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A Comparison of Medication-Assisted Treatment Options for Opioid Addiction

A Review of the Literature

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Abstract

In individuals in the United States with opioid addiction, what is the effect of a medication-assisted treatment (MAT) in reducing the relapse and harm reduction when comparing the use of buprenorphine, methadone, and naltrexone? In 2017, it was estimated that 1.7 million individuals suffer from overuse of prescription opiates, 652,000 individuals suffer from heroin use disorder, and greater than 130 individuals die from opiate overdose daily (National Institutes of Health, 2019). Using a systematic literature review, the following results were found. Buprenorphine is currently the second most effective MAT in harm reduction and relapse prevention, can be initiated and maintained through primary care, has a low risk for overdose, but needs to be started only when moderate withdrawals have begun. Methadone is currently the gold standard in MAT and can be started in any stage of withdrawal; however, titrating to effective dose is a lengthy process, and it must be administered at a specialty clinic. Naltrexone in oral form has not been shown to be effective because of lack of adherence; however, the extended-release intramuscular injection form has been shown to reduce relapse and increase the quality of life before initiation individuals must be opioid free for 7–14 days. Choosing the proper MAT is highly individualized. It is recommended that more research be conducted in comparing all MAT options, looking at the quality of life on each MAT, researching motivations to stay on MAT and remain opioid free, and looking at the impact of external reward on adherence to the MAT program.

Keywords: Buprenorphine, Harm Reduction, MAT, Medication-Assisted Treatment, Methadone, Naltrexone, Opioid Addiction, Opioid Use Disorder, Relapse Reduction

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In the United States, opioid use disorders have been on the rise for the last two decades. In 2017, it was estimated that 1.7 million individuals suffer from overuse of prescription opiates, and an estimated 652,000 individuals suffer from heroin use disorder. Greater than 130 people die from opiate overdose daily (National Institutes of Health, 2019).

The consequences of untreated opioid addiction have unquantifiable societal costs affecting not only the individual and their families but also the community in which they live. Medical and mental health professionals have been called to arms to adequately treat opioid use disorders, but providers in the community are often unaware of appropriate treatment options. Pharmacological interventions for opioid dependence approach addiction from a biological basis that helps eliminate the inherent societal stigma that views addiction as a moral deficit and adequately treat the underlying physiological dependence. Multiple studies have shown that psychosocial treatment and therapeutic treatment without pharmacological intervention have been ineffective at long-term management and recovery from opioid dependence.

In this review of the literature, we are hoping to address the overarching question: What is the efficacy of medication-assisted treatment (MAT), comparing the use of buprenorphine, methadone, and naltrexone in the reduction of relapse and harm reduction? By comparing the aforementioned MAT options for opioid use disorder, we hope to offer a clearer picture on efficacy and appropriateness of the current options in reducing relapse and risky behaviors that worsen health and quality of life outcomes.

THEORETICAL FRAMEWORK

There are many theories that attempt to explain why a person becomes addicted to opioids or why a person will relapse after going through detoxification. The authors of this review have chosen to focus on Dr. Abraham Wikler's theory, entitled "A Theory of Opioid Dependence." Wikler (1980) found that when a physical dependence was developed, a pharmacological need also developed, and it was this pharmacological need that maintains an addiction when the initial euphoria that creates the physical dependence starts to wane. Wikler explains that this pharmacological need is appetitive (meaning gratification comes by getting more and more of the reinforcer, which in this case is an opioid) and not aversive (meaning gratification comes by getting less and less of the reinforcer).

The theory of opioid dependence further explains that "the processes of addiction and relapse may be divided into two successive phases namely 'primary' and 'secondary' pharmacological reinforcement" (Wikler, 1980, p. 177). Primary pharmacological reinforcement refers to the pharmacological effect of opioids on receptors within the body. Wikler (1980) explains that tolerance develops quickly to the direct pharmacological effects, and this leads to physical dependence. Furthermore, if the opioid is withheld, the reflex consequence of abstinence distress, or withdrawal or detoxification, is seen. When an opioid addict has gone through detoxification and then returns to the environment that promotes opioid use, they are exposed to the secondary pharmacological reinforcement phase (Wikler, 1980). Secondary pharmacological reinforcement is a new need or renewed craving for opioids, and when the addict uses a dose, the cycle of "renewed conditioning, detoxification, and secondary pharmacological reinforcement with relapse" starts and repeats (Wikler, 1980, p. 178).

Wikler (1980) also addresses relapse within his theory. He explains that "mere detoxification will not prevent relapse" when the addict returns to the environment that promotes opioid use. Wikler does promote the use of an antagonist and states that "if former addicts are placed on a blocking doses of an antagonist, the expectation of relapse will be much less likely to occur" (Wikler, 1980, p. 178). This brings these authors back to the purpose of this review: reviewing the effectiveness in reducing relapse of MAT, including buprenorphine, methadone, and naltrexone.

METHODS

We initiated our search using the databases CINAHL, MEDLINE, PsychArticles, and Academic Search Ultimate. Key terms utilized were *methadone* or *buprenorphine* or *suboxone/subutex* or *naltrexone* or *medication assisted treatment in the United States/U.S.* or *U.S.A* and *opioid use disorders* or *opioid addiction*. Results were limited by peer-reviewed studies within the last 5 years to ensure that we had the most up-to-date recommendations and results for adequate treatment of opioid use disorders. We have organized our review by analyzing the MAT options, buprenorphine, methadone and naltrexone, individually. In terms of grading the literature, we utilized the John Hopkins Evidence-Based Rating Scale (Dearholt & Dang, 2012). Research that was included ranged from Level I through Level IV, and all articles had a quality rating of A and B. We included one article with a rating of C, which was due to its small sample size.

BUPRENORPHINE

Buprenorphine is an opioid analgesic that is commonly used in MAT of opioid addiction (Vallerand et al., 2013). This medication works by binding to opiate receptors in the central nervous system and, because of its antagonist properties, can induce withdrawal symptoms, especially for patients who are physically dependent on opioid agonists (Vallerand et al., 2013). With treatment of opioid addiction, the dose of buprenorphine is 4–24 mg daily (Connery, 2015). The different dosage forms include sublingual tablet, buccal film, transdermal patch, and injectable solution (Vallerand et al., 2013). It is important to note that this medication is highly protein bound, is primarily metabolized through the CYP3A4 enzyme, and has an extensive first-pass effect (Vallerand et al., 2013). It is also important to note that, in patients with hepatic function impairment and in geriatric patients, a decrease of dosing up to 50% may be required (Epocrates, 2020).

In a review conducted by Connery (2015), it was found that, although buprenorphine is not the gold standard for opioid use disorder, it is the second-best choice. One study showed that 60% of participants remained opioid free while on buprenorphine treatment opposed to only 20% of participants remaining opioid free when they had no treatment or were on placebo treatment (Connery, 2015). It is also found that most patients on buprenorphine maintenance did not develop tolerance to the relapse–prevention efficacy of the medication (Connery, 2015), and this is because buprenorphine is effective in "reducing cravings, withdrawal and stress reactivity and competitively blocks or reduces the reinforcing effects of other opioids" (Connery, 2015, p. 65).

Nissly and Levy (2018) completed a longitudinal cohort study that encourages providers to view and treat opioid use disorder as a chronic disease. Some of the advantages of prescribing buprenorphine, as discussed by Nissly and Levy, include that it can be administered in-office, it can be safely initiated at home or in-office, and it has a low likelihood of overdose because of the medication's ceiling effect at 24 mg daily. This study highlights the harm reduction efficacy of buprenorphine and states this "regimen can be used to keep a patient alive while working toward sobriety" (Nissly & Levy, 2018, p. 546). Nissly and Levy caution that buprenorphine treatment should not be initiated until a patient is in moderate withdrawal, as if not "withdrawal can be precipitated by displacing full opiate agonists from opioid receptor" (Nissly & Levy, 2018, p. 546).

Once treatment is initiated, dosing must then be established. Greenwald et al. (2014) reviewed literature and concluded that there are three categories for optimal dosing: dosing for withdrawal suppression, dosing for those with a typical dose of abused opioids, and dosing for those with a higher-than-usual dose of abused opioids. For withdrawal suppression, most patients require 4 mg daily in either a single dose or divided into multiple lower doses (Greenwald et al., 2014). If a patient uses a typical dose of abused opioids, the buprenorphine dose can be optimized at 16 mg daily (Greenwald et al., 2014), again in either a single dose or in divided smaller doses. If a patient, however, uses a higher-than-typical dose of abused opioids, a higher dose would be required; at this level, an optimal dose was not established and does vary among patients (Greenwald et al., 2014).

An advantage to buprenorphine is the flexible dosing that adjusts to the patient's needs (Salisbury-Afshar, 2015), but how effective is it in retaining patients in the MAT program and in suppressing heroin use? Salisbury-Afshar (2015) conducted a randomized controlled trial that addresses this question. It was found that, compared to methadone, a low-dose buprenorphine (a dose of 2–6 mg) was less likely to retain a patient (Salisbury-

Afshar, 2015). This study also concluded, however, that at a medium-dose buprenorphine (a dose of 7–15 mg) and a high-dose buprenorphine (a dose of 16 mg and higher) showed no difference in retaining patients and no difference in suppression of self-reported heroin use (Salisbury-Afshar, 2015).

When reviewing the effectiveness of a MAT option, it is important to take into consideration the effectiveness against withdrawal symptoms and the risk of overdose from the treatment option. In a study conducted by Becker et al. (2015), it was found that buprenorphine combined with naloxone showed improvement in patient pain intensity and that the dose of the buprenorphine–naloxone combination "was not independently associated with clinically meaningful improvement in pain score." Morgan et al. (2019) found in a retrospective cohort study that treatment with buprenorphine for opioid use disorder is associated with a lower risk of overdose during active treatment compared to no treatment or naltrexone treatment.

METHADONE

Methadone is an opioid analgesic medication, an *N*-methyl-D-aspartate receptor antagonist, and a full mu opioid agonist with a high affinity for this receptor. Methadone binds to the opiate receptors in the central nervous system, altering the perception and response to painful stimuli and results in general central nervous system depression (Vallerand et al., 2013). Methadone is available orally as a liquid concentrate, oral powder, or in tablet form when treating individuals with opiate use disorder. Often, it requires only once-daily dosing. In terms of distribution, it is highly protein bound (85%–90%) and is lipophilic. Methadone's metabolism is hepatic, through the CYP-450 system, and has a half-life between 8 and 59 hours (Epocrates, 2020). Methadone's bioavailability varies widely from 36% to 100%, which results in a variable dosing pattern that is highly individualized. After a gradual monitored initial induction, there is a gradual titration over a period of several weeks, with the recommended dosing being 60–120 mg daily (Connery, 2015). Again, it is important to reiterate that the bioavailability variability results in highly individualized dosing of methadone.

Though dosing variability is a key consideration, there are treatment recommendations for adequate dosing of methadone to ensure retention. According to D'Aunno et al. (2019), underdosing remains a significant contributor to relapse. It is recommended that patients in methadone maintenance programs have doses >80–100 mg/day and maintain average plasma concentration of 400 ng/ml, as studies suggest that these patients remain in treatment the longest, with decreased illicit opioid use (D'Aunno et al., 2019).

Methadone is considered to be the gold standard for the treatment of opioid use disorder, with research supporting its efficacy in keeping individuals opioid free at rates as high as 60% (Connery, 2015). Throughout the 50 years of utilizing methadone as a treatment option for opioid dependence, it has been shown to be effective in increasing retention and is helpful in harm reduction. An aspect that enhances its effectiveness is that methadone can be initiated at any stage during treatment, which reduces the risk of dropout or relapse during the induction phase (Connery, 2015). Long-term retention and maintenance are essential in recovery from opioid dependence, and methadone as a MAT option has shown the greatest results in retention rates (Connery, 2015). Because methadone is a Schedule II opioid, it is necessary for the patient to obtain the drug through specialty clinics (Kinsky et al., 2019). This can result in limited access to methadone treatment, especially in rural areas.

In a nonrandomized observational study by Kinsky et al. (2019), the authors compared the cost-effectiveness, adherence, and outcomes of buprenorphine and methadone that were Medicaid members. The included individuals were eligible for both physical and behavioral health services and were prescribed either methadone (n = 125) or buprenorphine (n = 567). Kinsky et al. found the factors that appeared to influence adherence were age, gender, and the neighborhood where they resided. Older age, female gender, and the higher socioeconomic status of the neighborhood improved adherence rates to methadone maintenance therapy.

Kinsky et al. (2019) found individuals being prescribed methadone had a greater adherence rate than those prescribed buprenorphine of 49.1% versus 40.8%, though it was noted that it was not a significant difference (p = .096). Individuals who were nonadherent to MAT were greater than 3.5 times more likely to overdose on opioids than those who were adherent, though the authors note that there may be confounding variables that influence this result. The per-member-per-month cost when adherent to methadone decreased pharmacy costs (−$13.27), but pharmacy costs increased significantly ($1173.00) when nonadherent (p = .011).

When considering the efficacy of a medication in harm reduction, one must account for the quality of life of the individual and their ability to function. In a systematic review conducted by Maglione et al. (2018), the researchers investigated functional outcomes in individuals participating in MAT. Though there appear to be some deficits when comparing attention and memory with those of healthy controls, there appears to be no significant difference comparing cognitive, social/behavioral, or physical outcomes in individuals prescribed buprenorphine versus methadone.

NALTREXONE

Naltrexone is an opioid antagonist at various opioid receptor sites (Epocrates, 2020). In terms of absorption, it is almost completely absorbed. It is widely distributed but is subject to the first-pass effect that causes variable bioavailability, ranging from 5% to 40%. For the treatment of opioid use disorders, naltrexone is available in oral tablets; but because of the frequency of dosing, it has been shown to have adherence rates of less than one third (Jarvis et al., 2018). It is more notably being studied in the injectable form of naltrexone (extended-release naltrexone [XR-NTX]), which is an injection of 380 mg once every 4 weeks. It can be supplemented with oral naltrexone for individuals with breakthrough cravings.

It is required that the individual be opioid free for a period of 7–14 days prior to induction of naltrexone. This period is essential to prevent "severe opioid withdrawal due to its antagonist activity" (Connery, 2015, p. 68).

In a nonblinded randomized trial of XR-NTX conducted by Korthuis et al. (2017), 16 individuals with opioid use disorder, 27 individuals with alcohol use disorder, and 8 individuals with both opioid and alcohol use disorder in an outpatient HIV clinic were randomly assigned to treatment as usual or treatment with XR-NTX. In this study, it was found after 16 weeks, the baseline mean days of opioid use of 20.3 (*SD* = 12.29), decreased significantly to 7.7 mean days (*SD* = 11.32; Korthuis et al., 2017). Changes in opioid use in the past 30 days were insignificant, as the baseline was 12, and it was reduced to 11 days (Korthuis et al., 2017). The most astonishing finding was that the individuals with opioid use disorder had a 100% retention rate (Korthuis et al., 2017). As previously discussed, retention in treatment is a key indicator in the overall effectiveness in treatment. With that said, this was a small study of a specific population and would need to be repeated on a larger scale for the results to be adequately generalized to the opioid use disorder population.

Individuals who are incarcerated historically have poor outcomes for remaining opioid free but seem to be an ideal population for XR-NTX treatment, as they are in a position to be free from opioids for the necessary 7- to 14-day induction. Murphy et al. (2017) conducted a randomized control study across five sites in the U.S. Northeast, analyzing the cost-effectiveness of XR-NTX in terms of the quality of life outcomes and abstinent years and its economic impact. All individuals had criminal justice involvement.

Though they found that treatment as usual was less expensive, the individuals who received the injection did have a greater quality of life per the questionnaire. In addition, they were found to be "less likely to relapse or had a longer median time to relapse" (Murphy et al., 2017, p. 1442). It is important to note that the current cost of XR-NTX may not be the cost in the future, as it is a relatively new medication, which may impact the cost-effectiveness of treatment. There are several limitations with this study, such as a limited, nonrepresentative sample in a specific region of the country, and missing data, as well as the cost-effectiveness being related to individuals with criminal justice involvement. Another possible confounding variable was whether the outcomes are the result, such as the individual being on parole.

Friedmann et al. (2018) focused on the use of XR-NTX for the treatment of opioid use disorder in the incarcerated population. In this pilot study, patients self-referred to the study while incarcerated. The patients were randomly assigned to either have the initial dose of XR-NTX administered prior to release ($n = 9$) or postrelease ($n = 6$). The patients were followed for 6 months. Those who were administered the XR-NTX prior to release had greater retention in treatment, and abstinence from opioids was confirmed by urine drug screens. It is noteworthy that the median time to relapse among the prerelease group was 9 weeks, whereas the postrelease group had a median relapse time of 4 weeks (Friedmann et al., 2018). Because this was a small study, at one location, the generalizability of the findings is limited, though the results confirm that incarceration provides a unique opportunity to treat opioid use disorder using XR-NTX, as discussed by Murphy et al. (2017).

In a systematic review of XR-NTX conducted by Jarvis et al. (2018), the authors addressed induction and adherence rates as well as if XR-NTX decreased opioid use. The rates of induction success varied from 33% to 72%, and it was found that the success rate of induction was markedly less successful when compared to buprenorphine or methadone (41.7% vs. 100%) in individuals who were not previously detoxified from opioids (Jarvis et al., 2018). The demographics associated with the success of induction included older age, lower opioid use at baseline, recent success of long-term detox for nonparole participants, and shorter term detox for those on probation or parole.

Jarvis et al. (2018) found that adherence rates decreased over time, across studies, but that offering incentives for engagement in treatment increased retention and adherence by approximately one third in one study. It appears that having some external motivating factor, whether through rewards or risk of punishment, is an important concept to explore in achieving adherence early on in MAT. By increasing retention rates, it has been shown that opioid use outcomes are improved. The current state of literature, according to Jarvis et al., does not allow for firm conclusions on the long-term efficacy of the use of XR-NTX in assisting with remaining opioid free when compared to other MAT options.

CONCLUSION

Buprenorphine, methadone, and naltrexone each has benefits and risks when being prescribed for opioid use disorder and prescribed as part of a MAT program.

Buprenorphine is currently considered the second best choice for a MAT program but speaks to efficacy by "reducing cravings, withdrawal and stress reactivity and competitively blocks or reduces the reinforcing effects of other opioids" and by the fact that patients do not develop tolerance to the relapse prevention effect of buprenorphine (Connery, 2015). Another benefit to consider is the low likelihood of overdose because of the ceiling effect at 24 mg; this reduces harm, as it can be used to "keep a patient alive while working toward sobriety" (Nissly & Levy, 2018, p. 546). Although this medication cannot be started until a patient is in moderate withdrawal, it can be started and maintained by a provider in a clinic setting (Nissly & Levy, 2018) and has three optimal dosing categories (Greenwald et al., 2014), which can make reaching and maintaining an adequate dose quicker and easier.

Methadone is currently the gold standard medication for MAT programs (Connery, 2015); however, it is unclear if this is because it has been used for the past 50 years or if it truly is the gold standard. Perhaps the biggest benefit is that

methadone can be initiated at any stage of opioid abuse (Connery, 2015), meaning before any withdrawal symptoms occur or if a patient has been opioid free for a lengthy period of time. Patients who use methadone for long term show effective decreased illicit opioid use (D'Aunno et al., 2019) and have the greatest retention in MAT programs (Connery, 2015). However, because of the wide range of bioavailability, this medication is highly individualized, has a gradual initial induction that can take several weeks of gradual titration to find the patient's maintenance dose (Connery, 2015), and must be dosed at a specialty clinic (Kinsky et al., 2019). This lengthy process of finding the correct maintenance dose can lead to underdosing, which is a significant contributor to relapse (D'Aunno et al., 2019), and nonadherence to the program increases the risk of overdose (Kinsky et al., 2019).

Naltrexone is a newer medication that is being used for opioid use disorder. It has been shown, in one study, to have a 100% retention rate (Korthuis et al., 2017), and in patients who were incarcerated, naltrexone increased the median relapse rate to between 4 and 9 weeks after release (Friedmann et al., 2019) and increased quality of life (Murphy et al., 2017). Korthuis et al. (2017) also showed a significantly reduced number of opioid use days over a 16-week study; however, there was no change over a shorter 30-day period. Retention rates might be high, but the adherence rate is shown to decrease over time and is less than one third (Jarvis et al., 2018). Perhaps the biggest deterrent for naltrexone is the patient must be opioid free for 7–14 days before induction (Connery, 2015). Jarvis et al. (2018) also showed that success rate of induction is the least successful of the three medications discussed in this review.

RECOMMENDATIONS

According to Winkler's theory of opioid dependence, detox alone does not address the problem of opioid addiction, and complementing recovery with assistive medication would greatly improve the possibility of remaining opioid free for this population. When approaching MAT options, it is essential to look at the motivating forces for the individual to pursue recovery and simultaneously viewing opioid use disorder as having a biological basis that can be adequately treated through modern pharmacology. Most importantly, it is imperative to treat opioid use disorder, as adequate treatment with MAT has been shown to improve outcomes, prevent relapse, and reduce harm when compared to no treatment. By having an individualized and scientifically informed approach, with the goal of a holistic, nonjudgmental assistance in recovery, we may be able to better address the societal epidemic that the United States is currently experiencing.

Across all MAT options, adherence to the medication appears to be a key indicator in efficacy and harm reduction. Motivations to maintain opioid free should be further researched. Because there appears to be improved retention in programs with external rewards/punitive measures, it would be beneficial to research the impact of positive rewards on adherence for individuals with opioid use disorder.

Further research is needed in comparing buprenorphine, methadone, and naltrexone in the use of MAT treatment programs. Each medication has benefits and cautions when prescribing for opioid use disorder. An individualized patient treatment plan is needed when prescribing for a MAT program. This plan needs to not only look at a patient's opioid use disorder; including dose, route, and how often the use occurs, but also consider the patient's environment, access to treatment, motivation for retention, and support to remain opioid free, as these factors affect retention in a MAT program.

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