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Review Article

The Current State and Outlook of Medically Assisted Treatment for Opioid Use Disorder

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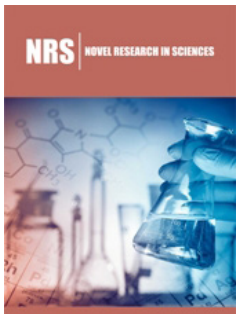

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Abstract

The opioid epidemic in the United States is a public health emergency. The abuse and misuse of prescription opioids have led to an alarming rate of opioid use disorder. The FDA has approved three drugs for Medically Assisted Treatment (MAT): methadone, buprenorphine, and naltrexone. Despite decades of success with the use of methadone, the majority of people with opioid use disorder do not have access to MAT. The use of buprenorphine and naltrexone as an alternative to methadone is increasing, but not quickly enough to keep up with the growing epidemic.

A multitude of barriers prevents patients from receiving MAT, including the lack of treatment centers and specialized healthcare providers who can prescribe the medications. Furthermore, the stigma surrounding opioid use disorder and MAT is pervasive and prevents both patients from seeking care and physicians from providing care. In order to meet this crisis, care must be deregulated, and physicians must receive training and be willing to prescribe a MAT. Ongoing research continues to show the benefits of MAT and the medications that are already approved.

Methadone

The treatment is available through federally approved Opioid Treatment Programs (OTP) and is taken daily. The Substance Abuse and Mental Health Services Administration only began certifying opioid treatment programs in 2001. The number of approved programs was only 10% of all substance abuse treatment facilities in 2015. This approach appears to be supported by the findings that the longer patient interacts with treatment, the better the outcomes. However, the patients often drop out of treatment or cycle in and out of treatment [1]. Only patients who take part in a Methadone Maintenance Treatment (MMT) program for an extended period of time are permitted to administer their doses at home [2]. In addition, federal law states that patients must routinely utilize counseling services. State and municipal governments often place additional requirements on patients [3].

Methadone has undergone extensive review in the past few decades and remains the standard in MAT. Several studies have proven it to be more effective as compared to no treatment or abstinence [4]. Recipients of methadone treatment are more attracted to and remain in treatment more often as compared to drug-free approaches. During methadone treatment, studies have shown a reduced risk of fatal overdose, reduction in crime, and expressed improvement in quality of life [1]. Methadone maintenance treatment (MMT) has also been shown to decrease opioid use and drug-related mortality [5].

While a daily dose of 30mg of methadone has proven to be sufficient in preventing opioid withdrawal for 24 hours, under this dose, many patients continue to use non-prescribed

opioids. Rates of abstinences increase with a higher daily dose, between 60 and 100mg of methadone. The correct and adequate dose is essential in methadone treatment, as the drug must suppress opioid withdrawal, reduce the desire to use non-prescribed opioids, and prevent overdose [1]. Lower doses may also be associated with an increased risk of dropping out of treatment programs [6].

Buprenorphine

Buprenorphine has been in use for a much shorter time as compared to methadone, only being identified as a treatment option for opioid-dependent in 2002. By 2010, a sublingual film formulation was approved, in addition to the tablet formulation. Currently, the drug is also approved as an injection and implantable device. In 2017, a monthly buprenorphine injectable was approved and in 2016 an implantable buprenorphine device was approved which lasts six months [7]. Similar to methadone, buprenorphine is regulated by the federal government. The Drug Addiction Treatment Act of 2000 permits physicians to prescribe the drug to up to 30 patients as an opioid use disorder treatment. This is only approved after the position engages in training activities in competency tests. Once physicians have 30 patients in treatment, they can petition the drug enforcement agency to increase their allowance to 100 patients. Once a position has treated 100 patients with buprenorphine for a year, they are allowed to offer the treatment to 275 patients [8].

Buprenorphine can suppress opioid withdrawal for 24 hours and a dose of around 8 mg daily. However, for the drug to be effective in reducing the use of non-prescribed opioids the dose must be higher. Published trials show that adults greater than 16mg daily are more effective than a dose less than 16mg [1]. The drug has proven to alleviate withdrawal signs and symptoms, lessen cravings, and block subjective effects of non-prescribed opioids at the right dose [9]. At higher dosage, buprenorphine has proven to be just as effective as methadone and reducing opioid use and increasing treatment retention [7].

The drug is also offered in an extended-release form which is injected subcutaneously once a month. Extended-release buprenorphine is designed to provide consistent exposure to the drug over the dosing interval at an average plasma concentration of at least 2-3ng/mL. This treatment method lessens the challenges posed by the daily collection of medication, varying levels of buprenorphine in between doses, and the use of supplemental buprenorphine. In a trial over 24 weeks, the rate of abstinence was above 40% for participants in the treatment groups and only 5% in the placebo group. Treatment success, defined as abstinence for at least 80% of the study, was also significantly greater in the treatment groups as compared to the placebo group [9].

In the form of tablets and films, buprenorphine is offered in combination with naloxone. Naloxone is a short-acting antagonist which helps to less desirable effects which can lead to misuse of buprenorphine. A combination of buprenorphine analog zone has proven to be cost-effective in the long term. Despite the medication cost being higher than the medication cost of methadone, buprenorphine avoids the cost of OTP's and higher transportation costs for patients, so it may be overall more cost-effective. In addition, buprenorphine exhibit fewer drug interaction concerns and lower overdose risk as compared to methadone, when used in conjunction with Naloxone [7].

Naltrexone

Naltrexone was first synthesized in 1963 but was only approved by the FDA as a once-daily tablet in 1984. In 2010, an injectable form of naltrexone was approved to be administered monthly. Currently, this extended-release form is the most popular [7]. Naltrexone is the long-acting version of naloxone, which is approved for intravenous use, subcutaneous autoinjector, and nasal spray. While naloxone is utilized in overdose situations, naltrexone can be administered as monthly injections in its extended-release form. A 50mg dose of naltrexone can provide an opioid receptor blockade that lasts for 24 to 36 hours.

Naltrexone acts as an antagonist, rather than an agonist, which both methadone and buprenorphine act as Naltrexone does not produce any positive opioid effects, and this can lead to inconsistent treatment use and drop out. Patients who stop treatment early are then at higher risk of fatal overdose [1]. While naltrexone lacks the same potential for abuse that the antagonist poses, more research must be done before its advocacy can be determined. In a trial, the rate of opioid abstinence for participants treated with naltrexone was similar to those treated with buprenorphine, but many participants could not be included because they failed to initiate naltrexone.

As compared to methadone, naltrexone is more accessible; any licensed prescriber can offer the treatment and many insurances cover the cost. This option also mitigates some of the stigma associated with other forms of MAT as it does not pose the same challenges with addiction and drug interaction. Naltrexone has proven to increase treatment retention and lessen the risk of overdose, but longer-term outcomes have yet to be examined [7]. Unlike other MAT, patients must already be in a period of abstinence to initiate treatment [1]. This presents a significant barrier to initiating care which is a limitation for the treatment.

Barriers to Care

Regulations

The Narcotic Addiction Treatment Act, signed by President Nixon in 1974, outlined regulations for the use of methadone in the treatment of opioid use disorder. Since that time, only minor revisions have been applied to the regulations [10]. There still lies great barriers in patient access to methadone, despite the well-reviewed success of the drug. Although the opioid epidemic has spread into both urban and rural communities, Opioid Treatment Programs remain concentrated in urban communities. This presents a significant challenge in treating patients outside of urban areas. Within the first month of treatment, patients must travel to and from an OTP 24 times. With so few approved treatment facilities, the necessary travel and cost of travel are unique barriers of access

for methadone, when compared to treatments for other chronic diseases [10]. The high need for travel may also contribute to the lack of consistent use of treatment often seen in patients.

Although access to buprenorphine is less restricted as compared to methadone, almost half of the counties in the United States lack a physician who is approved to provide treatment. Out of the thousands of providers who are waiver to prescribe buprenorphine, three-fourths of them are limited to treating 30 patients at a time [11]. Many physicians have shown to be unwilling to prescribe for opioid addiction. In Maine, the seat contacted over 100 positions with an opportunity to complete the eight hours of training required for approval and $5000. A year and a half after this was offered, none of the physicians contacted agreed to participate. Some of the physicians who do you complete the proper training and are approved to prescribe buprenorphine may not have the right motivations. 1,350 of 12,780 physicians who prescribe buprenorphine have been disciplined for misconduct, such as overprescribing or fraud. The 11% rate of misconduct is higher than the general rate of misconduct among physicians [6].

Physicians who are interested in becoming waivered often must convince other colleagues, who likely carry some of these misperceptions. Current regulations prevent hospitalists from prescribing the treatment on hospital discharge and discourage correctional clinicians from initiating treatment prerelease or continuing treatment after arrest. Continuity of treatment is difficult when patients change providers. Much of the regulations are based on assumptions that patients desire buprenorphine for euphoria, despite the fact that the majority of illicit buprenorphine is used to reduce withdrawal symptoms [11].

Lack of Integration of Care

Other nations, including Australia and the United Kingdom, have allowed primary care physicians to prescribe methadone and allowed local pharmacies to dispense methadone. In the United States, current regulations prevent this integration of methadone prescription and dispensation into primary care. Under federal law, federally qualified health centers and or pharmacies can only dispense methadone, with observation, if a treatment shortage can be proven. While this is a move in the right direction, some state regulations prohibit this, and the use has remained limited. These regulations put patients residing in rural areas at a particular disadvantage because there may be no easily accessible specialty substance use treatments [10].

The hub and spoke model of treatment, found in Canada and Finland, makes use of specialized care centers and primary care clinics. The specialized care centers handle the intake, induction, and stabilization of patients. The centers also continue to manage complex cases on their own. However, most patients, once they are stabilized on methadone treatment, are sent to primary care clinics to continue care. While this model still ensures the initiation of methadone treatment is handled by specialized and approved providers, it introduces a new challenge of coordination and integration of care between the centers. Furthermore, not all primary care centers may have the same access to substance abuse services or physicians willing to administer methadone treatment [12]. For this approach to treatment to be successful, both physicians and patients must be willing to participate in the accessibility of services must be greater.

The hub and spoke model requires physicians who are knowledgeable and comfortable with managing methadone treatment. Many physicians do not receive substance use training or choose not to treat people with substance use disorders. Physician attitudes towards MMT are challenged by lack of knowledge, preference for non-pharmacological treatment approaches, and perception that patients receiving MMT are a difficult population to work with. If patients receive methadone treatment from physicians with these negative attitudes, the patients are at greater risk of dropping out of treatment prematurely [6]. Physicians with negative attitudes towards patients with opioid dependence may force dosage reduction and tapering [12]. Despite this, the hub and spoke model lessons some other challenges included long wait times to receive the daily dose, limited availability to receive the daily dose, and lack of privacy [6].

Stigma

Outside of healthcare providers, substance abuse carries a greater stigma as compared to other mental health struggles in the United States. Negative attitudes, such as the desire to separate oneself from people who use drugs persist throughout the country. This stigma is not escaped through seeking treatment for substance abuse disorder. Many patients experience stigma when participating in MAT as the treatment is viewed as an alternative form of addiction. The presence of methadone clinics creates community stigma and in certain cases, community opposition [6]. Due to the stigma surrounding opioid use, many medical schools like education and opioid addiction and treatment [13].

The stigma is, in turn, reinforced by the strict regulations and laws which not only limit access to care but criminalize those seeking care [6]. A study using the Self-Stigma Scale-Short to measure the self-stigma of patients engaged in MMT found that four-fifths of the pursuit participants had a score above 2.5, which suggests high levels of self-stigma. Another study, using the internalized stigma of mental illness scale found that 85% of people with substance abuse disorder scored above 2.5 [14]. These studies highlight the compounding stigmas which patients seeking care for opioid use disorder face. Stigma is experienced both externally and internally.

Obstetric care

Significant challenges also face opioid-dependent women during pregnancy concerning MMT. Even though MMT has been used to treat pregnant women with an opioid use disorder since the 1970s, many women still struggle to find OB/GYN's with experience treating opioid-dependent pregnant women. Women often delay or avoid seeking out prenatal care in fear of the exposure of their opioid use. Starting MMT introduces many lifestyle changes,

including medication and counseling visits, and doses may have to be adjusted during pregnancy. Programs that integrate opioid treatment and prenatal care have shown to be successful, but very few have been implemented [15].

The integration of opioid use disorder treatment and obstetric care results and improvements in maternal and neonate health, but few women receive MAT during pregnancy. Across the nation, there is a lack of treatment programs for pregnant women. Less than 25% of opioid-dependent pregnant women receive any treatment and even less receive MAT [16]. Despite the proven benefits of MAT in pregnant women, rates of use of opioid pharmacotherapy have not increased significantly in the past 20 years. Increasing the access and use of MAT in pregnant women is essential, as obstetric providers can play a key role in initiating and continuing treatment programs throughout pregnancy [17].

Patient retention

Low levels of patient retention occur across the treatments utilized. With methadone treatment, between 40 and 60% of patients left treatment within 12 to 14 months. With buprenorphine treatment, within six months almost half of the patients have left treatment. This increases up to 60% by the 12-month mark [6]. The risk of leaving treatment increases for patients with low-income backgrounds and or patients with disabilities [18]. It is worth noting that despite the high levels of attrition with MAT, these levels are even greater among patients who do not receive MAT as a part of their treatment.

Location of Care

Some opioid-related use patterns and consequences occur at higher rates in rural residents as compared to urban residents. This only heightens the challenge of expanding care into rural areas. Both injection of heroin or prescription opioids and use of opioids occur at higher rates in rural areas. Despite this, rural residents are less likely to be administered naloxone during an opioid overdose. Residents of rural areas are often subject to long travel times to reach clinics, including crossing state lines. Healthcare providers are often aware of the travel barrier and may offer MAT less frequently to rural patients as compared to urban patients treated in the same clinic [19].

Looking ahead

To mitigate some of the challenges posed by insufficient training and education, lack of care coordination, and provider stigma, solutions must come from a range of perspectives. MAT training could be incorporated into graduate school education, as is done with other medications that require individualized dosing, such as warfarin. Low rates of recent family residency graduates are trained to prescribe buprenorphine, only 10%, with even less participating in prescribing the drug [11]. Some states, including Massachusetts, are already taking steps to incorporate training into medical education. Other prescription opioids can be prescribed without any extra training, despite being associated with misuse and overdose [7].

Telemedicine

Telemedicine is a viable solution to improve patient access to healthcare providers who integrate MAT with obstetric care. In a study comparing the treatment of pregnant women who received obstetric care through telemedicine and those who received care in person, only 44% of neonates whose mothers engaged in telemedicine were treated for NAS, while 62% of the neonate in the in-person care group were treated. Add the 6 to 8 weeks postpartum visit, less than 10% of mothers in the telemedicine group tested positive for a urine drug screen, while more than 20% of individuals in-person group tested positive. No significant difference was found in rates of retention in treatment, rates of NAS, or length of hospital stay [16]. These findings are encouraging and provide options for pregnant women in rural areas who may not otherwise have access to this care.

The treatment of opioid use disorder with telemedicine is increasing in popularity for all patients. Telemedicine helps to circumnavigate the challenges posed by the lack of OPTs and buprenorphine-waivered physicians. West Virginia University expanded its Comprehensive Opioid Addiction Treatment program as a part of its telepsychiatry program. This is the first remote clinic used to prescribe buprenorphine. Patients gained the ability to receive care from buprenorphine prescribers and in-person counseling [20].

After a drug treatment center in rural Western Maryland lost its buprenorphine waivered physician and could not find a replacement, a pilot program to provide telemedicine for patients in MAT was developed. This pilot study established that the telemedicine model could be successful in rural areas, even if other addiction treatments are already available. The study also showed the reach of a program with minimal in-person contact. While the study was limited by the majority of patients already in treatment or a state of opioid abstinence at the time of enrollment, the program still demonstrates the efficiency of telemedicine as part of a rural drug treatment program [21].

The coronavirus pandemic created an even greater barrier to seeking and maintaining MAT. However, the pandemic also created the opportunity to increase the adoption of telemedicine for MAT. The drug enforcement agency permitted the initiation of buprenorphine treatment through telemedicine. In Florida, a student-run clinic was able to complete 22 initial visits over the first nine weeks of operation. 15 patients were offered MAT and 12 of those patients were able to successfully receive their medication from a pharmacy [22]. Patients who did not have access to video conferencing technology were allowed to complete their visits over the phone.

The case for deregulation of buprenorphine has been growing in the past few years. Buprenorphine does not require a waiver when it is prescribed for pain and is safer than other full opioid agonists. At the physician level, the waiver required to prescribe buprenorphine could be removed. With a combination of education and the removal of the waiver, access to buprenorphine would

greatly increase [7]. Deregulation will not only improve and expand access but also lessen the stigma surround prescribing and receiving buprenorphine. The presence of regulations creates a false narrative that undercuts the understanding of opioid use disorder as a chronic medical condition akin to others treated by physicians [11].

Currently, there is a push to ensure that the modification of regulations due to the pandemic is made permanent. The Ryan Haight Act includes the requirement of an in-person visit in order to initially prescribe controlled substances. With so few buprenorphine-waivered physicians, this is a significant barrier to care which causes more harm than good. The prescription of buprenorphine through telemedicine has exhibited no significant difference in patient retention, medication adherence, or obstetric outcomes when compared to in-person care. The HHS Secretary has the power to waive the Ryan Haight Act restrictions for telemedicine during public health emergencies. The opioid epidemic is a public health emergency, and therefore the HHS Secretary can continue to allow telemedicine for MAT after the resolution of the pandemic [23].

Obstetric care

Treating pregnant women with opioid use disorder with buprenorphine has shown to have some benefits over treatment with methadone. Patients treated with buprenorphine throughout their prenatal care show a lower rate of birth defects, lower risk of preterm birth, higher rates of optimal birth weight, and less severe Neonatal Abstinence Syndrome (NAS). Still, over half of the neonates treated with buprenorphine required pharmacotherapeutic treatment for NAS. Some of the risks of treating pregnant women with buprenorphine may be medicated by administering lower doses. Higher buprenorphine doses are negatively correlated with birth weight and length [24]. Dosage is also an independent predictor for the severity of NAS.

An increase in the use of buprenorphine in urban areas has driven up the use of MAT and pregnant women. Over a six-year period, the use of buprenorphine more than doubled, while the use of methadone decreased. Federal, state, and local agencies have taken out initiatives to increase the number of buprenorphine-waivered physicians to improve access to care. This is an indication that providers are moving from offering methadone to buprenorphine treatment [17]. The next step is the development of programs that integrate obstetric care with MAT and behavioral health counseling, to encourage retention in treatment and reach better outcomes.

Naltrexone is being explored as an alternative to methadone or buprenorphine for pregnant women with opioid use disorder. In a study comparing the outcomes of patients treated with naltrexone and patients treated with methadone or buprenorphine, no significant difference was observed in obstetric outcomes. However, there was a significant difference in the rate of neonatal abstinence syndrome. The rate of NAS was significantly greater for neonates receiving methadone or buprenorphine treatment. None of the neonates who were treated with naltrexone to delivery were treated for signs of NAS. Naltrexone does cross the placenta, and maternal and fetal levels are similar, yet no change in fetal heart rate was recorded when initiating treatment [25]. The data provides a positive outlook in implementing naltrexone treatment to lessen the risk of NAS.

Treatment for Adolescence

As rates of opioid use continue to increase, the rates of use in adolescents also increase. Adolescents have shown a rapid escalation in opioid use severity and high risk for overdose, making accessibility to MAT essential Despite copious research showing that MAT is necessary and effective for treatment for opioid use disorder, many adolescents do not have access to this care. Of the small number of adolescents who do receive treatment for opioid use disorder, less than 3% receive MAT [26]. Among the small percentage, the treatment is often short-term detoxification and not long-term management. Buprenorphine is ideal to implement with adolescents because it is approved for patients as young as 16 years old. In addition, the increased accessibility of buprenorphine as compared to methadone and the lack of need for daily clinic visits, making it the more ideal option.

Early data show rates of opioid abstinence in adolescence to be comparable to the rates in adults when treated with buprenorphine. Adolescents who received buprenorphine over a 56 day period were 35% opioid negative, as compared to 17% opioid negative for those who only received treatment for 28 days. The opioid abstinence rate increases to 57% with 12 weeks of buprenorphine treatment. Furthermore, patients are more likely to remain in treatment when receiving treatment for a longer period of time [26]. There's also a greater reduction in injection drug use associated with longer periods of treatment. After just two weeks of detoxification, 35% of adolescents or still injecting, as compared to only 15% of adolescents who receive treatment for 12 weeks.

Despite these early findings, more research in a trial is necessary to determine how to approach buprenorphine treatment in adolescents. The individual nature of treatment for opioid use disorder requires different treatment plans for each patient. In previous studies, adolescents have been treated with various buprenorphine doses, anywhere from 2 to 32mg daily. When treating adolescence, the titration of buprenorphine must be individualized based on the severity of the disorder and pain. Not enough data is available to determine the optimal length of treatment and how to decide when to stop treatment [26]. Adolescents, in particular, may be less engaged with treatment that requires daily medication adherence and may benefit from the flexibility of Limited home self-administration [27]. There is an important balance between lessening the risk of leaving treatment and necessary flexibility to encourage adherence, yet to be determined.

Conclusion

Cultural and systematic change is required in order to overcome the many barriers to initiating and maintaining MAT.

The strict regulations appear to be motivated by stigma more than the safety and are preventing patients from receiving adequate care. The lack of integration of care creates yet another hurdle for people with opioid use disorder to overcome. If someone does initiate care, a physician's lack of training or negative attitude can also prevent them from receiving care. This is demonstrated clearly in the treatment of pregnant women with opioid use disorder. Few healthcare providers exist to integrate addiction treatment and obstetric care, how many potential patients delay or deny care for fear of the exposure of their addiction. Healthcare providers who are trained and approved to prescribe MAT concentrate in urban areas, leaving many rural residents without easy access to care.

The opioid epidemic will only continue to spread unless we increase access to care, improve quality of care, unless in the stigma surrounding opioid use and addiction. By incorporating education about opioid use disorder and treatment options, MAT can become standard, and more physicians will be comfortable prescribing this method of care. As more research is done with buprenorphine and naltrexone, these medications are emerging as ideal alternatives to methadone for opioid-dependent pregnant women. Buprenorphine has shown to produce greater rates of optimal weight and length of infants. While naltrexone has shown to greatly decrease the rate of NAS.

The push for the use of telemedicine to prescribe buprenorphine has been increasing over the years and the coronavirus pandemic necessitated it. MAT provided through telemedicine has shown to produce similar obstetric outcomes and retention rates as compared to in-person care. As low as the rates of MAT is for adults, it is even smaller for adolescents, despite producing comparable outcomes. Long-term maintenance for buprenorphine has proved to be successful in adolescents. It provides more flexible care that fits their lifestyle. The future of treatment for opioid use disorder and the course of the opioid epidemic depends on taking the above steps to offer MAT to as many people in need as possible.

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