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Review Article

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Review of medication-assisted treatment for opioid use disorder

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Abstract

Context: The American opioid epidemic has necessitated the search for safe and effective means of treatment for opioid use disorder (OUD). Medication-assisted treatment (MAT) encompasses select medications that are proven effective treatments for OUD. Understanding the mechanisms of action, indications, and implementation of MAT is paramount to increasing its availability to all individuals struggling with opioid addiction.

Objectives: This review is based on an educational series that aims to educate healthcare providers and ancillary healthcare members on the use of MAT for the treatment of OUD.

Methods: The database PubMed was utilized to retrieve articles discussing the implementation of MAT. Boolean operators and Medical Subject Headings (MeSHs) were applied including: MAT and primary care, MAT and telehealth, methadone, buprenorphine, naltrexone, MAT and osteopathic, MAT and group therapy, and MAT and COVID-19.

Results: Three medications have been approved for the treatment of OUD: methadone, naltrexone, and buprenorphine. Identifying ways to better treat and manage OUD and to combat stigmatization are paramount to dismantling barriers that have made treatment less accessible. Studies suggest that primary care providers are well positioned to provide MAT to their patients, particularly in rural settings. However, no study has compared outcomes of different MAT models of care, and more research is required to guide future efforts in expanding the role of MAT in primary care settings.

Conclusions: The coronavirus disease 2019 (COVID-19) pandemic has led to changes in the way MAT care is managed. Patients require a novel point-of-care approach to obtain care. This review will define the components of MAT, consider the impact of MAT in the primary care setting, and identify barriers to effective MAT. Increasing the availability of MAT treatment will allow for greater access to comprehensive treatment and will set the standard for accessibility of novel OUD treatment in the future.

Keywords: medication-assisted treatment; opioid use disorder; OUD.

As the opioid epidemic worsens, medical providers are searching for safe, effective means for treating opioid use disorder (OUD) [1]. The opioid crisis began in the 1990s as a result of pharmaceutical companies reassuring medical communities that opioid pain relievers had no risk of addiction. Misuse of both prescription and nonprescription opioids became rampant. In 2017, the United States Department of Human and Health Services declared a public health emergency, announcing strategies to combat the crisis [2].

There have been nearly 500,000 deaths from opioid overdose between 1999 and 2019 [3]. A study of 25 emergency departments in six states showed that opioid-related overdose visits increased from 3,020 in January 2018 to 3,486 in December 2020 [4]. In the United States, the economic cost of OUD and fatal opioid overdose during 2017 totaled $1,021 billion [5]. With the concurrence of the coronavirus disease 2019 (COVID-19) pandemic, it is estimated that the economic recession resulting from the pandemic may lead to a large increase in deaths from drug overdose, with projected excess deaths depending on the course of the pandemic and response[6].

Medication-assisted treatment (MAT) for OUD is an effective approach to treatment utilizing FDA-approved medications in conjunction with various behavioral

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health approaches [1]. The greater implementation of MAT will help address the growing public health crisis with devastating consequences such as opioid-related overdoses, misuse during pregnancy, rising incidence of neonatal abstinence syndrome, and increasing injection drug use contributing to the spread of infectious diseases such as HIV and hepatitis C [7].

Based on an educational module written to train health professionals about medication management for OUD and best practice methods, this review will define the components of MAT, consider the impact of MAT in the primary care setting, and identify barriers to effective MAT.

Methods

A literature search was conducted utilizing the database MEDLINE® with the Medical Subject Heading (MeSH) of "MAT" restricted to human studies published from 2004 through 2021 yielding over 78,000 results, with 6,296 being clinical trials and 1,356 being meta-analyses. Reference lists from the identified articles were also reviewed. Clinical practice guidelines, major relevant professional organizations, and government legislation were reviewed. The literature search was conducted between December 2019 and February 2020. A second literature search was conducted in January 2021 to reflect the impact of the COVID-19 pandemic on MAT. Boolean operators and MeSH headings were applied including: MAT and primary care, MAT and telehealth, methadone, buprenorphine, naltrexone, MAT and osteopathic, MAT and group therapy, and MAT and COVID-19. Four authors screened and reviewed these results independently. A total of 54 articles were included in the final review.

Discussion

MAT in primary care

OUD treatment has been traditionally managed in specialty care settings. However, barriers to specialty care, such as long waitlists, lack of child care, and geographical access, can interfere with access to care. Primary care models, which can meet patients at their point of need, are an innovative approach to link vulnerable patients to the care they require [8].

When compared to specialty care treatment facilities, a systemic review by Lagisetty et al. [9] including 35 interventions (10 randomized controlled trials and 25 quasi-experimental interventions) found primary care models equally effective in treating OUD. Despite variabilities between treatment models, successful primary care MAT programs shared some similar components: the utilization of integrated clinical teams, incorporating patient agreements, and utilizing home inductions to increase convenience. Multidisciplinary and coordinated care delivery models are also suggested as an effective strategy in primary care; however, definitive research remains necessary.

A review by Korthuis et al. [10] examined primary care-based models for the treatment of OUD by conducting interviews with 11 informants (8 nonfederal and 3 federal) with experience implementing MAT. Four components were consistently noted: pharmacotherapy with buprenorphine or naltrexone, provider and community educational interventions, coordination of OUD treatment with other medical and psychological needs, and psychosocial services like counseling. Common themes included the importance of a nonphysician coordinator and the use of tiered approaches.

Primary care-based models also have the added advantage of addressing comorbidity outcomes. A study by Haddad et al. [11] evaluated the management of prevention healthcare outcomes with primary care management of OUD from an observational cohort study of 266 opioid-dependent patients. Greater than 3 months of treatment on buprenorphine was positively associated with achieving a recommended quality composite health indicators screening score of ≥80%. Additionally, Roll et al. [12] surveyed 28 patients receiving shared medical appointments for buprenorphine management therapy. Researchers found that 60% of patients learned more about comorbidities like hepatitis C and 43% reported receiving appropriate immunizations since starting the intervention.

Rural primary care providers may find themselves in a unique position to utilize MAT. In a retrospective cohort study of 7,930 Medicaid-enrolled adults residing in 23 rural counties in Pennsylvania, Cole et al. [1] examined the relationship between rural patients with OUD, their engagement in MAT, and the distance to MAT providers. Those enrolled with primary care showed higher MAT utilization with greater proportions receiving any MAT (32.7% vs 25%) and a higher mean number of buprenorphine or naltrexone injections (11.1 vs 9.3). Among 1,186 enrollees with OUD receiving MAT, the mean travel distance to prescribers ranged from 0.8 to 395.9 miles and the distance to the nearest MAT prescriber showed significant association to likelihood of receiving any MAT ($p<0.001$). This conclusion is also supported by a 2018 cross-sectional study by Jones et al. [13] where researchers compared deaths secondary to opioid overdose with the availability of buprenorphine providers in 846 counties across the United States. Although the availability of buprenorphine providers and the rate of opioid deaths were only weakly

correlated (correlation coefficient 0.18, p<0.001), their results demonstrate an imbalance between opioid overdose death burden and the availability of buprenorphine providers, particularly in the Midwest and the South.

Methadone

Methadone is a slow-acting opioid agonist indicated in the treatment of OUD and opioid withdrawal management. Although methadone is only available through approved opioid treatment programs, federal and state laws allow take-home doses for select patients who have demonstrated treatment progress [14, 15].

Methadone treatment aims to suppress opioid withdrawal, block the effects of illicit opioids, reduce opioid craving, and facilitate patient engagement in psychosocial and nonpharmacological interventions. Methadone treatment has shown superiority over abstinence-based approaches [16]. While methadone is a frequently utilized medication in MAT, both patients and providers should be aware of the potential risks associated with treatment. Methadone treatment increases the risk of arrhythmias including QT interval prolongation and torsades des pointes [17, 18]. Obtaining a history of structural heart disease, arrhythmia, syncope, and other risk factors for QT interval prolongation is critical before starting treatment. Methadone also presents with numerous drug-drug interactions due to cytochrome P450 isoenzymes involved in its metabolism. MAT providers should closely monitor for interactions that could potentiate or synergize methadone's effects on a patient. Methadone is safe for use in pregnant patients [14, 15].

Practice guidelines published by the American Society of Addiction Medicine (ASAM) Methadone Action Group [14, 15] recommend an initial dose range from 10 mg to 30 mg, reassessing every 2–4 h when peak levels are reached. Following an initiation period, methadone dosing is based on the goals of treatment and patient dependence. Less than 30 mg per day can lessen acute withdrawal but is not as effective in suppressing cravings. Most patients fare better if their initial 30 mg to 40 mg per-day dose is gradually increased to a 60 mg to 120 mg per day maintenance dose. Randomized trials have shown that patients demonstrate better retention in treatment with higher doses of 80–100 mg per day [19, 20]. A dose-response effect is observed for methadone treatment retention rates [21, 22]. Doses above 120 mg per day are utilized with select patients due to the increased purity of heroin and the strength of prescription opioids resulting in increased difficulty to block opioid effects. The optimal length of treatment is not well established; however, relapse rates are highest for patients who drop out [14, 15].

Naltrexone

Naltrexone is a long-acting, full opioid antagonist. Like buprenorphine, naltrexone can be prescribed in the outpatient setting for OUD. Unlike buprenorphine, naltrexone can also be prescribed outpatient for alcohol use disorder treatment [14, 15]. Both formulations, oral and extended-release (ER) injectable, have demonstrated treatment efficacy; however, oral naltrexone is not recommended except under limited circumstances because retention in depot naltrexone is better than usually observed in studies utilizing oral naltrexone [23]. Trials are often limited due to high dropout rates and poor adherence [14, 15]. Adding an agent that improves dopaminergic function to complement naltrexone is a novel approach being studied to encourage adherence [24].

Treatment goals include prevention of relapse, inhibition of illicit opioid effects, opioid craving reduction, and the facilitation of patient engagement in psychosocial and nonpharmacological interventions [14, 15]. Oral naltrexone is best for those who can be closely supervised and are highly motivated because it has high rates of nonadherence and a high risk for overdose upon relapse [23]. ER injectable naltrexone is most effective for patients who have failed other MAT options or are unable to obtain agonist treatment. Both formulations are generally well tolerated; however, patients should be cautioned regarding the high-risk opioid overdose with subsequent relapse due to diminished tolerance and heightened sensitivity [14, 15].

Before naltrexone administration, the patient must be adequately detoxified from opioids with no physical dependence. A naloxone challenge can be utilized when uncertain of detoxification, monitoring for signs and symptoms of withdrawal. Oral naltrexone can be dosed at 50 mg daily or three times weekly with two 100 mg doses followed by one 150 mg dose. ER injectable naltrexone can be given every 3–4 weeks by deep intramuscular injection in the gluteal muscle at a set dosage of 380 mg per injection [14, 15].

Naltrexone ER is associated with side effects such as insomnia, clinically insignificant elevation of transaminases, hypertension, naso-pharyngitis, and influenza [25]. Although naltrexone does not reduce respiratory drive, relapse with high-dose opioids may result in accidental overdose death due to diminished opioid tolerance. Unlike methadone and buprenorphine, naltrexone

ER is not recommended for use in pregnant or breastfeeding women [14, 15].

Buprenorphine

Buprenorphine is a partial opioid agonist utilized to treat OUD [26]. Buprenorphine has the ability to relieve a patient's drug cravings while maintaining a higher safety profile than other MAT medications. Due to buprenorphine's "ceiling effect," increasing dosages will not cause equally increasing respiratory depression in patients [27]. As such, buprenorphine is less likely to cause fatal respiratory depression during overdose [28, 29]. Caution should be applied when combining buprenorphine with other sedative medications, potentially causing higher levels of sedation. Buprenorphine, like methadone, is safe for use in pregnant patients [14, 15]. It demonstrates less peak-dosing suppression of fetal heart rate and less severe neonatal abstinence syndrome than methadone [25].

A critical distinction of buprenorphine therapy is its ability for outpatient prescription following the Drug Addiction Treatment Act (DATA) of 2000 [30]. Any physician can prescribe buprenorphine following completion of an online training course. This distinction can increase access to MAT in otherwise inaccessible patient populations. Following a closely monitored initiation phase, dosing is usually 2 mg to 4 mg to reduce the risk of precipitating withdrawal [14, 15]. If well tolerated, the dose can be increased fairly rapidly to a dose that provides stable effects for 24 h and is effective, with evidence suggesting that doses of 16 mg and greater may be more effective at suppressing illicit opioid use [23]. The FDA recommendation limits dosing to 24 mg per day because higher doses may increase diversion risk [14, 15]. Retention on buprenorphine across low (2 mg–6 mg per day), medium (7 mg–15 mg per day), and high (≥16 mg per day) doses is significantly superior to placebo [31]. However, only high-dose buprenorphine reduces opioid use significantly compared to placebo [32].

Buprenorphine can also be administered with naloxone as a single-dose tablet or buccal film [14, 15]. The goal of combining naloxone, an opioid antagonist, with buprenorphine is to discourage buprenorphine abuse. If the buprenorphine/naloxone product is crushed for the purpose of injection, naloxone will antagonize the agonistic effects of buprenorphine [33]. The FDA recently approved several new buprenorphine formulations for the treatment of OUD, including an ER injection, but data regarding their effectiveness are limited [14, 15]. Some emergency departments are now initiating buprenorphine therapy to patients experiencing withdrawal symptoms [34]. This new strategy has demonstrated promising results toward improving rates of MAT initiation, and its expansion is likely to continue over time [34, 35].

The Substance Abuse and Mental Health Services Administration (SAMHSA) recommends appropriate counseling and social support programs for patients receiving buprenorphine therapy [36] "Group-based" buprenorphine treatments have gained interest since their inception, providing both buprenorphine prescription and group counseling together in a destigmatized environment. This model also increases the number of patients that a single physician could treat, addressing areas with limited access to MAT providers [37]. Some studies have suggested possible benefits of this treatment model [38, 39], particularly in prolonging treatment retention. Despite these advantages, the available supporting research has been limited and varied [38]. A 2017 literature review [39] examined 10 studies, 4 of which utilized small-group models and 6 of which utilized group psychotherapy. The authors concluded that there was limited evidence to support group-based buprenorphine therapy but that much of the literature available was either weak or potentially biased. Based on the limited research available and isolated reports of success, this practice has some feasibility and expands buprenorphine access for patients.

Osteopathic supplementation to MAT

A report issued by SAMHSA noted that in the last 20 years, there have been over 100,000 deaths in the United States that resulted from prescription opioids [36, 40]. In the United States, chronic pain affects 100 million adults, reducing quality of life and productivity. Of those who receive opioids for the treatment of chronic pain, one in four struggle with opioid addiction. Dependence and tolerance to opioids increases the likelihood of developing addiction by 40 times. Although opioid medications are effective, they are best utilized for postsurgical pain, brief periods of acute pain, acute cancer pain, and palliative or end-of-life care [41].

Application of an osteopathic approach when treating chronic pain encourages utilization of an integrative treatment approach. A similar approach may be adopted in the treatment of OUD, particularly with co-occurring chronic pain [41]. A randomized controlled trial with 455 patients analyzing OMT and ultrasound therapy for chronic lower back pain showed a statistically significant decrease in prescription drug use in those receiving OMT treatment.

As an adjunctive therapy, OMT serves as a noninvasive treatment with minimal side effects that can play a key role in holistic patient treatment [42].

A cross-sectional cluster observational study conducted by Rodondi et al. [43] investigated the prevalence of use and the perceived usefulness of treatment modalities for recurrent pain in primary care among 499 patients with chronic or recurrent low back pain. The five most frequent modalities utilized by patients were physical therapy (81.8%), osteopathic treatment (63.4%), exercise therapy (53.4%), opioids (52.5%), and massage therapy (50.8%). Women were significantly more likely to utilize osteopathic treatment whereas patients >75 years old were less likely to utilize osteopathic treatment. Higher level of education was significantly associated with increased use of osteopathic treatment for chronic lower back pain. Additionally, current smoking was associated with significantly greater odds of having utilized opioids and significantly lower odds of having followed exercise therapy. More research is necessary to characterize the patient demographic most likely to utilize osteopathic medicine as a treatment for chronic pain instead of opioids.

Barriers to MAT

Barriers to facilitating MAT successfully include inadequate provider education, cost-related barriers, and the inability to implement a coordinated care approach that is associated with greater benefit [10]. A qualitative study of MAT-providing physicians demonstrated that physicians request further training with respect to medication tapering, billing, and additional training for support staff [44]. Additional barriers to effective MAT include the lack of trained primary care providers, reimbursement models that do not support care coordination and psychosocial services, the persistent stigma associated with MAT, and long travel times for patients in rural areas [10]. Providers also note that coordinated care is crucial in busy academic settings where physicians have limited availability during clinic hours [45].

MAT selection

When considering MAT options, individualized and population management treatment approaches must be considered. An individualized approach to MAT examines the individual patient's access to MAT, treatment setting, occupational risks, comorbid conditions, and patient motivation. A population management approach considers the public health impact of OUD and the cost-effectiveness of treatment options. It plays a larger role in the prevention of community opioid diversion, overdose deaths, and infectious disease transmission [46].

Begin by assessing whether the patient is actively seeking to abstain from illicit opioid use. If the patient is actively abstaining, consider either antagonist or agonist MAT. If the patient is not actively abstaining, consider agonist MAT to maintain opioid tolerance and risk reduction of accidental opioid overdose death. Next, assess whether the patient has significant co-occurring chronic pain. If the patient does have co-occurring pain, consider agonist MAT to reduce pain-related opioid relapse. If there is no chronic pain, consider implementing either an agonist or antagonist treatment [46].

Additional considerations include exclusions to ER antagonist therapy including patients who are pregnant or are planning a pregnancy, those who have experienced a recent opioid overdose, or a patient currently displaying high overdose risk behavior. An office-based outpatient setting is favorable to patients committed to complete abstinence from substance abuse and have no recent accidental or intentional substance overdose or opioid diversion. Structured care settings should be considered for patients who have recently stabilized alcohol or substance use disorders, those with a recent history of substance overdose, and patients receiving agonist MAT who have a recent history of opioid diversion [25].

COVID-19 impact

The treatment of OUD has been significantly impacted by the COVID-19 pandemic, necessitating the use of novel strategies to accommodate patient management. National organizations are providing guidance on how to meet the needs of patients during the COVID-19 pandemic. The Drug Enforcement Administration (DEA) has adopted policies to allow DEA-registered practitioners to prescribe controlled substances without having to interact in person with their patients. Of note, methadone cannot be prescribed for maintenance or detoxification treatment and must still be administered or dispensed directly to the patient for that purpose [47, 48]. Regular face-to-face appointments for high-acuity patients should still be considered in accordance with current restrictions. While there is concern over the inability to conduct urine drug screens through telehealth visits, unnecessary exposure to COVID-19 should be considered in an overall harm reduction approach to OUD [49].

Prior research has demonstrated comparable patient retention, ratings of therapeutic alliance, and medication adherence for telehealth-delivered medication maintenance treatment compared to in-person treatment [50, 51]. The Rhode Island Buprenorphine Hotline is a phone hotline that functions as a tele-bridge clinic where people with moderate to severe OUD can be linked with a DATA 2000 waivered provider who provides an initial assessment and, if appropriate, prescribes buprenorphine for unobserved induction and linkage to outpatient treatment. This service has been viewed as a promising model to bridge gaps in treatment access that both preceded and are exacerbated by the COVID-19 pandemic [52].

Access to medication is a major concern for MAT during the COVID-19 pandemic. Many insurance providers have adjusted policies to allow for enhanced reimbursement, and pharmacies have allowed for early/extended refills during the pandemic. MAT providers need to ensure that patients have access to medication to increase treatment retention and success during and after the pandemic [47, 53].

Limitations

This review is limited to a single database. As such, studies outside of MEDLINE were not included. Additional limitations include studies with small sample sizes, particularly in assessing group-based MAT and barriers to MAT. The ASAM practice guideline utilized in this review was published in 2015; however, an updated guideline was published in the May/June 2020 issue of the *Journal of Addiction Medicine* [15]. Initiation and maintenance doses listed in this review have been updated to reflect this. The nature of MAT initiation and management has been quickly evolving as a result of the COVID-19 pandemic, and a second literature search was conducted to include these changes.

Conclusions

Expanding access to MAT is a crucial component of OUD treatment. Primary care-based models for MAT are shown to reduce mortality for OUD and have equivalent efficacy to MAT in specialty substance treatment facilities. However, research directly comparing specific structures and processes of care models is still needed [9, 10]. Patients may require novel point-of-care approaches, demonstrated by the modifications made to MAT administration during the COVID-19 pandemic [9]. Despite the effectiveness of MAT for OUD, current rates of engagement and retention suggest that new medications and devices need to be explored. Improved outcomes may motivate changes in societal attitudes toward OUD [49].

SAMHSA-funded "Providers Clinical Support System for MAT" is a free resource that offers learning opportunities for providers interested in prescribing MAT. Interested providers should view their website at http://pcssmat.org/for more information [54].

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