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**METHADONE VERSUS BUPRENORPHINE-NALOXONE AS A  
TREATMENT FOR OPIOID DEPENDENT INDIVIDUALS**

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## **ABSTRACT**

**Objective:** To investigate if buprenorphine/naloxone compared to methadone improves treatment retention and effectiveness among opioid dependent individuals. **Design:** Systematic literature review. **Methods:** Searches were conducted in PubMed and Scopus using the terms methadone, buprenorphine-naloxone and opioid dependence. In PubMed the following filters were applied: humans, English, randomized controlled trials and meta-analysis. Studies that had opioid dependent subjects, treatments comparing buprenorphine-naloxone and methadone and outcomes measures of treatment retention and efficacy were included. **Results:** Otiashvili et al. found that daily observed doses of methadone and buprenorphine-naloxone were effective in reducing illicit buprenorphine and other illicit opioid use. Kamien et al. found that maintenance treatment with 16mg of buprenorphine-naloxone reduced opioid use at a rate equivalent to that achieved with 90mg of methadone. Hser et al. found that methadone appeared to be associated with better retention in treatment for opioid dependence than buprenorphine-naloxone, as does that use of higher doses of both medications. Buprenorphine-naloxone is associated with lower continued use of illicit opioids. **Conclusion:** Buprenorphine-naloxone may be more effective at preventing illicit opioid use than methadone, although this is inconsistent among the three studies. Retention rates are also inconclusive with only one study demonstrating higher retention rates with methadone treatment. With buprenorphine-naloxone demonstrating a better safety profile, fewer withdrawal effects, ease of use and less divergence, we recommend buprenorphine-naloxone over methadone as a first line treatment in opioid-dependent individuals.

## **INTRODUCTION**

Opioids are a class of compounds that bind to mu-receptors in the central and peripheral nervous system eliciting an analgesic and euphoric effect. Opioid dependence has developed into a pervasive issue in North America, exacting an incredulous financial strain through costs associated with healthcare, mental illness, unemployment and crime. It is estimated that the cost of prescription opioid dependence in the U.S. alone amounts to nearly \$55.1 billion dollars annually.<sup>1</sup> The burden of opioid dependence in the United States is worsening, as the use of heroin and illicit use of prescription opioids are steadily increasing. As of 2014, it was estimated that 586,000 and 1.9 million Americans had a substance use disorder involving heroin and prescription pain relievers, respectively. With this expansion in opioid misuse, the unfortunate consequence of opioid overdose has also become prevalent. It was estimated that there were 10,574 deaths related to heroin overdose and 18,893 deaths related to prescription pain relievers in the U.S. in 2014.<sup>2</sup>

Substance dependence, characterized by a compulsion to seek and take a drug, a loss of control in limiting intake and a negative emotional state when drug excess is withdrawn, is the result of complex and multifactorial processes involving genetic, epigenetic, cellular and molecular mechanisms.<sup>3</sup> The behavior begins as a transition from occasional and controlled drug use to a loss in control and subsequent dependent behavior. Dependence manifests as several maladaptive behaviors which occur in stages: intoxication/binge, negative affect/withdrawal and preoccupation/anticipation that reinforce the addictive behavior. The intoxication/binge stage involves the acute, pleasurable stimuli associated with drug utilization. Opioids directly bind to receptors in the ventral tegmentum and nucleus accumbens resulting in dopamine release and euphoria, which ultimately reinforces drug use. Chronic drug exposure downregulates dopamine and other neurotransmitters involved in the neurocircuit associated with the acute reinforcing effects. Upon drug withdrawal, several mechanisms contribute to aversion and substance-seeking behavior. It is postulated that low dopamine levels cause anhedonia and amotivational

symptoms, which consequently heighten the desire for the abused substance. The preoccupation/anticipation stage is characterized by an increased craving for the drug long after acute withdrawal. It is often triggered by stress, which activates brain circuits involved in reward processing and thus stimulates the compulsion for drug use. Both dopamine and glutamate have been implicated in neuroplastic changes that alter brain circuitry to seek after abused substances rather than functional behavior in response to stressors.<sup>4</sup>

There are two main medical treatment approaches to opioid addiction: direct supervised detoxification and opioid-substitution treatment. Although complete abstinence from opioid use is ideal, relapse rates are high and therefore long-term substitution is the mainstay of treatment. The main objective of treatment is to prevent illicit opioid use and injection behavior and to minimize concomitant risks such as hepatitis C infection and HIV. In young patients with a short history of oral opioid dependence and a strong support system, complete abstinence is probable and more aggressive treatment approaches can be initiated.<sup>5</sup>

Detoxification can be achieved through the use buprenorphine/naloxone. Buprenorphine, originally developed as an analgesic, is a synthetic form of the opioid thebaine, which functions as a partial mu-receptor agonist and kappa- receptor antagonist. It binds to mu-receptors with a higher affinity than endogenous opioids and illicit opioids such as heroin, which are full-mu agonists. Therefore, binding of buprenorphine will precipitate withdrawal symptoms in intoxicated individuals as a partial-mu receptor agonist displaces a full-mu receptor agonist. However, since buprenorphine is a partial mu-receptor agonist, it produces a mild euphoric and sedation effect, which can minimize withdrawal symptoms compared to a full mu-receptor antagonists.<sup>6</sup> Naloxone, a mu-receptor antagonist, binds with a high affinity to mu-receptors and blocks the activation of these receptors. Naloxone has a poor bioavailability when given orally but if injected, precipitates withdrawal symptoms, thus discouraging the improper use of the medication.<sup>4</sup>

Patients are usually started on 2-4 mg of buprenorphine/naloxone within 6-24 hours of the last opioid dose. Withdrawal symptoms, commonly described as flu-like symptoms, including nausea, vomiting, diaphoresis, yawning, fatigue, myalgia, diarrhea and mydriasis occur within 36-72 hours of drug-cessation. Drug cravings tend to occur sooner, within 4-6 hours after the last opioid dose. It is critical that treatment begin within this timeframe to reduce withdrawal symptoms and increase the probability of patient compliance.<sup>7</sup> If treatment is started too soon, buprenorphine will exhibit a withdrawal effect as it displaces the full-agonist of the abused opioid. Delaying treatment increases the risk of illicit drug use in order to minimize the negative symptoms of drug withdrawal.

Stabilization and maintenance is achieved once the patient no longer has withdrawal symptoms or cravings. Both buprenorphine/naloxone and methadone have proven to be effective in maintenance treatment. Methadone was developed in 1964 as a response to the post-WWII heroin epidemic in New York City.<sup>8</sup> It functions as a complete mu-agonist and is prescribed in legally certified clinics in which daily appointments are required for drug administration. Patients are usually maintained on a dose of 80-120mg QD. Since methadone is a complete mu-agonist, there is no ceiling-effect, which allows for the potential of abuse, overdose and mortality as a result of respiratory depression. This led to the utilization of buprenorphine and subsequently buprenorphine/naloxone as a more convenient and safe approach to opioid dependence. It has been shown that higher maintenance doses of buprenorphine (8-16mg) are more efficacious in retention rates compared to lower doses (1-4 mg).<sup>9</sup> Although, doses should be individualized such that the most minimal dose is prescribed that prevents withdrawal, cravings and illicit opioid use. This can often take several months of weekly increment adjustments.<sup>10</sup>

Several studies have been conducted on the effectiveness of both methadone and buprenorphine but there is limited information on the use of buprenorphine/naloxone. This study aims to investigate the effectiveness of buprenorphine/naloxone compared to methadone in treatment retention and effectiveness among opioid dependent individuals.

## **PICO**

*Population:* Opioid dependent individuals

*Intervention:* Methadone

*Comparison:* Buprenorphine-naloxone

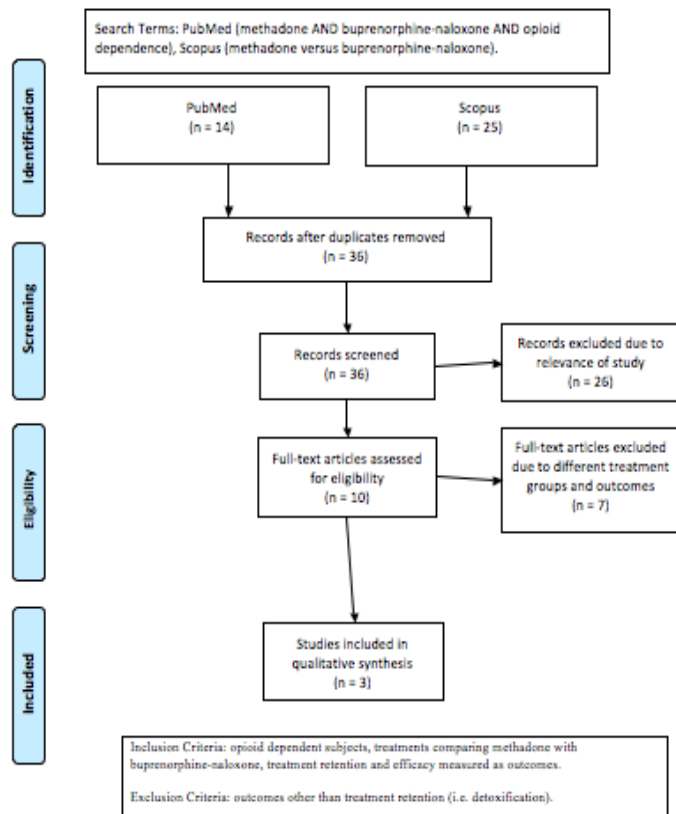
*Outcome:* Improved retention rates and efficacy in treatment programs

## **CLINICAL QUESTION**

Among opioid dependent individuals does methadone as compared to buprenorphine-naloxone improve retention rates and efficacy in treatment programs?

## **METHODS**

An initial literature search of PubMed using the search terms “methadone” and “buprenorphine-naloxone” and “opioid dependence” yielded 14 results. Inclusion criteria included randomized control trials and meta-analyses with publication dates within the last 5 years. A further literature search of Scopus using the search term “buprenorphine-naloxone versus methadone” yielded 25 results. Duplicate articles were removed resulting in a total of 36 results. These studies were initially excluded based on relevance to the research study aim. For example, some studies examined the characteristics of opioid dependent individuals or the abuse potential of these maintenance drugs. Once 26 irrelevant studies were excluded the remaining studies were assessed and excluded based on treatment outcomes. For example, studies with detoxification or quality of life improvement as outcomes were removed and only those that measured treatment retention and efficacy were included. A total of three articles were selected to be included in this analysis.



## **RESULTS**

### **Study 1**

*Methadone and Buprenorphine-Naloxone are Effective in Reducing Illicit Buprenorphine and Other Opioid Use, and Reducing HIV Risk Behavior-Outcomes of a Randomized Trial. Otiashvili et al. <sup>11</sup>*

**Objective:** to determine treatment retention with buprenorphine-naloxone or methadone in buprenorphine injection users and the impact of these treatments on substance use and HIV prevalence in the Republic of Georgia.

**Study Design:** the study was conducted at the Addiction Research Center of Alternative Georgia, which is a non-profit research institute affiliated with the Center for Medical, Socio-economic and Cultural issues, an addiction program that provides in-patient detoxification, psychosocial outpatient treatment and methadone maintenance.

<b>Table 1.</b> Inclusion and exclusion criteria for study participation. ICD-10=10 <sup>th</sup> revision of the International Statistical Classification of Diseases and Related Health Problems.	
<b>Inclusion Criteria</b>	<b>Exclusion Criteria</b>
Opioid dependence with physiologic features based on the ICD-10 for the past 3 or more years	Under the age of 25
Buprenorphine injection $\geq 10$ times within the past 30 days.	On methadone maintenance in the last 4 weeks
Opioid positive urine test	No home or cellular number at which the patient could be reached
Stable address within the Tbilisi area	Unwillingness or inability to give informed consent

Patients were recruited through various methods, which included fliers, word-of-mouth and advertisements and further selected based on several criteria (table 1). Selected patients were stratified based on gender and age then randomized 1:1 to methadone or buprenorphine-naloxone treatment groups through the Statistical Computer Program R version 2.6.2, which synthesizes a random allocation sequence.

Methadone and buprenorphine-naloxone were administered under direct supervision 7 days a week. Before treatment introduction, an initial assessment was conducted. Baseline assessments were then obtained weekly for 12 weeks then at week 20, whereas comprehensive assessments were gathered at weeks 4, 8, 12 and 20 (table 2.). Opioid craving was assessed by an opioid-specific visual analogue scale.

The urine drug screen screened for the following: opioids, benzodiazepines, amphetamines, buprenorphine, methadone and Tetrahydrocannabinol (THC).

<p><b>Table 2.</b> Tests performed at each assessment. The urine drug screen tested for opioids, benzodiazepines, amphetamines, buprenorphine, methadone and THC. ASI= Addiction Severity Index, 5<sup>th</sup> edition, TLFB=a timeline follow-back for self-reported drug use, RAB=Risk Assessment Battery, a self-reported measure of drug and sexual HIV risk behaviors.</p>		
<b>Initial Assessment</b>	<b>Baseline Assessment</b>	<b>Comprehensive Assessment</b>
Physical Exam	Urine drug screen	ASI
CBC	Opioid craving	RAB
Glucose	TLFB	
Bilirubin		
AST/ALT		
HIV and Hepatitis B/C testing		
Urine drug screen		

**Study Results:** A total of 80 patients were assessed between January 25 and September 27, 2011. All participants were Caucasian, 4 of which were female with an average age of 34 years. The mean years of opioid injection use was 5.8. The main drugs injected among participants were heroin, buprenorphine, opium, desomorphine and amphetamines.

The number of urine samples tested positive for opioids was significantly different between the two treatment groups ( $p=0.03$ ). Although there is a significant difference between the treatment groups in the number of opioid-positive urine screens, the overall quantity was low in both groups. Only 1.5% of samples in the methadone treatment group and 0.2% in the buprenorphine-naloxone group tested positive.

Injection risk behavior, which included needle, cooker, cotton and syringe sharing, was significantly reduced among both treatment groups with no significant difference between buprenorphine-naloxone and methadone ( $p=0.1$ ). Only 10% and 23% of total risk assessment battery (RAB) reports indicated injection risk behavior in buprenorphine-naloxone and methadone treatment groups respectively.

At the 20 week follow-up, 66 participants were evaluated, of which, 37 participants were still on maintenance therapy with 34 on methadone and 3 on buprenorphine-naloxone. Significantly fewer patients were using opioids illicitly in those being treated (5.6%) compared to those no longer on maintenance treatment (27.6%,  $p<0.001$ ).

**Study Critique:** Strengths include daily observed dosing and therefore ensured compliance and limited loss to follow-up during the initial 12-week study (85% of participants completed the study, 5 participants in the Suboxone (Buprenorphine/naloxone) and 7 in the methadone study left) with the intention to treatment method utilized for those lost to follow-up.

There were several limitations to this study. The study duration was short being only 12-weeks long, which may not sufficiently determine the efficacy of drug maintenance therapy. The sample population was nearly exclusively male with only 4 female participants, which limits the application of this study to females in the general population. The lack of follow-up at 20 weeks was also a substantial limitation. Only 3 participants were using Suboxone as maintenance therapy at 20 weeks. Furthermore, the reasons for the lack of Suboxone use were not addressed. The authors also claimed that both medications significantly reduced opioid cravings but no data was reported to verify such a statement.

**Study 2**

*Buprenorphine-Naloxone Versus Methadone Maintenance Therapy: A Randomized Double-Blind Trial With Opioid-Dependent Patients. Kamien et al. <sup>12</sup>*

**Objective:** to compare buprenorphine-naloxone with methadone for maintenance treatment of opioid dependence.

**Study Design:** this study took place at a licensed, outpatient opioid-treatment facility for adults in Denver, Colorado, called the Vine Street Center. This facility offered a range of pharmacotherapies for the treatment of opioid dependence along with comprehensive counseling services.

<b>Table 3.</b> Inclusion and exclusion criteria for study participation.	
<b>Inclusion Criteria</b>	<b>Exclusion Criteria</b>
<p>At least 18 years of age</p> <p>In good health</p> <p>Met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria for opioid dependence</p> <p>Met Food and Drug Administration criteria for methadone maintenance treatment</p> <p>Using heroin or prescription opioids or receiving methadone maintenance treatment</p>	<p>Evidence of active psychosis, manic-depressive illness, organic psychiatric disorders or serious medical illnesses</p>

Patients were recruited through newspaper and poster advertisements as well as referred from local treatment programs. They were then selected based on inclusion and exclusion criteria (Table 3). Patients



were not excluded from the study for having codependence on other drugs. Participants received a full explanation of the procedures of the study and were then provided written informed consent before being enrolled into the study. After enrollment they completed a comprehensive intake interview to determine study eligibility.

The study was a 17-week, double-blind, double-dummy, randomized clinical trial that compared 4 study groups: 8 mg buprenorphine-2 mg naloxone, 16 mg buprenorphine-4 mg naloxone, 45 mg methadone and 90 mg methadone. Double-dummy is a technique used to keep the study blinded when the two treatments can not be made identical, in this case one medication was a liquid and the other a tablet, so both groups received a liquid and a tablet, one of which was the placebo. Minimum likelihood allocation, a method of assigning participants to different groups while taking into account continuous and discrete factors simultaneously, was used to randomly assign the participants sequentially to 1 of the 4 groups while controlling for gender, methadone and/or Vine Street Center treatment history, and duration of regular opioid use (< or  $\geq$ 15 years).

Participants were required to attend the clinic daily for medication. All participants, regardless of the group they were assigned, received an oral solution first, followed by the tablets to meet the double-blind and double-dummy requirements. The nurse provided patients with either methadone or placebo solution to drink and then a buprenorphine-naloxone tablet or placebo tablet in a plastic cup.

Urine samples were collected 3 times a week under observation before medications were administered and analyzed on site for the presence of opioids. They were also collected on a randomly chosen day each week in the same manner. Breath alcohol samples were collected on urine testing days as part of routine clinical procedure, as participants were not allowed to attend clinic intoxicated.

Each participant received 1-hour of individualized, manualized behavioral counseling with a trained therapist every other week throughout the study. These sessions focused on lifestyle changes and also incorporated AIDS education.

If participants failed to obtain their medications on 3 consecutive days or if they did not provide urine samples on 5 consecutive days where it was required then they were withdrawn from the study and offered alternative treatment at the center or referral to other treatment facilities. Those who fell into this category were offered a compassionate extension of treatment where they could continue to blindly receive treatment for the remainder of the study but they were not included in the study results any longer.

The primary outcome measure in this study was the amount of opioid abstinence achieved over time. Missed urine samples were considered positive for analysis purposes. Medication compliance was measured by the number of medication doses ingested by each participant. Retention time was measured by the percent of patients active in the study over time and was calculated from the day of the first dose to the day of the last dose.

Statistical analysis was performed using analysis of variance (ANOVA) or chi-square tests. ANOVA is a collection of statistical models used to determine differences among and between treatment groups. A Chi-square test is a statistical means of comparing the fit between observed and theoretically expected

values. Hierarchical linear modeling (HLM), an ordinary least square regression-based analysis taking the hierarchical structure of data into account, was used to examine opioid abstinence and use of non-opioid drugs over time. The Kaplan-Meier statistic was used with 95% confidence intervals to estimate retention time. Significant differences between the different groups were determined using Log rank chi-square tests.

**Study Results:** a total of 268 participants were chosen to participate in the study and were randomly assigned to the 4 study groups. A malfunction of the minimum-likelihood allocation computer software resulted in uneven numbers being assigned to the groups, but they did not differ based on gender, ethnicity, age, years opioid use, previous history of methadone treatment, or history of treatment at the Vine Street Center.

The percentage of urine samples that were opioid-free over time among drug groups and drug doses did not differ significantly. In general, participants increased their percentage of opioid-negative urine samples over the course of the study and was not predicted by either drug type or dose. Results from the homogeneity of proportions test found the percent of participants with at least 12 consecutive opioid-negative urine samples differed by dose but not by drug. Those receiving higher doses of either buprenorphine-naloxone or methadone were more likely to have at least 12 consecutive opioid-negative urine samples as compared to those receiving the lower doses.

ANOVAs were conducted to determine if the treatment groups differed in the amount of medication ingested and demonstrated no significant difference in medication compliance based on drug or dose.

The most commonly used drugs other than opioids among study participants were cocaine and cannabinoids. HLM models showed that nonopioid drug use did not change significantly over time or across the different study groups.

Kaplan-Meier survival analyses and log rank chi-square tests were used to estimate retention time and found no significant difference based on the drug used.

Ninety percent of participants who completed the study elected to continue treatment under the compassionate extension of treatment program and there were similar percentages of participants in each treatment group who decided to continue treatment. Medication and dose received during the study did not significantly affect the duration of time that participants chose to receive treatment after the end of the study.

**Study Critique:** the strengths of this study included conservative analytical procedures (ex: all missing urine samples were considered positive), a rapid buprenorphine dose induction procedure and therapeutic maintenance dose of each study medication used, the study being conducted at a licensed, community-based opioid treatment center and exposing patients to buprenorphine-naloxone for longer time periods than previous studies.

Limitations of this study included the uneven number the participants assigned to the 4 treatment groups and the steadily decreasing numbers of patients due to study dropout leading to loss to follow-up. There

was also the potential that participants could tell which tablet or solution was placebo even though they tried to control for this.

### **Study 3**

*Treatment Retention among Patients Randomized to Buprenorphine/Naloxone Compared to Methadone in A Multi-site Trial. Hser et al.*<sup>13</sup>

**Objective:** to examine patient and medication characteristics associated with retention and continued illicit opioid use in methadone versus buprenorphine-naloxone treatment.

**Study Design:** this was a secondary analysis of an original study that was a multisite, open-label, phase IV study to assess liver function in participants randomized to receive either methadone or buprenorphine-naloxone. The study took place at 9 federally licensed opioid treatment programs across the United States. Participants were used from the original study. There were 1,269 eligible participants. Two women were excluded from the study since they became pregnant and required medication reassignment. This led to the 1,267 participants that were actually included in this study. The higher dropout rate seen in the buprenorphine-naloxone group resulted in an uneven number of study participants in the two groups.

Participants had to go to the clinic daily for observed medication administration excluding Sundays, holidays, and when take-home medications were deemed appropriate by Federal/State law. The study was conducted over a 24-week period and then tapered over of  $\leq 8$  weeks or referred for continued treatment with study completion at 32 weeks.

Assessments were conducted on a weekly basis including urine drug screens and adverse event assessments. Self-reported drug use data were collected every four weeks. Participants who missed 14 or more consecutive days of the medication were withdrawn from the study.

Treatment completion was defined as a participant continuing the assigned medication for 24 weeks without being withdrawn from the study. Treatment retention was calculated based on the number of days in treatment since randomization until the last day the medication was taken.

Chi-square tests or t-tests were used to determine statistically significant differences between the two study groups. The Kaplan Meier method and log rank tests were used to assess the unadjusted survival function. Cox proportional hazard models, used in survival analysis to assess the importance of different covariates in the survival times of individuals through the hazard function, were performed to compare survival rates between the two groups. The generalized estimating equations approach, used to estimate a possible unknown correlation between outcomes, was used to find the relationship between dose and opioid use over time.

**Study Results:** This study found that days of opioid use in the past 30 days did not significantly differ between the group taking buprenorphine-naloxone and methadone.

This study showed that significantly fewer participants in the buprenorphine-naloxone group completed the 24 week treatment compared to those in the methadone group. This was due to significantly more participants in the buprenorphine-naloxone group dropping out of the study within the first 30 days than in the methadone group. Even among those who stayed in the study more than 30 days, the buprenorphine-naloxone group still showed a significantly lower completion rate than the methadone group. It was also found that more buprenorphine-naloxone participants than methadone participants dropped out because they no longer wished to participate in their assigned treatment regimen.

Doses of methadone greater than 60 mg demonstrated 80% or better retention with 120 mg or higher showing a 91% completion rate. Buprenorphine-naloxone, on the other hand, showed a linear relationship between dose and retention rate with increasing doses yielding better retention rates. The highest dose in this category was 30-32 mg resulting in a completion rate of approximately 60%.

For the urine analysis, increased dose was found to be negatively related to continued opiate use. Buprenorphine-naloxone participants had lower likelihood of positive opiate test results for every mg dose increase compared to those in the methadone group. Additionally, opiate use was significantly lower in the buprenorphine-naloxone group than the methadone group during the first 9 weeks of treatment.

The Cox model was used to identify additional measures to help predict retention rates. It was found that younger age, Hispanic populations, and use of opioids, amphetamine, cannabinoids or cocaine were associated with dropout from the study and shorter retention rates. Location (programs on the west coast) and higher dose of medication were associated with lower risk for dropping out of the study. It was also found that gender affected the two study groups opposite one another. In other words, males in the buprenorphine-naloxone group were less likely to drop out while males in the methadone group were more likely to drop out.

**Study Critique:** the strengths of this study included being the first large scale randomized trial to compare treatment retention of participants on buprenorphine-naloxone and methadone, being conducted in community treatment programs in the United States, revealing additional findings regarding buprenorphine-naloxone dose and treatment retention, and identifying additional participant characteristics predicting dropout (age, ethnicity, other drug use, etc.).

Limitations of this study included limited measures of participant motivation as well as program and community characteristics that are likely to influence treatment retention, such as location of treatment centers and years of regular opioid use. Other limitations that should be noted are that it was an open-label and unblinded clinical trial.

## **DISCUSSION**

Complete abstinence from opioid use is the ideal objective in the treatment of opioid dependence but is improbable with exceedingly high relapse rates. For example, one study, which followed opioid-dependent individuals 30 days after a 3-day inpatient medically supervised opioid withdrawal program, discovered that only 17% had remained abstinent.<sup>14</sup> Therefore, treatment efforts are directed at preventing illicit use and its subsequent consequences such as impaired social functioning and disease risk.

Examining treatment retention rates and absence from use of illicit opioids are therefore cornerstones in assessing the effectiveness of maintenance treatment.

Hser et al. (2014) demonstrated that treatment retention was significantly higher in those treated with methadone compared to buprenorphine-naloxone ( $p < 0.01$ ). Of those treated with methadone, 74.1% remained in treatment at 24 weeks compared to 46.1% of those treated with buprenorphine-naloxone. Conversely, Otiashvilis et al. (2013) showed no difference in retention rates at 12-weeks but higher retention rates among those on methadone (92.5%) than those on buprenorphine-naloxone (7%) at 20 weeks. This large discrepancy seen between the drugs is consistent with numerous other studies and could be the result of multiple factors.<sup>9,15</sup> It has been postulated that poorer retention rates for buprenorphine are due to the fact that it functions as a partial mu-receptor agonist and therefore does not have the full opioid effect and is less satisfying to patients. Another possibility is that it is easier to withdraw from buprenorphine, as withdrawal symptoms are substantially milder than those seen with methadone. Others have speculated that buprenorphine retention is inferior to methadone because buprenorphine can induce withdrawal symptoms upon initiation by displacing heroin, a full agonist.<sup>9</sup> This is less convincing since retention rates of buprenorphine-naloxone were shown to be the same as methadone at 12 weeks in the Otiashvilis study and higher in the Kaimen et al. study (35 vs. 33 participants). Another consideration is that research values of buprenorphine-naloxone retention rates may not accurately reflect in-practice retention rates. In order to ensure research accuracy, research subjects must take the drug in-clinic. This detracts from the potential benefit of taking buprenorphine-naloxone at home, which may actually increase patient compliance and retention rates.

Buprenorphine-naloxone was superior to methadone in treatment efficacy. Illicit opioid use was significantly lower among the buprenorphine-naloxone group within the first 9 weeks of treatment compared to methadone ( $p < 0.01$ ). Similarly, there were significantly more opioid-positive urine samples in the methadone group than the buprenorphine-naloxone group ( $p = 0.03$ ). Albeit, all three studies indicated that both buprenorphine-naloxone and methadone were effective at decreasing illicit opioid use. Use of concomitant opioids may be lower with buprenorphine-naloxone treatment as a result of the “ceiling effect”. Higher doses of buprenorphine-naloxone saturate mu-receptors without an additional euphoric effect and prevent euphoria from the supplementation of another opioid. In contrast, higher doses of methadone or the addition of another opioid will lead to a greater euphoric effect, preventing the discouragement of illicit opioid use.

These studies gleaned further insight on dosing regimens. Increased dosage was associated with both higher retention rates and less likelihood of illicit opioid use. Kamien et al. (2008) showed a higher retention rate among those on high dose (16mg) buprenorphine-naloxone (12.5 weeks) than low dose (8mg) buprenorphine-naloxone (12.1 weeks) although, retention rates were lower among high dose (90mg) methadone (12.2 weeks) compared to low dose (45mg, 13.2 weeks). The reason for poorer retention rates among the high dose methadone treatment group remains unclear and is inconsistent with findings from Hser et al. (2014), which showed higher retention rates with higher doses for both treatment groups. Furthermore, higher doses were associated with fewer positive urine samples in both studies. These findings are consistent with other studies and may suggest that dosage is more important than the drug used. A meta-analysis conducted by Barnett et al. (2001) slightly favored methadone in treatment retention but dosing had the most substantial impact on outcomes. Patients on 60mg of methadone were 5

times more likely to withdraw from treatment than those on 80mg. Additionally, an 8-12mg dose of buprenorphine was more effective than 60mg of methadone, although, 80mg of methadone was superior to all other treatment modalities.<sup>16</sup>

## **CONCLUSION**

With an inconsistency in retention rates and somewhat equivocal effectiveness observed between buprenorphine-naloxone and methadone, it is essential to take into consideration other influential characteristics of these drugs. The benefits of utilizing buprenorphine-naloxone have been examined in several studies and include less dependence and tolerance, lower risk for fatal overdose, and cardiotoxicity (QT prolongation and torsade des pointes), longer duration of action and fewer withdrawal symptoms.<sup>9,17,18</sup> Maintenance therapy with buprenorphine-naloxone also demonstrates a substantial advantage over methadone in that methadone typically requires daily visits to a licensed opioid treatment clinic for supervised administration whereas buprenorphine-naloxone can be dispensed at pharmacies with a one-month supply and 6 refills.<sup>16</sup> This lessens provider burden and may function to enhance patient compliance. Furthermore, buprenorphine-naloxone has markedly less divergence rates than methadone and when used illicitly; it is typically only used to combat opioid withdrawal symptoms or reduce the use of other opioids.<sup>20</sup> This is in large due to a less satisfactory euphoria generated by buprenorphine compared to methadone, which is reflected by its low street value and lack of divergence.<sup>20,21</sup> Therefore, if methadone is replaced by buprenorphine-naloxone for the treatment of opioid dependence, this may substantially reduce the illicit use of prescription opioids. Consequently, we recommended buprenorphine-naloxone as a first-line treatment for opioid-dependent individuals.

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