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Evaluation of successful rehabilitation treatments for opioid addiction

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Thesis

**EVALUATION OF SUCCESSFUL REHABILITATION TREATMENTS FOR
OPIOID ADDICTION**

by

JYLA HICKS

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requirements for the degree of
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Approved by

First Reader

Gwynneth Offner, Ph.D.
Associate Professor of Medicine

Second Reader

Karen Symes, Ph.D.
Associate Professor of Biochemistry

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ABSTRACT

The opioid epidemic in America and worldwide is growing leading to an increase in opioid addiction ultimately ending in overdose and death. The specific aim of this paper is to evaluate the different treatment methods that aid with opioid addiction. The main medicated-assisted treatments (MATs) that will be discussed are buprenorphine and methadone. In addition to these two MATs, behavioral therapy treatment will also be of focus as it is often paired with a MAT to obtain the best treatment outcome. This paper will evaluate multiple factors that define successful opioid addiction treatment and treatment outcomes. These factors may include patient characteristics, relapse time if applicable, and length of sobriety after treatment completion also with other aspects.

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LIST OF ABBREVIATIONS

APA.....	American Psychiatric Association
BUP.....	Buprenorphine
CDC	Center for Disease Control
HIV	Human Immunodeficiency Virus
MAT.....	Medication-Assisted Treatment
MET	Methadone
MMT.....	Methadone Maintenance therapy
NCHS.....	National Center for Health Statistics
NIDA.....	National Institute on Drug Abuse

INTRODUCTION

Opioids such as fentanyl, morphine, codeine and vicodin are all medications that are prescribed to aid with pain relief but are also highly addictive (Aronson et al., 2016). Physicians struggle daily when trying to make the decision of how to treat chronic pain while avoiding potential opioid addiction. For example, fentanyl, a synthetic opioid often used for chronic pain relief, is a great addition to treatment when administered properly at the correct dosage (Aronson et al., 2016). Problems often arise for the reason that fentanyl dosages are often illegally tampered with due to the potency of fentanyl which is 1000 times more powerful than traditional opioids such as pethidine (Aronson et al., 2016). The grave increase in potency compared to other opioid medications often allows fentanyl to be easily abused which leads to addiction, overdose and ultimately death.

The number of opioid related overdoses and the mortality rate of those addicted to opioids is increasing at an fast rate. According to the Center for Disease Control (CDC) National Center for Health Statistics (NCHS), the average death rate per 100,000 people in 2014 was 14.7 compared to 9.4 in 2004 (CDC/NCHS, 2017). The progressive growth in opioid abuse and opioid related overdoses is a serious everyday problem in the United States with over 115

people dying daily from drug overdoses (CDC/NCHS, 2017). The increasing number of opioid related deaths has caused an urgency to find successful remediation treatments for this relatively new epidemic.

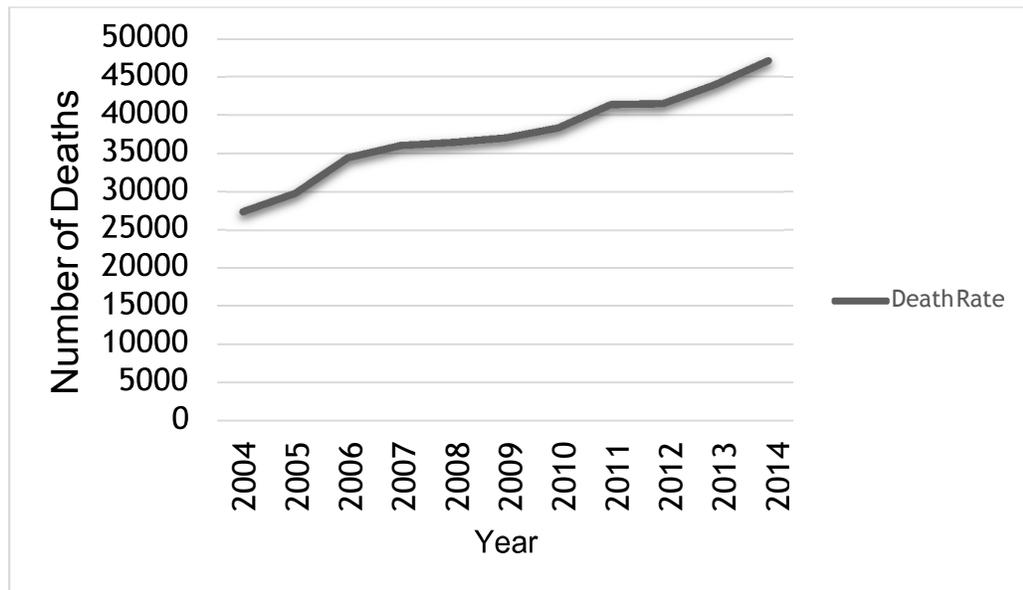


Figure 1. Number of Drug Related Deaths Involving Opioid Analgesics and Heroin Data based off deaths in the United States in 2004 spanning to 2014 (Chen et al., 2014).

Opioid addiction not only comes with associated health risks and effects but also lends to economic problems such as increased health care costs and societal costs (Lipman & Webster, 2015). The estimated cost of drug addiction treatment and preventative addiction services in the United States totaled to 4.5 billion dollars over ten years ago (Mart et al., 2005). This astounding dollar

amount becomes more eye-opening knowing that the 4.5 billion dollars only covered 3% of the total societal cost (Mart et al., 2005). Table 1 displays the associated health care cost increase as a result of patients newly diagnosed with opioid addiction.

Table 1. Increase in Health Insurance Cost Due to Opioid Addiction
Data based off Medicare and Medicaid Databases (Florence et al., 2013)

Insurance Type	N	Appraised Cumulative Effects (95% Confidence Interval)
Medicare	6,917	\$17, 052 (\$13,472, \$20,632)
Medicaid	30,454	\$13,743 (\$12, 341, \$15,145)

Societal costs are not exclusive to dollar amounts but should also include the negative experiences and stress the family and friends of those abusing opioids deal with. Consequences that the families may have to deal with can include shame, miscarried expressions of anger, and an overall negative environment that involves the drug abuser (Center for Substance Abuse Treatment, 2004). Finding the most successful treatment option for opioid abuse will lead to an overall greater and more efficient way to treat addiction. The improvement in treatment success will create wide stretch rewards such as decreases in crime rates, lowered economic and societal costs, and improved

global health due to a decrease in infections such as human immunodeficiency virus (HIV) and hepatitis (Schwartz et al., 2008). The three treatments that will be discussed in depth are behavior therapy, buprenorphine, and methadone.

Behavioral Therapy

According to the Controlled Substance Act put in place under President Richard Nixon, physicians are mandated to offer or refer behavioral therapy treatment when treating opioid dependence with MATs such as buprenorphine and methadone (Controlled Substance Act, 1996). Although this requirement has been put in place, few studies on what behavioral therapy treatment type is most successfully paired with MATs have been examined. The National Institute on Drug Abuse (NIDA) has worked to tackle this deficit in knowledge and expand the development of behavioral therapies by creating a scientific framework that includes three stages to guide the expansion of new behavioral therapies (Onken et al., 1996).

Stage one is a preliminary period that sets the basis for creating an entirely new behavioral therapy or making significant changes to a preexisting therapy (Onken et al., 1996). Stage one can be compared to brainstorming while completing investigative research that supports the need to make alterations to existing therapies or to create an entirely new field. During stage two,

effectiveness testing is taking place in order to evaluate the therapies and ensure that they show promise for use in the future (Onken et al., 1996). Stage two can be seen as the most important stage because it will show the efficacy of the treatment but stage three is vital to show that the proposed study will be effective in the field and not only in a controlled experimental setting (Rounsaville et al., 2001).

Methadone

Methadone is often used by physicians to relieve chronic pain or to assist with opioid abuse detoxification and rehabilitation (Grissinger, 2011).

Methadone is often selected as a treatment option due to its long-lasting effects which means fewer doses are needed to have pain relief or suppress drug cravings (Brown, 2004). While taking methadone, one may experience side effects that may seem monogamous with opioid abuse such as dizziness, vomiting, and fatigue (Macey et al., 2013). Death as a result of a methadone overdose is possible due to the depressing physiological nature of the drug so dosage is vital to maintain at a healthy amount to decrease risks (Chou et al., 2015).

Methadone maintenance therapy (MMT) is a treatment used specifically to combat illicit drug use (Mattick et al., 2009). Treatment usually takes place at an outpatient clinic where the medication is given by a licensed health provider

(Mattick et al., 2009). The length of time persons will be on methadone treatment varies and depends on multiple factors (Joseph et al., 2000). Some of the factors determining the duration of MMT is the length of drug use before methadone treatment starts, the method of abuse such as intranasal or intravenous and also the type of drugs abused (Joseph et al., 2000). MMT can be an excellent treatment option when prescribed and used correctly, if not, abuse of methadone can lead to physical dependence similar to illicit drugs (Joseph et al., 2000).

Buprenorphine

Buprenorphine is a medication used in the treatment of opioid addiction that holds similar organic molecular structure and activity to morphine and fentanyl (Cowan et al., 1977). Figure 4 shows examples of opioid analgesics including buprenorphine which are similar to morphine and fentanyl, two commonly abused drugs (Martin et al., 2016) and also methadone which will be discussed in greater detail.

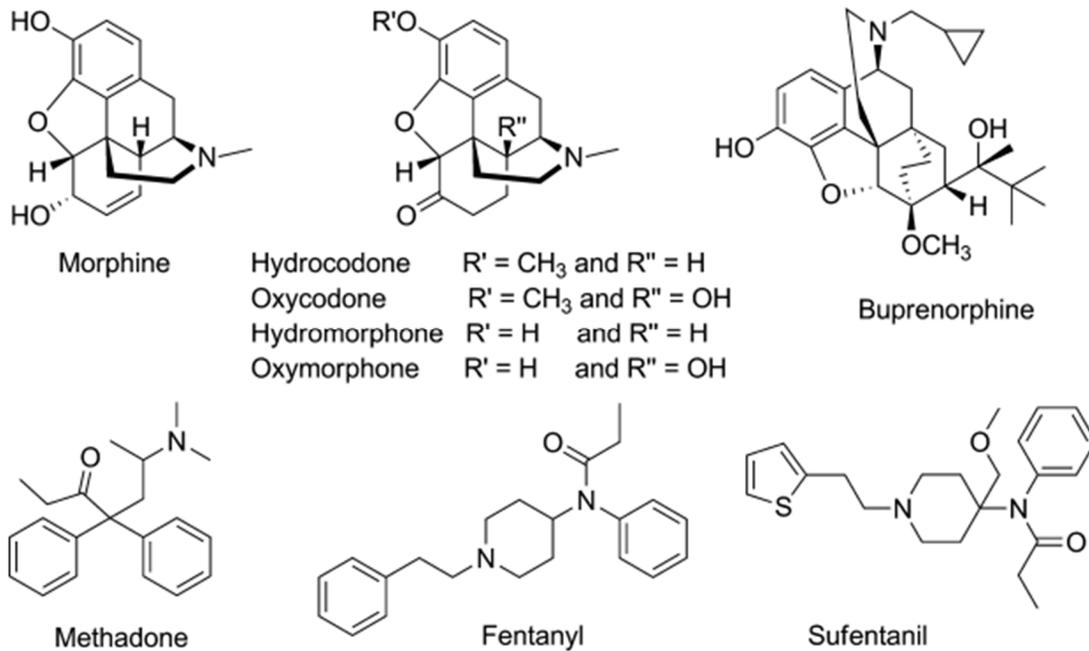


Figure 2. Examples of Opioid Analgesics used for Moderate to Severe Pain Treatment (Martin et al., 2016).

The three receptors in the brain that opioids and endogenous peptides exert their pharmacological actions on are kappa, mu, and delta (Raynor et al., 1994). Once activated, these receptors can activate an array of behavioral physiological changes that include autonomic functions such as heart rate and respiration, but also other bodily changes like mood and pain awareness (Raynor et al., 1994). The physiological and behavioral effect of the binding molecule on the receptor depends on its affinity and efficacy (Khroyan et al., 2015). The mu receptor when activated causes constipation, slowed respiration and feelings of euphoria which is the key effect that leads to potential abuse (Khroyan et al.,

2015). By contrast, the kappa receptor when activated reduces constipation, increases respiration and causes feelings of dysphoria instead of euphoria (Khroyan et al., 2015).

Once abused, drugs like morphine and fentanyl can easily lead to death being that they bind with extremely high efficacy to the mu receptors which will cause a slowness of breath and potentially lead to death. Buprenorphine also has a partial high affinity for the mu receptor just like morphine and fentanyl but also is an antagonist to the kappa and delta receptors which will combat those deadly side effects of over stimulating the mu receptors (Khroyan et al., 2015). Buprenorphine is a great alternative to morphine due to its lipophilic quality and ability to last for a substantial amount of time in the body which helps fight opioid addiction (Mello et al., 1993). MAT with buprenorphine will be examined to look at how successful it is with opioid dependence rehabilitation.

PUBLISHED STUDIES

The behavioral therapy treatments used to rehab drug abuse and dependence that were successful in stage two of the scientific framework to expand behavioral therapies set by the NIDA include family/community approaches, motivational interviewing, contingency management, and cognitive behavior approaches (Onken et al., 1996). These behavioral therapy treatments are seen to be specifically successful when dealing with opioids and other drugs such as cocaine and marijuana dependence (Onken et al., 1996).

Contingency Management

The behavioral therapy treatment coined contingency management is often used in combination with prize reinforcement as treatment for opioid addiction (Lewis, 2009). Contingency management is constructed on the theories of B.F. Skinner's operant conditioning using the model to reinforce positive behaviors with a reward (Lewis, 2009). In the case of contingency managed opioid treatment, the positive behavior would be abstaining from drug use and being monitored by drug tests while the reward could be of monetary value or a strongly desired item by the opioid-dependent patient. The goal of this treatment

is to reinforce the positive behavior so that the likelihood of it reoccurring is increased and the likelihood of relapse is decreased (Higgins, 1997).

Granted that MATs for opioid dependency combined with behavioral therapy have seen to be effective, the type of behavioral therapy and MAT used may skew effectiveness results and are still under research. For example, Warren Bickel and colleagues found that adding behavioral treatments such as contingency management with prize reinforcement and the community/ family therapy approach with MAT using buprenorphine increased successful rehabilitation outcomes rather than no combined behavioral therapy treatment at all (Bickel et al., 1997). However, Ling and colleagues compared two different behavioral therapy treatments, cognitive behavioral therapy, and contingency management with MAT using buprenorphine and found no significant difference in opioid use when buprenorphine is not combined with behavioral therapy (Ling et al., 2013). Both studies compared behavioral therapy combined with MATs with buprenorphine but received different results that could be attributed to various external variables and will be further examined.

The effects of adding behavioral therapy treatment to opioid detoxification and rehabilitation was further researched by Bickel and colleagues using thirty-nine opioid dependent participants (Bickel et al., 1997). Table 2 and

Table 3 display the participant characteristics and attributes that were surveyed before starting the trials. The participants were randomly recruited over a 16-month period by strategies such as newspaper and media postings.

Table 2. Participant Characteristics Including Demographics and Opioid Use Measuring Contingency Management and Buprenorphine Treatment

Data based off pretrial interview responses (Bickel et al., 1997)

	% or M ± SD	
Characteristic	Behavioral Group (N=19)	Standard Group (N=20)
Demographics		
White	100	95
Male	63	65
Never married	42	40
High schooleducation	95	85
Employed	37	45
Age (years)	33.6 ±7.3	34.6 ±8.0
Opioid Use		
Prior treatment	79	80
Years of regular use	8.8 ± 7.1	11.4 ± 7.4
Age of first use	20.4 ± 4.7	21.0 ± 3.9
Dollars spent weekly	225 ± 266	338 ± 310

Table 3. Participant Characteristics Including Opioid Use Preferred Route Measuring Contingency Management and Buprenorphine Treatment

Data based off pretrial interview responses (Bickel et al., 1997)

Characteristic	% or M ± SD	
	Behavioral Group (N=19)	Standard Group (N=20)
Opioid Use - Preferred Route		
Intravenous	63	65
Oral	21	20
Intranasal	16	15

During the one-week period of treatment, patients were assigned to either the standard or the behavioral group using minimum likelihood allocation based on certain characteristics (Bickel et al., 1997). Treatment was administered by master-level counselors trained specifically for the study and overseen by two higher level psychologists that reviewed each patient’s status on a weekly basis to review progress (Bickel et al., 1997). The behavioral therapy treatment used was contingency management combined with community support. Contingency management with prize reinforcement was maintained using a voucher system that rewarded patients monetarily based on clean urine samples (Bickel et al., 1997).

The voucher system used by Bickel directly translated to points that were worth dollars and patients received the cash equivalent in services such as dinner at restaurants or phone amenities (Bickel et al., 1997). Each urine sample negative for drugs was worth 29 points that translated to \$0.125 a point or \$3.63 for each sample. Every drug free urine sample provided by the patient earned a point value increase by one. For example, the second negative urine sample would earn the patient 30 points and the third negative urine sample would earn the patient 31 points. After three consecutive negative urine samples the patient earns an additional \$5 award. The trial was a 26-week long period with the first week used as a baseline to establish correct buprenorphine doses and the last two weeks were void of voucher rewards to wean the patients off the reward system. Altogether, during the 23-week voucher trial period the patient could earn up to \$658.38 (Bickel et al., 1997).

The results displayed in figure 2 show that there is a better overall outcome with the behavioral therapy treatment as opposed to the standard treatment with no therapy (Bickel et al., 1997). The percentage of patients that completed treatment in the behavioral therapy treatment group was more than double the standard treatment group at fifty-three percent versus twenty percent (Bickel et al., 1997).

BEHAVIORAL TREATMENT DURING OPIOID DETOXIFICATION

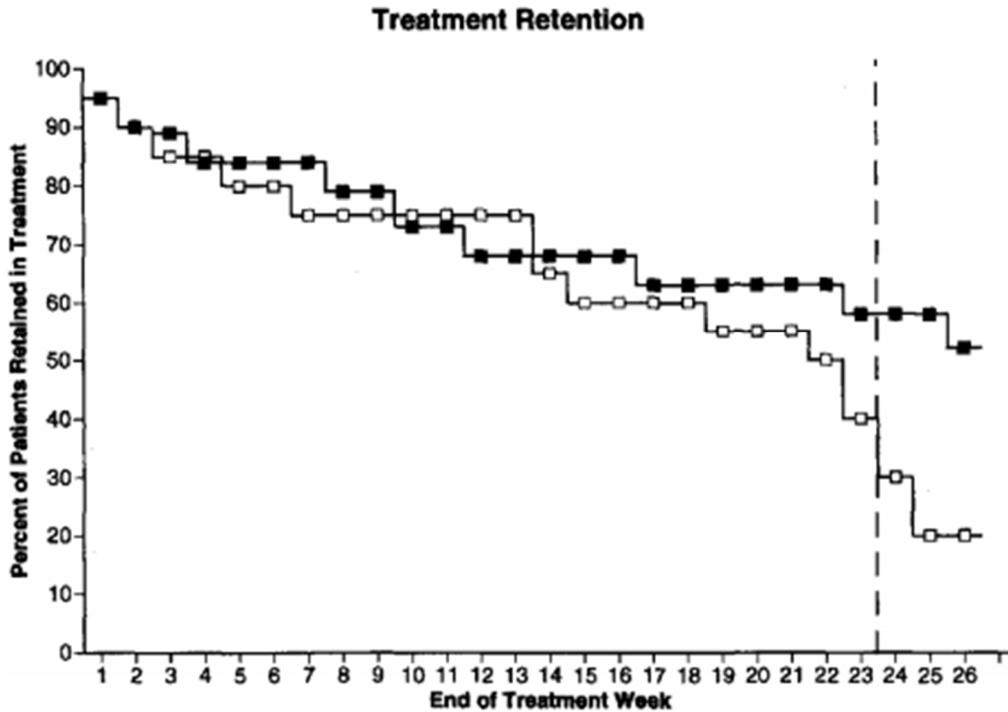


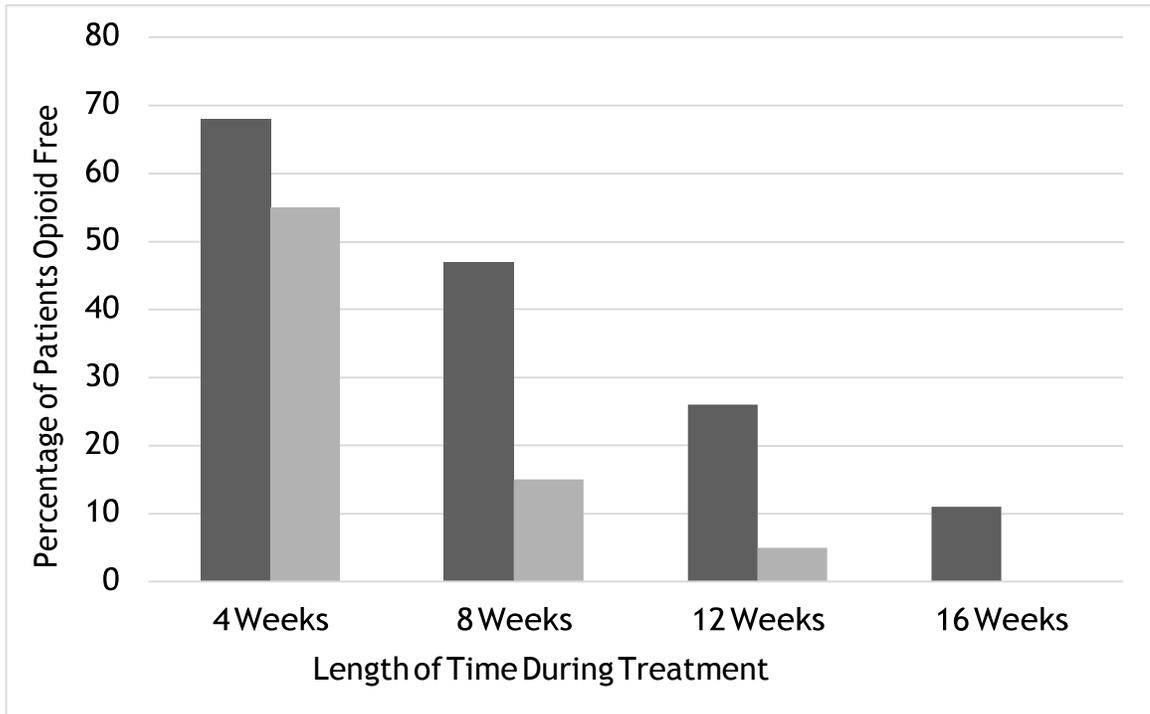
Figure 3. Percentage of Patients Retained in Treatment at the End of Each Treatment Week. The dashed vertical line before Week 24 indicates the start of the placebo period as a function of treatment week. Closed squares indicate behavioral treatment; open squares indicate standard treatment (Bickel et al., 1997).

According to the trial standards, continuous abstinence occurs when a patient provides consecutive opioid free urine samples (Bickel et al., 1997).

Results from the trial showed that patients in the behavioral therapy treatment group displayed continuous abstinence at a greater rate than the standard treatment group as shown in Figure 3 (Bickel et al., 1997). During treatment weeks 4, 8, 12, and 16, the behavioral therapy treatment group had a continuous

abstinence patient level of 68, 47, 26, and 11 percent compared to the standard treatment group where percentages were 55, 15, 5, and 0 (Bickel et al., 1997).

Figure 4. Percentage of Patients Attaining Continuous Opioid Abstinence. Dark bar indicates behavioral treatment; light bar indicates standard treatment (Bickel et al., 1997).



Cognitive Behavioral Therapy

Cognitive behavioral therapy treatment has been used in the past not only to aid with psychological disorders (Ammar & Khoury, 2014), but also substance abuse disorders with drugs such as opioids and cocaine (Iwano et al., 2013).

Substance abuse treatment using cognitive behavioral therapy originally stemmed from cognitive behavioral therapy treatments developed for

psychological disorders such as depression and anxiety (Meichenbaum, 1995) but was later applied to substance abuse disorders (Marlatt & Gordon, 1985).

Cognitive behavioral therapy can take place in a group or individual counseling session that focuses primarily on behavior changes and skills to help make the desired transformation happen (Ling et al., 2013). According to the American Psychiatric Association (APA) there are two key components of cognitive behavioral therapy when dealing with substance abuse disorders which includes:

“1) an emphasis on functional analysis of drug use-that is, understanding drug use with respect to its antecedents and consequences- and 2) emphasis on skills training” (Carroll et al., 2004).

The cognitive behavioral therapy approach focuses on the patient directly to foster the skills needed for a successful rehabilitation to obtain sobriety and avoid relapse. Examples of skills needed for a successful rehabilitation from drugs includes actively self-monitoring thoughts and behaviors that take place during high-risk drug usage, not only understanding drug cravings but also being knowledgeable of healthy ways to cope with them, and most importantly having the strength to strongly refuse drugs or drug exposure (Carroll et al., 2004). Cognitive behavioral therapists work with patients to apply these skills

not only to substance abuse related issues but also to different situations that could be beneficial to the patient in their everyday life (Carroll et al., 2004).

The evaluation of successful rehabilitation treatments using cognitive behavior therapy combined with buprenorphine was completed by Moore and colleagues (Moore et al., 2016). The study length was 26 weeks and included 48 patients addicted to opioid medication with their characteristics being shown in Tables 4 and 5.

Table 4. Participant Characteristics Including Demographics and Opioid Use Measuring Cognitive Behavioral Therapy and Buprenorphine Treatment

Data based pretrial evaluations (Moore et al., 2016)

Characteristic	Cognitive Behavioral Treatment (N=48)
% White (n)	94% (45)
% Male (n)	71% (34)
% Never married (n)	62% (30)
% High school education (n)	87% (40)
% Full-time Employed (n)	51% (24)
Age (years), mean	32.4
Opioid Use	
% Prior attempted detoxification	24% (11)
% Prior treatment (not detox)	49% (22)
Years of opioid use, mean	6.6

Table 5. Participant Characteristics Including Opioid Use Preferred Route Measuring Cognitive Behavioral Therapy and Buprenorphine Treatment

Data based pretrial evaluations (Moore et al., 2016)

	%
Characteristic	Cognitive Behavioral Treatment (N=48)
Opioid Use - Current route of administration	
% Intravenous (n)	2% (1)
% Oral (n)	37% (17)
% Intranasal (n)	61% (28)

During the 26-week study period, opioid use was assessed by patient self-report and weekly urine screenings. The patient's addiction severity index was also measured monthly by a trained research technician. The addiction severity index is a structured interview evaluation to identify and record potential high risk category responses that affect substance abuse patients (McLellan et al., 1992). At the end of the trial, all samples were totaled and consecutive abstinence from opioids was based on self-reporting but verified by the urine screening results. Treatment completion was measured by retention variables that defined it as completing the trial up until week 24 and not being withdrawn due to factors that include missing more than three physician sessions or missing required medications for more than one week. Completion included 24 weeks

since the trial included a 2-week induction/stabilization period and then 24 weeks of maintenance.

The cognitive behavioral therapy trial was randomized into two groups so that patients would either be in a primary-care physician management group or in a physician management group with cognitive behavioral therapy. Both groups received the buprenorphine medication with an individualized dose depending on the needs of the patient that included distress or continued opioid use. The physician managed group without cognitive behavioral therapy met for 15 to 20 minutes and were run by internal medicine physicians who were not trained in cognitive behavioral therapy methods. The internal medicine physicians also administered the buprenorphine medication. Included in the sessions were self-report discussions, urine screenings, and brief discussions on ways to avoid opioid use.

Physician managed sessions occurred weekly for the beginning of the trial then after two weeks, the sessions occurred bi-weekly and at 6 weeks, the trial sessions became monthly. The cognitive behavioral therapy and buprenorphine treatment trial group met every week for 12 weeks with 50-minute sessions. Each session was guided by a clinician that was master or doctorate level certified. Every clinician in the behavioral therapy treatment group was trained

specifically in behavioral therapy and also supervised patients similar to the internal medicine physicians in the physician managed group.

Table 6. Treatment Outcomes of Opioid Use Groups Depending on the Addition of Cognitive Behavioral Therapy (Moore et al., 2016)

	Physician Management + Cognitive Behavioral Therapy (n = 23)	Physician Management (n = 26)
Completed treatment	48% (11)	54% (14)
Weeks in treatment	19.4 (6.9)	19.4 (6.2)
Number of missing urine screens	0.78 (1.17)	0.64 (0.95)
Number of urines negative for opioids	12.0 (8.4)	9.7 (8.1)
Longest consecutive weeks of opioid abstinence	8.9 (7.8)	5.7 (6.5)
Number of urines negative for all drugs	7.6 (7.9)	3.7 (5.4)

The results in Table 6 show that overall, physician managed treatment and cognitive behavioral therapy had a greater success rate at rehabilitation than

physician management alone. The physician managed group had a higher number of patients complete the treatment, but that is the only advantage when compared to the cognitive behavioral therapy treatment group.

Buprenorphine and Methadone

A study was completed to compare MAT with buprenorphine to MAT with methadone (ref). Participants included a total of 1,269 patients recruited from opioid treatment programs. The clinical profiles including demographics are seen in table seven and obtained through health surveys and a 4-week self-report screening period to provide current drug history summaries. Each participant was randomized with 740 participants in the buprenorphine treatment group and 529 participants in the methadone treatment group. The discrepancy in treatment group sizes is a consequence of patient dropout and rare treatment group changes as a result of pregnancy.

The study was 32 weeks long with a minimum of 24 weeks on medication and the last 8 weeks being variable for tapered medication or referral to a clinic to continue treatment. Medication was distributed daily except for Sundays or holidays where patients were issued a take home dose by clinic physicians. The initial study required that participants abstain from opioids for 12 to 24 hours so

they would ideally be in the early stages of withdrawal where the physician could individually evaluate and prescribe the correct dose for each patient. Opioid usage was monitored weekly with drug screenings while self-report data was evaluated every 4 weeks. The drug screenings were in the form of a urine sample that was monitored for temperature and strip tested for illicit drugs.

Table 7. Clinical Profiles at Baseline of MAT with Buprenorphine and Methadone (Hser et al., 2014)

	Buprenorphine (n=738)	Methadone (n=529)	Total (n=1267)
Age, mean (SD)	37.5 (11.2)	37.3 (10.9)	37.4 (11.1)
Female gender, %	32.0	32.1	32.0
White, %	69.4	74.1	71.4
Days using opioids in past 30 days	26.8	26.7	26.8
Cocaine-positive UDS, %	34.0	42.0	37.3
Amphetamine- positive UDS, %	8.7	9.5	9.0
Drug injection in past 30 days, %	68.3	69.3	68.7

SD = standard deviation, UDS = urine drug screen

The profiles in Table 7 show that both MAT groups with buprenorphine and methadone were similar. The overall general profile of a participant in this study was an early middle-aged white male. The study also included other ethnicities such as African American at 9% and Hispanic at 12%. Some participants in both treatment groups tested positive for drugs other than opioids and commented on alcohol use at mean of approximately 27%.

Table 8. Dropout reasons (%) of MAT with Buprenorphine and Methadone
(Hser et al., 2014)

	Buprenorphine (n=738)	Methadone (n=529)	Total (n=1267)
Dropout reasons, %	N = 398	N = 137	N = 535
Missed 14 or more days	63.1	68.6	64.5
No longer wish to participate	25.6	12.4	22.2
Administrative discharged	3.5	4.4	3.7
Not medically approved	3.8	3.7	3.7
Other reasons (incarceration, moved)	4.0	11.0	5.8

Table 9. Treatment Completion (%) of MAT with Buprenorphine and Methadone (Hser et al., 2014)

	Buprenorphine (n=738)	Methadone (n=529)	Total (n=1267)
Dropout during the first 30 days of treatment, %	24.8	8.3	17.9
Completed the 24-week trial, %	46.1	74.1	57.8
Retention (days in treatment), mean (SD)	103.8 (66.9)	141.3 (50.8)	119.4 (63.5)
Participants who stayed in treatment more than 30 days	N = 555	N = 529	N = 1040
Completed the 24-week trial, %	61.3	80.8	70.4
Retention (days in treatment), mean (SD)	133.3 (49.2)	152.8 (34.8)	142.2 (44.1)

SD = standard deviation

Shown in Table 9, during the first 30 days of treatment, the dropout rate for the buprenorphine treatment group was about three times higher at 24.8% versus 8.3% for the methadone treatment group. After the first 30 days, the

buprenorphine treatment group still had a lower completion percentage at 61.3% versus 80.8% for the methadone treatment group. Table 8 shows a similar percentage for 14 or more days missed at 63.1% for the buprenorphine treatment group and 68.6% for the methadone treatment group. When considering the other evaluated sections, researchers found that the majority of participants that dropped out of the buprenorphine treatment group did so because they no longer wished to participate in the study.

During Hser's study with buprenorphine and methadone, doses were increased as the trial progressed to accommodate for any changes needed by the patient and to test the hypothesis that higher doses would reduce opioid cravings and decrease potential relapse occurrences (Hser et al., 2014). Figure 5 displays the results of urine tests compared to the dosage over the 24-week trial period. The results show that increase in both buprenorphine and methadone doses decrease positive opioid urine test with buprenorphine having a greater influence on the decrease compared to methadone. Also, the plotted line graph in Figure 5 shows that opioid use was much lower in the buprenorphine treatment groups during the first ten weeks then eventually leveled out to similar levels with the methadone treatment group.

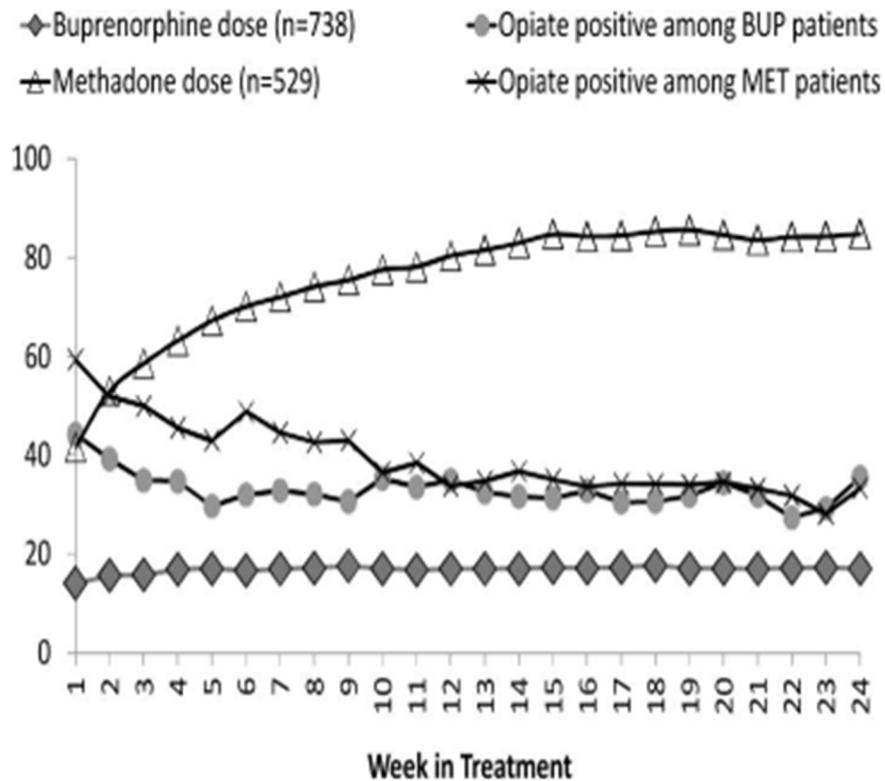


Figure 5. Average Dose and Positive Opiate Urine Test Across Weeks by Treatment Group (n=1,267) (Hser et al., 2014).

Hser and colleagues completed another study examining the long-term outcomes of using buprenorphine versus methadone MAT at multiple treatment programs across the United States (ref). The initial study began with 1,269 precipitants randomized to the buprenorphine treatment group (n=740) or the methadone treatment group (n=529). Due to several different variables across treatment sites only a total of 795 participants were interviewed for a follow up 2

to 8 years post study. Displayed in Table 10 are clinical profiles for all participants in the study.

Table 10. Clinical Profiles of Interviewed Samples at Baseline of Long-Term MAT of Buprenorphine versus Methadone (Hser et al., 2016).

	Randomized to buprenorphine (n=464)	Randomized to methadone (n=331)	Total (n=795)
Age at baseline, mean (SD)	37.4 (11.1)	37.4 (11.3)	37.4 (11.2)
Female gender, %	32.8	35.9	34.1
White, %	72.0	73.4	72.6
Days using opioids in past 30 days	26.8	26.7	26.8
In past 30 days, self-report use of Cocaine, %	30.2	37.2	33.1
In past 30 days, self-report use of Amphetamine, %	7.3	7.3	7.3

SD = standard deviation

For the follow up interviews, participants returned to their original clinic location where face-to-face interviews were held by research staff. The interviews lasted approximately 1 to 2 hours and, while at the clinic, participants were paid not only for the face-to-face interview but also to submit urine and saliva samples that were tested for drugs and HIV. The results of the follow up interviews, test samples, and self-reports given at the interview are shown in Table 11. The class of opiates/analgesics in Table 11 include prescription opioids such as oxycodone, and hydrocodone.

Table 11. Current Heroin and Opiate Use at the Follow-up Interview
(Hser et al., 2016).

	Randomized to buprenorphine (n=464)	Randomized to methadone (n=331)	Total (n=795)
Heroin use in the past 30 days (%)			
0	63.2	69.5	65.8
1-5	12.6	11.8	12.2
6-20	8.9	8.1	8.6
21-30	15.4	10.6	13.4
Mean (SD)	5.8 (10.5)	4.4 (9.3)	5.2 (10.1)

SD = standard deviation

Table 11. Current Heroin and Opiate Use at the Follow-up Interview Cont.
(Hser et al., 2016).

	Randomized to buprenorphine (n=464)	Randomized to methadone (n=331)	Total (n=795)
Use of other opiates/analgesics in the past 30 days (%)			
0	77.9	85.2	81.0
1-5	10.6	8.5	9.7
6-20	5.2	2.4	4.0
21-30	6.3	3.9	5.3
Mean (SD)	2.7 (7.4)	1.6 (5.9)	2.2 (6.9)
Positive urine test on heroin or opiate use (%)	42.8	31.7	38.1
Used heroin or opiates as indicated by urine test or self-report (%)	50.9	41.1	46.8

SD = standard deviation

Not included in the tables are the mortality rates which totaled 23 deaths in the buprenorphine treatment group and 26 deaths in the methadone treatment group. The buprenorphine treatment group had a significantly greater number of

patients that tested positive for heroin at the follow-up interview with 42.8% compared to the methadone treatment group at 31.7%. The trial accounted for treatment retention, and status as well, which showed that patients randomized to methadone treatment spent more time in treatment at 149.4 days in comparison to the buprenorphine treatment group at 111.4 days. Also noted is that 3.7% of participants in the buprenorphine treatment group and 4.9% in the methadone treatment group choose to continue a treatment option without opioid medications after the trial was complete. It is significant to note that both treatment groups experienced a decline in participation over the period of the trial but the methadone treatment group appeared to retain a greater number of patients.

When making the decision to choose a treatment plan for a disease that is heavily patient oriented, the patients' willingness to abide by the treatment plan is vital to its success. A study completed in Baltimore City examined the patient perspectives on MATs deciding between buprenorphine or methadone when equal access to both is provided (ref). This study was contained in another larger clinical trial where patients had the choice of which MAT to receive and ultimately choose buprenorphine. The study included 80 participants, whose patient characteristics can be seen in Table 12. The majority of the participants, at

85%, previously received buprenorphine off the street and 68% of the participants in the study were in a previous opioid agonist treatment.

Table 12. Participant Characteristics Involved in Choosing Buprenorphine over Methadone (Gryczynski et al., 2013)

Participant Characteristics (*n* = 80).

Background Characteristics	
Female, %	33.8
African American, %	93.8
Age, mean (SD)	45.2 (7.0)
Years of education, mean (SD)	11.5 (1.8)
Currently married, %	11.3%
Paid for working within last 30 days, %	31.3%
Substance Use Characteristics	
Injection Drug Use, %	22.5
Days of Heroin Use in Past 30 days, mean (SD)	21.1 (9.9)
Days of Cocaine use in Past 30 days, mean (SD)	7.4 (10.4)
Days of Other Opiate Use in Past 30 days, mean (SD)	5.4 (8.8)
Prior experience with non-prescribed street buprenorphine, %	85.0%
Prior Opioid Pharmacotherapy Experience	
No Prior Methadone or Buprenorphine Treatment	32.5%
Prior Buprenorphine Only	25.0%
Prior Methadone Only	15.0%
Both Prior Buprenorphine and Methadone	27.5%

Information was collected by research assistants prior to the beginning of the larger randomized clinical study to determine why buprenorphine was selected as the MAT of choice instead of methadone. Unlike other studies examined in this paper, the exclusion criteria were less stringent, only excluding pregnant women or participants with significant cognitive disabilities.

The study began with research assistants asking three open-ended questions and the first two were asked without any mention of methadone to avoid possible manipulation. The three open-ended questions were:

“(1) why did you decide to get treatment with buprenorphine?; a follow-up probe of (2) what was the single most important reason that you entered buprenorphine treatment?; and (3) why did you choose buprenorphine and not methadone treatment?” (Gryczynski et al., 2013).

After the open-ended questions, research assistants asked a series of 16 structured questions pertaining to choosing buprenorphine over methadone. The 16 questions were created specifically to address the contrasting qualities between the two MATs which included the pharmacology, route of consumption, and how the MATs are viewed in society. The answer choices for the questions were: *not at all important*, *a little important*, or *very important*, and the results to the questions can be seen in Table 13.

For the 16 questions there were six themes which included (1) Treatment Readiness (2) Withdrawal Avoidance (3) Normalcy (4) Preference over Methadone (5) Negative Effects of Methadone and (6) Sources of Knowledge. For theme one, treatment readiness, the discussion was heavily weighed on the patient and their reasons for wanting to enter treatment. Most answers were geared toward the notion of becoming healthy and drug free again rather than specifically wanting to seek treatment for buprenorphine. Theme two, withdrawal avoidance, was a big selling point for patients on why they choose buprenorphine over methadone because they felt as if the symptoms would be milder but also effective for suppressing cravings. Theme three, normalcy, was about the selection of buprenorphine over methadone due to the non-sedating effects which allowed patients to proceed with their daily routines.

Theme four, preference over methadone, touched on the overall notion that patients were choosing buprenorphine as a direct alternative to methadone with 52.5% unsolicitedly comparing the two MATs. Also with this theme, patients seemed to view buprenorphine as a less serious medication in comparison to methadone. Statements were made such as, "I see people do the methadone and it's nasty and it puts me to sleep.... Taking the buprenorphine is

like taking a vitamin, so it's strengthening me.” which represents the negative stigma methadone has in the drug treatment community (ref)

Overall theme four, preference over methadone, had a lot to do with the pharmacology of the two treatments and the preferred being whichever treatment allowed the least negative symptoms. Theme five, negative effects of methadone, spoke about the detrimental physical effects that occur as a result of taking methadone such as deterioration of bones and teeth, gastrointestinal problems, alterations in physical appearance and the possible increase in cravings for drugs other than opioids. Theme six, sources of knowledge, focused on where patients received their knowledge about buprenorphine. About one-third of the patients stated that they learned about buprenorphine in a non-clinical setting. Many patients seen buprenorphine in their communities and that first-hand experience drove them to receive formal treatment that was prescribed by a physician.

During this study it was noted that the personal experience of use of buprenorphine either directly or indirectly was *very important* to treatment choice by 73.8% of clinical patients and of *little importance* to 11.3% of patients. Along with personal experience, participants were extremely concerned with the possible physical effects that could occur due to the MATs so withdrawal

intensity was *very important* to 77.5% of patients. Those participants that were previously in MAT with methadone seemed to respond less conservatively than other participants who had not gone through methadone treatments using more *very important* statements when choosing buprenorphine over methadone.

Table 13. Responses to Structured Questions from Participant Involved in Choosing Buprenorphine over Methadone (Gryczynski et al., 2013)

Importance of reasons for choosing buprenorphine over methadone among new admissions to treatment with buprenorphine (n=80).

	Not at all Important %	A Little Important %	Very Important %
Positive Buprenorphine Experiences (self and others)			
You heard good things about buprenorphine and thought it may work for you.	10.0	16.3	73.8
You know people on buprenorphine who have been successful.	8.8	22.5	68.8
You tried buprenorphine on the street and it worked.	15.0	11.3	73.8
Treatment Delivery Structure			
You get take-home doses sooner with buprenorphine.	68.8	10.0	21.3
The rules at methadone programs are too strict.	91.3	1.3	7.5
Methadone programs are too crowded.	85.0	10.0	5.0
There is too much counseling with methadone treatment.	88.8	6.3	5.0
Methadone treatment is too expensive.	88.8	3.8	7.5
Pharmacological and Health Effects			
You don't like how methadone makes you feel.	25.0	15.0	60.0
Methadone is bad for you physically.	5.0	10.0	85.0
The withdrawal from methadone is worse than with buprenorphine.	8.8	13.8	77.5
You have to stay on methadone too long.	35.0	12.5	52.5
Methadone Stigma			
People on methadone aren't really clean.	46.3	20.0	33.8
People at methadone clinics aren't serious about recovery.	58.8	22.5	18.8
Other people (like friends, family or probation/parole officers) would not want you to take methadone.	56.3	12.5	31.3
You think methadone treatment is a "last resort" for people who can't stop using by any other means.	53.8	20.0	26.0

Interviewer's instructions, read verbatim: "I am going to list some other reasons that people may have for choosing buprenorphine treatment over methadone. For each reason I list, please tell me if the reason was not at all important, a little important, or very important."

DISCUSSION

The findings in the study of adding behavioral therapy treatment, specifically contingency management, to opioid detoxification with buprenorphine conclude that behavioral therapy treatment improves detoxification and rehabilitation success when compared to standard care (Bickel et al., 1997). The retention rates as shown in Figure 2 are significant because they indicate that the number of patients remaining in treatment with behavioral therapy was doubled compared to the standard therapy group. During treatment weeks the opioid abstinent patient numbers were greater in the behavioral therapy treatment group compared to the standard treatment group. When looking at the patient characteristics in Table 2, the demographics were extremely similar in both treatment groups which decreases many possible confounding variables.

A point of interest to note is that although the master-level counselors in this study were trained in contingency management therapy and overseen by higher level psychologists, they were used in both treatment groups. Unknowingly, the counselors could have been biased to the standard group with the assumed expectation that they would underperform and fail at sobriety without the behavioral therapy treatment which would cause them to

underachieve at a greater rate than normal. Another noteworthy aspect to the Bickel trial is that both groups had relatively small sample sizes with around 20 patients in each group. Although the results are still valid, the question of generalization of the study results become an issue.

Another study examining behavioral therapy combined with MATs by Moore focused on cognitive behavioral therapy specifically (ref). Along with the study on MAT and contingency management, the patient demographics in this study included a majority of middle-aged white men.

Research found that patients who received cognitive behavioral therapy in addition to their physician managed MAT with buprenorphine had better outcomes than those in the study that were only subjected to physician managed MAT with buprenorphine (Moore et al., 2016). The information in Table 6 shows that a greater percentage of patients in the physician managed group completed treatment and that patients in both groups completed a similar number of weeks in treatment but the results can be seen as masked due to the difference in treatment group size that manipulates the data percentages.

When examining the results further, data in Table 6 shows that patients in the physician managed group combined with cognitive behavioral therapy treatment had a greater number of urine samples negative for opioids and

negative for all drugs. Also, patients in the physician managed group combined with cognitive behavioral therapy treatment had the longest consecutive weeks abstinent from opioids when compared to the patients subjected only to physician management. Overall there seems to be an improvement in treatment outcomes when it comes to opioid rehabilitation that combines MATs and behavioral therapy treatment regardless of the behavioral treatment type.

Now examining different types of MATs, buprenorphine and methadone were both reviewed in the clinical setting by Hser and colleagues (ref). The first study focused on treatment retention among patients randomized to buprenorphine compared to methadone. The treatment results were significant starting with the treatment dropout amount that included 398 patients in the buprenorphine treatment group compared to 137 patients in the methadone treatment group (Hser et al., 2014). Buprenorphine treatment had a greater dropout percentage at 24.8 compared to methadone which was 8.3 percent (Hser et al., 2014). This alarming difference should signal that the beginning weeks of treatment are critical for those on MAT with buprenorphine and additional measures may need to be put into place such as a behavioral therapy treatment option.

The patients that remained in the trial in the buprenorphine treatment group had a lower number of positive urine samples compared to the methadone treatment group during the beginning period of the trial. These results show that buprenorphine can be effective but retention focused methods need to be established in order to retain patients in rehab treatments. Again, the suggestion of implementing behavioral therapy treatment sessions would potentially help resolve the significant patient dropout rates. Hser also completed a second study comparing the long-term outcomes of buprenorphine and methadone treatment.

Findings were similar to the previous study that compared buprenorphine and methadone. Both MATs were able to reduce the use of opioids in patients but at the follow-up it was clear that methadone was superior in receiving better results. During the initial treatment and also during the follow up, patients in the buprenorphine treat group had a higher use opioid and a lower treatment engagement when compared to the methadone treatment group. In total, both treatment groups had participant dropout which could be the result of a variety of issues from lack of support to low desired environments. Behavioral therapy treatments could help combat some of these issues being that counselors and psychologists not only provide skills to combat drug cravings but also assistance in daily life battles (Carroll et al., 2004).

The final study examined focused on patient perspectives of MATs and why buprenorphine was selected over methadone when both treatments were equally available. Many participants in the trial stated their preference for buprenorphine was due to the intense side effects that come with taking methadone (Gryczynski et al., 2013). The pharmacological health effects had the highest percentage rating for being very important to patients at 85% (Gryczynski et al., 2013). The main concern coming from patients was that methadone is physically dangerous and the withdrawal from methadone being significantly more difficult than buprenorphine (Gryczynski et al., 2013). Less important to the patients were the treatment delivery structure which shows that those looking for rehabilitation treatments prefer a better physical experience rather than convenience.

CONCLUSION

Overall, combining a behavioral therapy treatment such as contingency management or cognitive behavioral therapy with a MAT such as buprenorphine or methadone is shown to increase treatment retention rates which leads to a greater success rate in opioid rehabilitation. When selecting a MAT, many aspects are considered such as the pharmacological effect that the drug will have on a person and past experiences had with the MAT either first or second hand. Continued efforts are needed to research additional behavioral therapies that can be combined with MATs to receive the most successful treatment. According to this review the most successful treatment option for opioid rehabilitation would be a behavioral therapy treatment combined with MAT using methadone. Undesired side effects may be present, but ultimately the success of methadone treatment in direct comparison to buprenorphine makes this the ultimate choice when striving for the best rehabilitation treatment outcome.

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