Z., Johnson, K. C., Murphy, J. G., McDevitt-Murphy, M. E., Andrasik, F., & Sumrok, D. D. (2019). Adverse childhood experiences predict opioid relapse during treatment among rural adults. *The American Journal of Psychiatry*, *178*(7), 660–671. https://doi-org.milligan.idm.oclc.org/10.1176/appi.ajp.2020.20060816

ACEs have been cited as a predictor for substance use and rural populations tend to record higher numbers of opioid use. Including ACEs as a predictor of relapse, especially in the context of MAT, would be appropriate in my discussion. They included 87 patients who attended OUD treatment at a rural medical clinic with an average of 23.6 treatment visits that was accessible from archived medical records. This particular clinic offered both pharmacological and psychological therapy, which differs from other studies that include data from clinics that solely offer pharmacological assistance and lack an integrative care design. It was concluded that for every unit increase of ACE score, there

was a 17% (95% CI: 1.05–1.30, p = .005) increase in odds of relapse and each treatment visit was associated with a 2% (95% CI: 0.97–0.99, p = .008) reduction in odds of opioid relapse. However, these results should be considered with the context in which they were collected. The sample included 100% white individuals living in a rural area, making generalizability very limited. Derefinko et al. recognize this and go on to conclude that despite the fact that ACE may increase the risk for a poor response to MAT, consistent adherence to treatment will likely reduce the odds of opioid relapse. Future research should investigate which ACEs are most associated with relapse.

Guille, C., King, C., Ramakrishnan, V., Baker, N., Cortese, B., Nunn, L., Rogers, T., McRae-Clark, A., & Brady, K. (2021). The impact of lofexidine on stress-related opioid craving and relapse: Design and methodology of a randomized clinical trial. *Contemporary Clinical Trials, 111*. https://doi-org.milligan.idm.oclc.org/10.1016/j.cct.2021.106616

In light of particularly disturbing trends specific to women with OUD emerging, researchers identify a need for research accounting for gender differences and subsequent vulnerability to relapse. A double-blind, randomized, and placebo-controlled trial over a 32-day period is proposed to assess these gender differences in relation to the impact of Lofexidine on stress-related opioid cravings. Significant childhood trauma identified as an ACEs score of more than 4 would be used in data analysis because of evidence suggesting it can have a significant impact on stress. Addressing stress-related cravings in order to decrease the likelihood of relapse is appropriate, but often not incorporated into treatment practices. Guille et al., call attention to substantial literature suggesting worthwhile outcomes from implementing medications such as Lofexidine into treatment alongside buprenorphine and methadone. This particular source does well at highlighting

gender differences and the influence of ACEs on recovery. However, they exclude individuals with select medical illnesses and a history of current psychotic disorder or bipolar I affective disorder from participation. I would argue excluding these populations limits the generalizability of their results substantially due to the high prevalence of comorbidity amongst individuals seeking MAT.

Greiner, M. G., Shulman, M., Choo, T.-H., Scodes, J., Pavlicova, M., Campbell, A. N. C., Novo, P., Fishman, M., Lee, J. D., Rotrosen, J., & Nunes, E. V. (2021). Naturalistic follow-up after a trial of medications for opioid use disorder: Medication status, opioid use, and relapse. *Journal of Substance Abuse Treatment, 131*. https://doi-org.milligan.idm.oclc.org/10.1016/j.jsat.2021.108447

This study is applicable to my own report in many ways because it addresses system-level barriers to continuing treatment and naturalistic opioid use outcomes. Data was collected based on a 36-week follow up from a previous 24-week X:BOT comparative effectiveness trial of buprenorphine-naloxone and extended-release naltrexone. Of the original 570 participants, 428 (75%) individuals were included in the 36-week follow up. Most participants were unemployed, 27% were homeless, 13% were on parole or probation, and over half had a high school education or less. Correlations between these demographics and risk of relapse have been cited in previous research, and thus these numbers further emphasize the importance of case management when entering into medication-assisted treatment (MAT). Almost half (47.4%) at follow-up reported not being on medication. Although research contributes to the understanding that medication-assisted treatment can lower the risk of relapse, no difference is made if individuals cannot access these resources. Of those who retained treatment, fewer met relapse criteria

(16.4% vs 38.9%), they had fewer opioid use days in the past month (4.4 days vs 9.8 days), and they had less stimulant use (15.2% vs 27.7%). Additionally, only 2 of the individuals on MAT had overdose events versus 4 individuals who were not on MAT. An argument can be made the MAT has the potential to cut the prevalence of overdose in half.

Park, T. W., Larochelle, M. R., Saitz, R., Wang, N., Bernson, D., & Walley, A. Y. (2020). Associations between prescribed benzodiazepines, overdose death and buprenorphine discontinuation among people receiving buprenorphine. *Addiction*, *115*(5), 924–932. https://doi-org.milligan.idm.oclc.org/10.1111/add.14886

Findings specific to exclusively buprenorphine and to benzodiazepines emphasize previous conclusions and will prove to be beneficial in my own discussion on medication assisted treatment and retention. Researchers aimed to test the association between a prescription of benzodiazepine during buprenorphine treatment for OUD and fatal overdose. Furthermore, they correlated a prescription with non-fatal overdose, all-cause mortality, and buprenorphine discontinuation. Participants included 63,389 individuals analyzed from 5 Massachusetts government agencies linked data sets containing adult residents who received buprenorphine treatment in either tablet or film format between January 2012 and December 2015. Researchers concluded differently from previous studies, that a prescription during treatment was associated with an increased risk for fatal opioid overdose (hazard ration (HR) = 2.92), non-fatal opioid overdose (HR = 2.05), all-cause mortality (HR = 1.90), and a decreased risk of buprenorphine discontinuation (HR = 0.87). More specifically, of the 183 deaths which represented only 4% of their total participant pool, 31% occurred when individuals received a prescription during treatment

and twenty-four percent of these individuals filled at least one benzodiazepine prescription during treatment. Their unique findings could have been accounted for by adjusting their approach to include all emergency or hospital mental health encounters and psychiatric diagnoses. Furthermore, researchers' rationale included many confounding variables that could have been at play, including induced respiratory depression as a result of benzodiazepines, increased risk of inducing relapse to illicit opioid use as a result of the euphoric effects of benzodiazepines, and possible underlying mental health concerns warranting a benzodiazepine prescription. However, benzodiazepines can treat anxiety resulting in increased treatment adherence. Overall, there are many risks and benefits to prescribing benzodiazepine when simultaneously receiving buprenorphine treatment, and clinicians should apply caution when doing so.

Reimer, J., Vogelmann, T., Trümper, D., & Scherbaum, N. (2020). Impact of buprenorphine dosage on the occurrence of relapses in patients with opioid dependence. *European Addiction Research*, *26*(2), 77–84. https://doi-org.milligan.idm.oclc.org/10.1159/000505294

These findings are fairly straightforward and consistent with that of previous research; however, due to their real-world setting, these specific results are more compelling. Furthermore, covariates such as comorbidities, comedications, take-home versus office-based setting, dosing regimens, or demographics had no significant effect on results. It was concluded that a protective effect of higher buprenorphine dosages was significantly associated with lower risk of relapse. Unlike some other participant pools, this particular data set included 364 German adults pulled from data banks including 4 million individuals records qualifying for opioid dependence according to the ICD-10

between 2011 and 2012 and a least one buprenorphine prescription. Of the 364 participants, 166 suffered from relapse. Of the 133 individuals in the lowest dosage group, 85 suffered from relapse and of the 66 on a dose above 16 mg/day, 19 suffered from relapse. More specifically, a dosage higher than 16 mg/day was found to reduce the risk of relapse by 82% compared to less than 6 mg/day. Researchers note, "The results further showed that neither dosing regime, up-dosing, setting, demographic characteristics, comedication, nor comorbidities had a dosage-independent impact on the risk of relapses." These findings emphasize the importance of adequate dosing in relapse prevention and reveal a negative correlation between buprenorphine dosage and relapse.

Rudolph, K. E., Shulman, M., Fishman, M., Díaz, I., Rotrosen, J., & Nunes, E. V. (2022). Association between dynamic dose increases of buprenorphine for treatment of opioid use disorder and risk of relapse. *Addiction*, *117*(3), 637. https://doi-org.milligan.idm.oclc.org/10.1111/add.15654

A secondary analysis of a large, multi-site, and influential clinical trial was conducted to estimate the extent to which a hypothetical, or counterfactual, intervention would affect the risk of relapse between 20 days and the 24-week follow-up period. This intervention was described as increasing patients' buprenorphine dosage in response to opioid use. However, because the original clinical trial was not designed to test this, there are limitations to the results outlined. Furthermore, since there was not a broad policy for increasing buprenorphine dosages in response to opioid use, dosing was up to the clinician's discretion. Participants included 270 adults diagnosed with OUD according to the DSM-V, spanning across 8 community addiction treatment programs in the US who were treated with daily sublingual buprenorphine-naloxone. The vast majority were

mainly male, white, had a high school education or greater, reported current i.v. drug use, and had history of a psychiatric disorder. Rudolph et al. emphasize that previous literature denotes the recommended dosage of buprenorphine for maintenance to be between 12 and 24 mg. Researchers estimated that that increasing BUP–NX dose in response to recent opioid use would lower risk of relapse by 19.17 percentage points [95% confidence interval (CI) = −32.17, −6.18) (additive risk)] and 32% (0.68, 95% CI = 0.49, 0.86) (relative risk). Furthermore, most of the participants who relapsed stopped medication early, and "…results translate to a number needed to treat of six, meaning that treating six individuals with a dynamic BUP–NX regimen in which dosage is increased in response to opioid use would be expected to prevent one relapse." This conclusion raises a valid ethical question very relevant to my topic: If we can prevent one relapse and potentially save a life, why are we not implementing these strategies into routine medication assisted treatment for OUD?

Zhu, Y., Evans, E. A., Mooney, L. J., Saxon, A. J., Kelleghan, A., Yoo, C., & Hser, Y. I. (2018). Correlates of long-term opioid abstinence after randomization to methadone versus buprenorphine/naloxone in a multi-site trial. *Journal of Neuroimmune Pharmacology : The Official Journal of the Society on NeuroImmune Pharmacology*, *13*(4), 488–497. https://doi-org.milligan.idm.oclc.org/10.1007/s11481-018-9801-x

Researchers used data from a multi-site trial that randomized 1,269 opioid-dependent individuals to receive buprenorphine (n = 740) or methadone (n = 529) in nine states from 2006 – 2009. Of those 1,269 individuals, 699 adults were followed for at least 5 years (average follow-up time was 6.7 years). Their design was based on the premise that previous research indicates 5-year opioid abstinence is a good predictor of reduced

likelihood or relapse. It proved to be strong due to its uniquely long observational period and their consideration of non-medical use of prescription opioid medications. Data revealed that 232 (33.2%) of individuals had achieved 5-year abstinence from heroin and 20.7% of those individuals had remained abstinent from all opioids, which was notably lower than the rates of several earlier studies. Participants in the heroin-abstinent group were less likely to have been randomized to BUP, to use tobacco or cocaine, had fewer psychiatric disorders, were less likely to be Hispanic, and were significantly younger in comparison to the non-abstinent group. Furthermore, injection drug users and those treated in clinics on the west coast were less likely to achieve 5-year abstinence from heroin. The Addiction Severity Index (ASI) was also administered at the final follow-up interview, revealing that abstinent participants had significantly lower ASI scores and reported less severe problems in the following areas: employment, social and family relationships, legal status, and psychiatric health. This data will further strengthen my own discussion by providing more evidence for the claims made in reference to predictors of abstinence. Although consistent with previous findings, limitations of this study include its self-report design which could include bias and the influence of other potential correlates that may be associated with opioid abstinence. The influence of treatment history, the patient's motivation for change, etc. is what makes it difficult to identify what specifically fosters abstinence.