5-2021

Buprenorphine Versus Methadone for Treatment of Opioid Use Disorder

Ben DeVries
University of North Dakota, ben.devries@und.edu

Buprenorphine Versus Methadone for Treatment of Opioid Use Disorder

by

Ben DeVries, PA-S

Bachelor of Science, University of South Alabama, 2018

Contributing Authors, Daryl Sieg, MPAS and Dr. Jeanie McHugo

A Scholarly Project

Submitted to the Graduate Faculty of the University of North Dakota

in partial fulfillment of the requirements for the degree of

Master of Physician Assistant Studies

Grand Forks, North Dakota

May 2021

TABLE OF CONTENTS

Acknowledgements

I would like to express my sincere thanks to Professor Daryl Sieg and Dr. Jeanie McHugo for their input, advice and support throughout the development of this paper. I would also like to thank Dr. Amanda McDonald and Danielle Jones for sharing their experiences and knowledge gained through prescribing buprenorphine in a clinic setting. Finally, I would like to thank my wife and children for their patience and unwavering support throughout this entire process.

Abstract

The purpose of this literature review is to analyze the use of buprenorphine and methadone for the treatment of opioid use disorder. Comparison of overall safety, efficacy, morbidity and mortality between the two treatment options is accomplished throughout this literature review. The literature review was performed using databases: PubMed, Clinical Key, Cochrane and Up-to-date. Results were limited to studies completed within the past seven years. Methadone has been the treatment mainstay of opioid use disorder for decades. buprenorphine has increased in popularity and prevalence for treatment of opioid use disorder, especially after receiving FDA approval for such use in 2002. Several benefits of buprenorphine therapy were discovered including a significant reduction in overdose fatalities, more convenient dosing options and easier access to prescribing locations. Treatment retention rates of those receiving buprenorphine was found to be lower, sometimes quite significantly, than those who received methadone therapy. A review of the literature showed that those receiving methadone for the treatment of opioid use disorder have a higher likelihood of hospitalization or fatal overdose during the initiation of therapy. A significantly higher retention rate was shown in those receiving methadone, in comparison to buprenorphine. However, methadone use was found to have an association with occurrences of neonatal abstinence syndrome in those taking the medication during pregnancy. A common negative theme throughout the literature review was the lack of a control population when comparing buprenorphine and methadone. Conclusively, neither methadone nor buprenorphine were found superior when used for treatment of opioid use disorder. Careful consideration must be given to the patient's personal situation, drug use history and likelihood of compliance.

Keywords: buprenorphine, methadone, suboxone, opioid use disorder, OUD, opioids, narcotics, overdose, addiction, opioid treatment.

Buprenorphine Versus Methadone for Opioid Use Disorder

The overall number of drug overdose deaths decreased by 4% from 2017 to 2018, still, more than 67,000 Americans died from drug overdose in the year 2018, which included illicit drugs and prescription opioids. Synthetic opioid-involved death rates have increased by 10% over the same time period, this category includes primarily fentanyl and similar compounds, which accounted for 30,000 of the overdose deaths. Heroin was involved in nearly 16,000 deaths while roughly 15,000 deaths were attributed to prescription painkillers (Centers for Disease Control and Prevention, 2020). These numbers confirm the opioid overdose epidemic is still prevalent. Preventative measures are being used such as prescription drug monitoring programs and increasing public awareness. Medicinal treatment options for opioid use disorder has been limited, with methadone being the mainstay. Recently, buprenorphine has become a popular option for treatment of opioid use disorder as well. The purpose of this study is to determine whether decreased morbidity and mortality is achieved with methadone or buprenorphine in the treatment of opioid use disorder.

Statement of the Problem

Methadone, FDA approved for treatment of opioid addiction in 1972, is a full agonist which activates opioid receptors. This mechanism of action has successfully aided in the treatment of opioid addiction, however, also allows for abuse potential. For this reason, methadone treatment must take place in a specialized, highly structured clinic, often requiring daily in-clinic dosing. Buprenorphine is a partial agonist which activates opioid receptors but produces less of a response. Therefore, it reduces abuse potential while still offering successful treatment of opioid addiction. Due to the decreased likelihood of abuse, buprenorphine is the first medication used to treat opioid use disorder in a physician's office, and was FDA approved for

such use in 2002, however, this comes at a cost nearly triple that of methadone. Therefore, several questions are raised. Does the added cost of buprenorphine treatment lead to better outcomes, justifying the increased expense on the health care system? Is buprenorphine truly a safer medication in comparison to methadone? Does methadone or buprenorphine treatment lead to an overall decreased morbidity and mortality? This literature review will attempt to shed light on the aforementioned questions.

Research Question

In patients with opioid use disorder, does treatment with buprenorphine in comparison to methadone lead to overall decreased morbidity and mortality?

Methodology

A literature review was performed using databases: PubMed, Clinical Key, Cochane and Uptodate. Keywords and mesh terms were: methadone, suboxone, buprenorphine, methadone versus suboxone, opioid addiction, opioid use disorder, opioid addiction treatment and opioid use disorder treatment. Studies excluded were those that discussed methadone use for pain management, compared methadone to medications other than buprenorphine and studies that compared buprenorphine to medications other than methadone. Adequate results were found; therefore, the timeframe was limited to studies completed in the last seven years.

Literature Review

A review of the literature shows that both buprenorphine and methadone have been studied significantly with different facets of emphasis including but not limited to: effectiveness of buprenorphine or methadone therapy, safety of buprenorphine or methadone therapy, and compliance with methadone and buprenorphine therapy. It has been shown, both methadone and buprenorphine, are effective in treatment of opioid use disorder. However, due to different

mechanisms of action and different delivery methods of treatment, one may be more statistically significant in overall decreased morbidity and mortality.

Safety of Buprenorphine

Exposure to methadone, buprenorphine, and other opioids during pregnancy were examined in a retrospective chart review by Fernandez et al. (2019) which also included incidence and severity of neonatal abstinence syndrome between each exposure group. It was noted that in the year 2002, approximately 1 in 1,000 live births resulted in a case of neonatal abstinence syndrome from opioid exposure during pregnancy, compared to the year 2015 when the prevalence increased to nearly 6 in 1,000 live births. At the time of publication, Fernandez et al. (2019) reports methadone as the current gold standard of treatment for pregnant females with an opioid use disorder. Methadone treatment is associated with increased antenatal care, improved fetal growth, decreased mortality and fewer complications compared to ongoing opioid use. However, the majority of neonatal abstinence syndrome is caused by maternal methadone exposure. There were no significant differences in potential of maternal side effects between methadone and buprenorphine. It was shown that buprenorphine treatment, when compared to methadone treatment, lead to an approximately seven-day shorter hospital stay and approximately five-day shorter duration of treatment for neonatal abstinence syndrome. Buprenorphine treatment was also shown to have less fetal cardiac and movement suppression, improved neonatal growth parameters and less severe neonatal abstinence syndrome symptoms.

Within this retrospective chart review, groups were limited to three categories: exposure to buprenorphine, exposure to methadone and exposure to other opioids. Those with preterm delivery, major congenital anomaly, significant metabolic/genetic condition or those with pre-eclampsia were excluded from the study. A sample size of 931 subjects remained, which is

adequate for the retrospective chart review. The mode of delivery, either caesarean section or non-operative delivery, had no positive or negative statistical significance, further eliminating possible confounding factors.

While the overall sample size was adequate at 931, the sample population was limited to patients admitted to Thunder Bay Regional Health Sciences Centre. This selective location contains a large population of indigenous people, leading to potential skewed outcomes due to the lack of variation in ethnicity. Severity of opioid use disorder was not considered; therefore, it is unknown what method of drug use was preferred or how frequently opioids were used.

Safety of Methadone

Lemon, Caritis, Venkataramanan, Platt, and Bodnar (2018) completed a study with the goal of estimating the association of neonatal abstinent syndrome from in utero exposure to methadone and buprenorphine treatment, while also accounting for possible confounding severity of addiction. Effects of buprenorphine and methadone on incidence and severity of neonatal abstinence syndrome have been measured with past studies, however, severity of maternal addiction is typically not accounted for.

Methods of the study include a cohort of 716 live-born infants with an in-utero exposure to methadone or buprenorphine as treatment for maternal opioid maintenance therapy. Adjustment was made for parity, maternal race, age, delivery year, employment, hepatitis C, smoking, marital and insurance status. Probabilistic bias analysis was implemented to assess impact of unmeasured confounding severity of addiction.

Findings showed infants exposed to methadone in utero were more likely to experience neonatal abstinence syndrome than those exposed to buprenorphine (RR: 1.3, 95% CI: 1.2, 1.5). This finding remained constant following necessary adjustments for confounding factors. Severe

addiction was more prevalent in the methadone group than the buprenorphine group, however, adjustment for severity of addiction was not statistically significant.

A limitation of this study includes a sample population originating from only a single facility, *Magee-Women's Hospital in Pittsburg, PA*. While sample size was adequate, bias could be present due to a limited geographical area. Women in the methadone group were more likely to be single, unemployed, hepatitis C positive, multiparous and to have less than a high school education. This could represent prescribing bias and limit the accuracy of findings between the two sample groups.

Efficacy of Buprenorphine

The National Drug Abuse Treatment Clinical Trials Network conducted a study with the primary goal of assessing buprenorphine treatment for a patient population predominantly addicted to prescription opioid analgesics, excluding most heroin users. The results were subsequently analyzed by Weiss and Rao (2017). Secondly, a 3.5-year follow up study was completed to assess long-term outcomes of buprenorphine treatment for the original study population.

Methods included a two-phase adaptive treatment design with the intention of beginning a minimally intensive treatment approach and then advancing to a more intensive treatment for those who fail the initial phase. Phase one consisted of a four-week buprenorphine taper with patients randomized to buprenorphine alone or buprenorphine with opioid drug counseling. Phase two consisted of 12 weeks of buprenorphine stabilization followed by a four-week taper and eight weeks of follow-up. Randomization into buprenorphine only or buprenorphine and opioid drug counseling occurred in phase two as well.

Interestingly, findings showed that regardless of which phase was completed, successful outcome rates were not improved with opioid use counseling. Only 7% of participants had success at phase one and required no further treatment. Phase two had a 49% success rate; however at week 24, eight weeks after completing the second taper, abstinence success rates drop drastically to only 9%.

Limitations include abstinence defined as self-reporting no opioid use and an opioid-negative urine test. Relying on self-reporting allows for recall bias and potential inaccurate results. Another limitation for the three and a half year follow-up study was a poor follow-up rate, however, it was not specified as to what percentage of the initial population followed up. Finally, this study was aimed at analyzing treatment for prescription opioid users, even so, some heroin users were allowed in the study. This could lead to inaccuracies, as the type of opioid use is not completely isolated within the study.

Demetrovics et al. (2009) designed a study to monitor and evaluate the effects of buprenorphine treatment in heroin dependent patients. Opioid use disorder had been rapidly increasing throughout the Hungarian population, therefore, alternatives to the typical methadone treatment were needed. buprenorphine treatment was initiated, however, because this was a novel pharmacological intervention at the time, this study was completed to provide more information on the safety and efficacy of buprenorphine treatment for opioid use disorder.

Methods for this study included data collected from six outpatient centers administering buprenorphine as treatment for heroin dependent patients. Study population included 80 total patients (55 males, 35 females, mean age =30.2 years, SD 5.48). During the six-month period of treatment, data was collected at initiation of treatment and then at one, three and six months after

entering treatment. Measures included: laboratory examinations, HIV and HCV tests, severity of addiction, and prevalence of comorbid psychiatric disorders.

Findings included a 22.5% treatment dropout rate within the first month, the majority dropping out during the first week of treatment. Following the first month, dropout rate decreased and 40% of patients completed the six-month treatment. Despite the high dropout rate during the first month of treatment, in almost all studied psychological and psychosocial characteristics, positive changes were reported including increased employment rates, decreased legal incidences and decreased depression. Overall, it appears buprenorphine therapy has significant positive results for those who remain in treatment but has an alarming rate of dropout early in the treatment process.

Limiting the study was a small case population. Eighty patients initially enrolled of which only 32 completed the six-month treatment period, limiting the available data. Furthermore, details on the remaining population were not specified such as demographics and addiction severity, making it uncertain if bias of the sample population factored into the results. Strengths include accounting for other comorbid conditions in the sample population. Addiction severity, psychiatric comorbidity, personality dimensions, extent of craving, mental status, anxiety and perceived stress were all measured with standardized scales throughout the study duration.

Efficacy of Methadone

Potter et al. (2013) completed a secondary analysis exploring differences in baseline clinical characteristics and opioid replacement therapy outcomes with certain categories considered. These categories included heroin users, opioid analgesic users and combined users. Further consideration was given to route of use, injection or non-injection.

Methods included using data from the original randomized, open-label, multi-center, phase four study to assess liver function in participants randomized to buprenorphine or methadone. Of the original 1,269 participants, 731 completed the 24-week treatment phase. Outcomes revealed opioid use during the final 30 days of treatment and treatment attrition. Regardless of treatment group placement, findings of this study showed heroin use and injection of illicit drugs is associated with treatment attrition and opioid misuse during treatment. More significantly, there was no evidence of buprenorphine being superior to methadone for treatment of opioid analgesic users versus heroin users.

A significantly high dropout rate in the buprenorphine group created a limitation that must be considered. Eighteen months after the study was initiated, the initial randomization scheme of 1:1, buprenorphine to methadone, was changed to 2:1 to compensate for uneven cases. Inconsistencies could have been introduced with changing the ratio after initiation of the study. Strengths of this study include complete randomization of participants which eliminates patient selection bias and confounding variable bias. More so, the initial data was collected with the purpose of assessing liver function in patients randomized to buprenorphine or methadone, therefore any bias towards treatment outcome of the two groups is unlikely.

Srivastava, Kahan, and Nader (2017) completed a thorough literature review for both buprenorphine and methadone individually comparing efficacy, safety, and adverse effects. Subpopulations were analyzed including: injection and oral prescription opioid users; different life stages including adolescents, pregnant females and the elderly; social factors including rural communities, work and family responsibilities; different health statuses including patients requiring regular primary care and patients at high risk for methadone toxicity.

Following the review, differences were found between buprenorphine and methadone regarding safety and efficacy. Duration of treatment was shown to have a direct correlation between relapse and overall morbidity and mortality. Therefore, average duration of treatments in each group weighed significantly on the final outcomes. For injection opioid users, methadone is recommended since treatment retention rates are significantly higher than that of buprenorphine treatment. Methadone was also found to be more effective at reducing withdrawal symptoms and cravings, given its full opioid agonist effects compared to the partial opioid agonist effects of buprenorphine. For oral prescription opioid users, buprenorphine is recommended for socially stable individuals for two reasons; it's safer side effect profile and higher likelihood of treatment retention due to a more stable and supportive social environment. However, risk of dropout can likely be mitigated by promptly placing the patient on methadone if buprenorphine treatment is unsuccessful.

For adolescents, methadone is recommended mostly due to the significantly increased treatment retention rate compared to buprenorphine. On average, methadone retained individuals for 354 days while buprenorphine retained individuals for only 58 days, showing the potential for positive outcome in adolescents is drastically higher in the methadone category. Pregnant women again showed an increase in retention within the methadone group, although the comparison to the buprenorphine group did not reach statistical difference, therefore could be deemed equivocal. The buprenorphine group did show a shorter length of stay for neonates suffering from neonatal abstinence syndrome, however, neonatal abstinence syndrome has not been shown to have adverse long-term effects. In the elderly population, buprenorphine is recommended over methadone, as there has been little research done within this population.

methadone is considerably more potent and can increase risk of opioid-related falls and adverse events in the elderly.

Limitations include lack of information on type of opioids used within each category, duration of use, frequency of use and history of treatment successes and failures. All of which could positively or negatively affect the findings presented within each category.

Morbidity and Mortality Associated with Buprenorphine and Methadone Therapy

A study conducted by Soyka, Zingg, Koller and Kuefner (2008) was designed to compare the efficacy of buprenorphine and methadone in a flexible-dose regimen. Identifying possible outcome predictors was a secondary goal of the study. Methods include a six-month, randomized, prospective clinical study comparing the efficacy of buprenorphine and methadone treatment for opioid use disorder. Retention rate, consumption of other illicit drugs, withdrawal symptoms and side effects were also examined. All patients received standardized psychotherapy focusing on activation of resources and coping with social conflicts. Inclusion criteria was opioid dependence, history of heroin abuse and minimum age of 18. Exclusion criteria included acute psychosis and any regular substitution treatment or psychosocial treatment one month prior to the study.

Findings of this study demonstrated a favorable outcome for both treatment groups with an overall retention rate of 52% and no significant difference between the two groups, methadone 55.3% versus buprenorphine 48.4%. Overall, the study supports substitution treatment with either buprenorphine or methadone as they are both equally effective. When those who switched treatment methods during the trial were excluded, retention rate was nearly identical between the two groups, methadone 53.7% versus buprenorphine 53.6%. An association was made with age of patient and success of treatment; the younger the patient age

when beginning to use opioids regularly, the higher the likelihood of treatment dropout. The buprenorphine group showed lower rates of other drug use; however the difference was not significant.

A limitation of this study is a rather small sample size of only 140 opioid-dependent patients. While this sample size was considered adequate for the study, it cannot be ruled out that significant differences between the treatment groups may have occurred with a larger sample. Also, more psychosocial domains should be considered to completely evaluate treatment outcomes such as physical, mental, and social well-being following treatment, which was not considered within this study.

Kelty and Hulse (2017) designed a retrospective-prospective cohort study with the goal of comparing rates of fatal and non-fatal opioid overdoses in opioid dependent patients treated with methadone, buprenorphine or implant naltrexone. A secondary goal was identifying risk factors for fatal opioid overdoses.

Methods included comparing 5,646 opioid dependent patients who received treatment with buprenorphine, methadone or implant naltrexone against state mortality and hospital data. Participants were required to be at least 18 years of age. Rates of overall fatal and non-fatal opioid overdoses were calculated for each treatment group. Rates of fatal and non-fatal overdoses were also calculated for three time periods including ‘induction’, ‘on-treatment’ and ‘off-treatment’.

Findings showed, that when comparing pre-treatment and post-treatment rates of opioid poisoning which required hospitalization, there was a statistically significant reduction in patients who were treated with buprenorphine (RR: 0.66, CI: 0.51-0.84). No significant reduction in rates of hospitalization associated with opioid overdose were observed in the methadone group

(RR: 1.08, CI: 0.85-1.37). There were no fatal overdoses in the buprenorphine group during the first 28 days of treatment, also known as the induction phase. High rates of fatal opioid overdose were observed during the induction phase of those treated with methadone. During the treatment period, buprenorphine was found to be protective against opioid poisonings with 9.25 non-fatal opioid poisonings to every one fatal opioid poisoning, compared to a 6.77:1 ratio for the methadone group. Buprenorphine also had significantly lower hospital admissions for non-fatal opioid poisoning ($p=0.018$) than methadone.

Non-fatal opioid poisonings which required hospitalization were included in the study. Non-fatal opioid poisonings which required emergency department visits or those that did not seek medical care, were not included. Further limiting the study is the lack of randomization as patients self-selected their treatments, potentially contributing to bias. Strengths include a large sample size of 5,646 patients, 3,515 treated with methadone and 3,250 treated with buprenorphine. Also, patients were taken from a large geographic area of Western Australia.

Zhu et al. (2018) completed a prospective study using data collected from the 2013 study "Starting Treatment with Agonist Replacement Therapy (START)". The primary goal included identifying participants associated with a five-year opioid abstinence in those who received either buprenorphine or methadone treatment.

Methods included a multi-site trial that incorporated 1,269 opioid-dependent patients randomized to receive either buprenorphine or methadone in nine different site locations. Furthermore, the START follow up study involved three separate follow up interviews at one-year intervals following the original randomization to buprenorphine or methadone. These interviews were utilized to assess continuing abstinence from opioids at five or more years

following initiation of therapy. Characteristics of individuals from both samples, those remaining abstinent from opioids and those who had relapsed, were assessed for contributing correlations.

Study results showed, of the 699 patients who received either buprenorphine or methadone, 145 remained completely abstinent for a minimum of five years. Correlations for those failing abstinence included history of injection drug use and randomization to buprenorphine. Cocaine use was also shown to increase abstinence failure.

A limitation of this study includes data being self-reported. Recall error, bias and subjectivity could negatively affect the data. Also, participants with a follow up period of less than five years were excluded, expanding the follow up period below five years could have altered results and shown better correlations. Finally, while some characteristics were considered for participants, many were not, including treatment history and duration of drug use. A strength of this study includes a large sample size from multiple locations across a large geographic area. Another is the long duration of abstinence required to be included, most similar studies follow participants for less than 12 months. Also, many baseline characteristics were considered for each participant and factored into each sample group allowing for examination of possible bias or confounding factors.

Hickman et al. (2018) analyzed records for 49,279 patients who received methadone or buprenorphine between January 1998 and July 2014 for treatment of opioid use disorder. Data was pulled from the Clinical Practice Research Datalink which contains records from 674 general practitioner practices and more than 11 million patients. Within this data set, it was found that 606 general practitioner practices had at least one patient on treatment for opioid use disorder. The final data set yielded 17,373 exposure to methadone treatment episodes and 9173 exposure to buprenorphine treatment episodes. Confounding factors contributing to mortality

were considered, and adjusted for, which included 17 chronic illnesses. Other possible influences on mortality were also considered and adjusted for including benzodiazepine co-prescriptions, gabapentoid co-prescriptions, history of self-harm, overdose poisoning, alcohol problems, and several others. Analysis was separated into three categories; first four weeks of treatment, remainder of treatment time, and four weeks following end of treatment.

Conclusions included buprenorphine treatment having a lower all-cause mortality in each treatment category. After adjustment for confounding variables, there was evidence of reduced drug-related mortality at initiation of treatment with buprenorphine when compared to methadone.

Limitations of this study include potential bias of prescribing; showing potential for buprenorphine recipients to be of older age, have decreased severity of opioid addiction/abuse, and to have more comorbid conditions. Methadone recipients had potential for more significant drug addiction/abuse history, alcohol abuse, imprisonment, homelessness and having co-prescriptions of benzodiazepines. Also, it was attempted to limit cases to those prescribed buprenorphine or methadone for opioid use disorder only, not to include those receiving prescriptions for pain management. Pain management patients may not have been completely eliminated due to available information and varying classifications.

Hser et al. (2016) compared long-term outcomes including mortality and opioid use among participants randomized to buprenorphine or methadone for treatment of opioid use disorder.

Methods for this study include follow-up of 1,080 opioid dependent participants who had entered opioid treatment between 2006 and 2009 and were randomized to buprenorphine or methadone treatment for up to 24 weeks. Of the original 1,080 participants, 797 were interviewed at a mean of four and a half years post-randomization.

This study revealed 23 deaths in the buprenorphine group (n=630, 3.6%) and 26 deaths in the methadone group (n=450, 5.8%), the difference was not statistically significant. Current opioid use at the time of interview was significantly higher in the buprenorphine group compared to the methadone group.

Saxon, Hser, Woody and Ling (2013) conducted a study with the goal of examining characteristics associated with retention and continued illicit opioid use in methadone versus buprenorphine treatment for opioid use disorder.

Methods include a secondary analysis of 1,267 opioid-dependent patients participating in nine opioid treatment programs who were randomized to either buprenorphine or methadone for 24 weeks. Patients were instructed to abstain from opioids for 12-24 hours prior to starting treatment. Assessments included urine drug screens and self-reported drug use data, collected every four weeks. Patients who missed more than 14 consecutive days of medication were terminated from the study.

Results confirmed the methadone group had 74% completion of treatment and the buprenorphine group had 46% completion of treatment. However, when the maximum methadone was increased to or exceeded 60mg/day, completion rate reached 80%. When doses of buprenorphine reached 30-32mg/day, completion rates were nearly 60%. Also, urine drug screens showed a significantly lower positive rate of other illicit drugs (OR=0.63, 95% CI=0.52-0.76, $p<.01$) in the buprenorphine group compared to the methadone group in the first nine weeks of treatment.

A limitation of this study was an open-labeled design which allowed each participant to know which medication treatment they were receiving. This could contribute to subjective bias and could have been eliminated with a double-blind model. Another limitation was patients who

missed 14 or more consecutive days of treatment were eliminated from the study. There was no further classification of participants who never missed a dose or missed less than 14 days and remained in treatment. Full compliance of treatment may influence final retention rates and needs to be considered.

Discussion

After significant review of the literature, a common theme presented, methadone and buprenorphine treatment are both effective treatment modalities for opioid use disorder. However, when comparing methadone treatment to buprenorphine treatment for opioid use disorder, there is no evidence of buprenorphine being superior to methadone for treatment of opioid use disorder as expressed by Potter et al. (2013). Consideration must be given to the patient and the situation to determine the most appropriate treatment plan. Close follow up and constant reevaluation should also be considered during therapy to monitor for a need in treatment alteration.

A concern associated with opioid use disorder treatment is overall treatment retention, further supported by Srivastava et al. (2017) discovering a direct correlation between relapse and overall morbidity and mortality. Demetrovics et al. (2009) found a 22% treatment dropout rate within the first month of buprenorphine treatment. This high dropout rate must be considered when placing a patient on buprenorphine therapy. Srivastava et al. (2017) recommended buprenorphine treatment for socially stable individuals who have a supportive social environment which increases likelihood of treatment retention. For injection opioid users and those with a less-stable social environment, methadone is recommended as treatment retention rates are significantly higher than that of buprenorphine. However, the higher dropout rate of buprenorphine can likely be mitigated by promptly placing the patient on methadone if indicated.

Medication dosage should also be considered for effective treatment. Saxon et al. (2013) found an increase of retention from 46% to nearly 60% when buprenorphine dosages reached 30-32mg/day. Therefore, higher doses should be considered for those with higher likelihood of treatment attrition.

Reduction of all-cause mortality must be considered when prescribing medication assisted treatment for opioid use disorder. Reduction or elimination of opioid use is the goal of both methadone and buprenorphine treatment. However, without a correlating reduction in morbidity and mortality, treatment may not be considered effective. Hickman et. al (2018) found buprenorphine to have a lower all-cause mortality in several treatment groups including: first four weeks of treatment, remainder of time in treatment and four weeks following end of treatment. More so, Kelty and Hulse (2017) discovered there was a statistically significant reduction in rates of opioid poisoning which required hospitalization in patients who were treated with buprenorphine. No fatal overdoses were observed in the buprenorphine group during the induction phase while high rates of fatal opioid overdoses were observed in patients treated with methadone during the induction phase. Overwhelmingly, it seems buprenorphine is the safer option when prescribing for medication assisted treatment of opioid use disorder.

Discussion of all-cause mortality should not go without addressing treatment of opioid use disorder order during pregnancy and the resultant neonatal abstinence syndrome. According to Fernandez et al. (2019) neonatal abstinence syndrome cases, mostly resulting from methadone exposure during pregnancy, have increased from 1 in 1,000 live births to nearly 6 in 1,000 live births over a 13-year span. At the time of publication, methadone was considered the gold standard for treatment of opioid use disorder, including pregnant women. However, it was shown that buprenorphine treatment lead to an approximately seven-day shorter hospital stay and five-

day shorter duration of treatment for neonatal abstinence syndrome. This benefit comes without difference of maternal side effects when comparing buprenorphine to methadone, more so, buprenorphine was shown to have less fetal cardiac and movement suppression. Collectively, this could make an argument for recommending buprenorphine as the first line treatment for pregnant females.

It cannot be ignored that a drawback to most available studies for buprenorphine and methadone treatment is the lack of a control population. Due to the nature of opioid use dependence, the ability to gather data on a population attempting to discontinue opioid use in the absence of formal treatment or medication is limited. Srivastava et al. (2017) did attempt to address this concern concluding that buprenorphine or methadone treatment was superior to abstinence-based treatment. However, information within the study addressing abstinence-based treatment was limited. No other example comparing medication assisted treatment to no treatment was discovered, therefore, claims of medication assisted therapy being superior to no therapy, should be evaluated carefully.

In conclusion, neither methadone nor buprenorphine treatment were found to be overall superior. Consideration must be given to each patient and their individual situation to select the correct treatment modality.

Applicability to Clinical Practice

The information provided within this literature review will allow medical providers to guide those suffering from opioid use disorder to the most effective treatment modality. It will also allow providers to give a clear and informed explanation to patients pursing medical treatment for opioid use disorder including, associated risks, success rates, therapy delivery methods and more.

References

Bruneau, J., Ahamad, K., Goyer, M., Poulin, G., Selby, P., Fischer, B., Wild, C. & Wood, E. (2018). Management of opioid use disorders: A national clinical practice guideline. *Canadian Medical Association Journal, 190*(9). http://dx.doi.org/10.1503/cmaj.170958

Centers for Disease Control and Prevention. (2020). America's drug overdose epidemic: Putting data to action. Retrieved November 09, 2020, from https://www.cdc.gov/injury/features/prescription-drug-overdose/index.html

Demetrovics, Z., Farkas, J., Csorba, J., Nemeth, A., Mervo, B., Szemelyacz, J., Fleischmann, E., Kassai-Farkas, A., Petke, Z., Orojan, T., Rozsa, S., Funk, S., Kapitany, M., Kollar, A., Racz, J. (2009). Early experiences with Suboxone maintenance therapy in Hungary. *Neuropsychopharmacologia Hungarica, 11*(4), 249-257.

Fernandez, S., Bruni, T., Bishop, L., Turuba, R., Olibris, B., & Jumah, N. (2019). Differences in hospital length of stay between neonates exposed to buprenorphine versus methadone in utero: A retrospective chart review. *Paediatrics & Child Health, 24*(2), 104-110. http://dx.doi.org/10.1093/pch/pxy091

Gowing, L., Ali, R., White, J., & Mbewe, D. (2017). Buprenorphine for managing opioid withdrawal. *Cochrane Database of Systematic Reviews, 2*. http://dx.doi.org/10.1002/14651858.cd002025.pub5

Hickman, M., Steer, C., Tilling, K., Lim, A., Marsden, J., Millar, T., Strang, J., Telfer, M., Vickerman, P. & Macleod, J. (2018). The impact of buprenorphine and methadone on

mortality: A primary care cohort study in the United Kingdom. *Addiction, 113*(8), 1461-1476. http://dx.doi.org/ 10.1111/add.14188

Hser, Y., Evans, E., Huang, D., Weiss, R., Saxon, A., Carroll, K., Woody, G., Liu, D., Wakim, P., Matthews, A., Hatch-Maillette, M., Jelstrom, E., Wiest, K., McLaughlin, P. & Ling, W. (2016). Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial. *Addiction, 111*(4), 695-705. http://dx.doi.org/10.1111/add.13238

Kelty, E., & Hulse, G. (2017). A retrospective cohort study of birth outcomes in neonates exposed to naltrexone in utero: A comparison with methadone-, buprenorphine- and non-opioid-exposed neonates. *Drugs, 77*(11), 1211-1219. http://dx.doi.org/10.1007/s40265-017-0763-8.

Kunøe, N., Opheim, A., Solli, K., Gaulen, Z., Sharma-Haase, K., Latif, Z., & Tanum, L. (2016). Design of a randomized controlled trial of extended-release naltrexone versus daily buprenorphine-naloxone for opioid dependence in Norway (NTX-SBX). *BMC Pharmacology and Toxicology, 17*(1). http://dx.doi.org/10.1186/s40360-016-0061-1

Lee, J., Nunes, E., Novo, P., Bachrach, K., Bailey, G., Bhatt, S., Farkas, S., Fishman, M., Gauthier, P., Hodgkins, C., King, J., Lindblad, R. Liu, D., Matthews, A., May, J., Peavy, M., Ross, S., Salazar, D., Schkolnik, P., Shmueli-Blumberg, D., 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. http://dx.doi.org/10.1016/s0140-6736(17)32812-x

Lemon, L., Caritis, S., Venkataramanan, R., Platt, R., & Bodnar, L. (2018). Methadone versus buprenorphine for opioid use dependence and risk of neonatal abstinence syndrome. *Epidemiology, 29*(2), 261-268. http://dx.doi.org/10.1097/ede.0000000000000780

Mattick, R., Kimber, J., Breen, C., & Davoli, M. (2003). Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Systematic Reviews, 3*(3). http://dx.doi.org/10.1002/14651858.cd002207.pub2

Potter, J., Marino, E., Hillhouse, M., Nielsen, S., Wiest, K., Canamar, C., Martin, J., Ang, A., Baker, R., Saxon, A., Ling, W. (2013). Buprenorphine/naloxone and methadone maintenance treatment outcomes for opioid analgesic, heroin, and combined users: Findings from starting treatment with agonist replacement therapies (START). *Journal of Studies on Alcohol and Drugs, 74*(4), 605-613. http://dx.doi.org/10.15288/jsad.2013.74.605

Saxon, A. J., Hser, Y., Woody, G., & Ling, W. (2013). Medication-assisted treatment for opioid addiction: Methadone and buprenorphine. *Journal of Food and Drug Analysis, 21*(4). http://dx.doi.org/10.1016/j.jfda.2013.09.037

Saulle, R., & Vecchi, S. (2015). Supervised dosing with a long acting opioid medication in the management of opioid dependence. *Cochrane Database of Systematic Reviews, 4.* http://dx.doi.org/10.1002/14651858.cd011983

Socias, M., Ahamad, K., Foll, B., Lim, R., Bruneau, J., Fischer, B., Wild, C., Wood, E. & Jutras-Aswad, D. (2018). The OPTIMA study, buprenorphine/naloxone and methadone models of care for the treatment of prescription opioid use disorder: Study design and rationale. *Contemporary Clinical Trials, 69*, 21-27. http://dx.doi.org/10.1016/j.cct.2018.04.001

Soyka, M., Zingg, C., Koller, G., & Kuefner, H. (2008). Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: Results from a randomized study. *The International Journal of Neuropsychopharmacology, 11*(05). http://dx.doi.org/10.1017/s146114570700836x

Srivastava, A., Kahan, M., & Nader, M. (2017). Primary care management of opioid use disorders: Abstinence, methadone, or buprenorphine-naloxone? *Canadian Family Physician, 63*(3), 200-205.

Weiss, R., & Rao, V. (2017). The prescription opioid addiction treatment study: What have we learned. *Drug and Alcohol Dependence, 173*. http://dx.doi.org/10.1016/j.drugalcdep.2016.12.001

Zhu, Y., Evans, E., Mooney, L., Saxon, A., Kelleghan, A., Yoo, C., & Hser, Y. (2018). Correlates of long-term opioid abstinence after randomization to methadone versus buprenorphine/naloxone in a multi-site trial. *Journal of Neuroimmune Pharmacology, 13*(4), 488-497. http://dx.doi.org/10.1007/s11481-018-9801-x