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Medication-assisted recovery for opioid use disorder: A guide

Considering offering medical intervention for OUD to reduce mortality? It's essential to understand the clinical benefits, limitations, and regulation of available agents.

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PRACTICE RECOMMENDATIONS

› *Consider resource availability (eg, treatment programs and regulatory barriers), in addition to patient- and medication-specific factors, when designing the most individualized, advantageous medication-assisted recovery plan, to reduce the risk for mortality.* (B)

› *Schedule early (< 2 weeks) and frequent follow-up with patients who are starting medications for opioid use disorder (particularly methadone), to manage risk when mortality is highest and to support recovery.* (C)

› *Set and manage patient expectations for control of withdrawal symptoms when initiating medications for opioid use disorder (particularly buprenorphine).* (B)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Medication-assisted recovery (MAR)—the preferred terminology for the service formerly known as *medication-assisted treatment*—entails a comprehensive set of interventions for managing opioid use disorder (OUD), including medications for opioid use disorder (MOUD). Despite the benefits of MAR—reducing opioid use, opioid-related mortality, and health care costs[1-3]—only 11% of patients with a diagnosis of OUD received MOUD in 2020.[3]

Primary care physicians, including family physicians, are well positioned to provide MAR across the patient's lifespan. However, many family medicine clinicians do not possess the logistical knowledge or resources to implement this service.[4] In this article, we describe options for, and barriers to, MAR and societal issues that have an impact on the care of these patients.

Pathophysiology of OUD

Opioids relieve pain by stimulating μ-opioid receptors and activating the brain's reward system. These pleasurable effects motivate repeated use.[5] Frequent opioid exposure causes neuroadaptation, tolerance, and dependence. For patients with OUD who are misusing illicit or prescription opioids, periods of abstinence following neuroadaptation lead to withdrawal symptoms that vary in intensity, depending on the drug, dose, and duration of use. Upregulated noradrenergic tone and dopamine deficiency manifest as numerous signs and symptoms of withdrawal, including[5]:

- *Physiologic*: secretory (diaphoresis, rhinorrhea, lacrimation, vomiting, diarrhea) and stimulatory (mydriasis, piloerection, hypertension, tachycardia, insomnia)
- *Psychological*: pain, cravings, dysphoria, anxiety.

A single episode of opioid withdrawal is not directly life-threatening, but untreated episodes can progressively amplify

When medication-assisted recovery services are rendered in primary care, treatment retention improves by 25%—highlighting a role for family medicine clinicians in treating OUD.

negative feedback and reinforce continued opioid use.[6] Left untreated, withdrawal can be terminal.

Medication-assisted recovery: Effective intervention

MAR services that integrate medical, behavioral, and psychosocial programs can reduce mortality from OUD 2-fold.[7,8] A meta-analysis found that, when MAR services are rendered in primary care, treatment retention improves by 25% (number needed to treat [NNT] = 6) and ongoing illicit opioid use is reduced by 50% (NNT = 6), relative to care at a specialty clinic[9]—highlighting a role for family medicine clinicians in treating OUD.

All 3 US Food and Drug Administration (FDA)–approved MOUD (methadone, buprenorphine, and naltrexone) reduce cravings; 2 (methadone and buprenorphine) mitigate withdrawal symptoms by activating the μ-opioid receptor; and naltrexone diminishes the reinforcing effects of use (**TABLE**[10-12]). It is crucial to recognize the pharmacologic distinctions among MOUD because untreated withdrawal syndromes increase dropout from treatment programs and subsequent relapse.[13]

The Hx of medication-assisted recovery

To understand the landscape of MAR, it is important to understand the history of opioid treatment in the United States. In 1966, Congress passed the Narcotic Addiction Rehabilitation Act (NARA), which secured federal assistance by which state and local governments could develop drug treatment programs.[14] NARA permitted legal offenders with OUD to be civilly committed to treatment programs, rather than prosecuted. However, limited resources and a burgeoning population led, instead, to low-cost outpatient programs saddled by strict requirements that lacked a basis for improving clinical outcomes.

At the time NARA was passed by Congress, OUD was viewed—inaccurately—as a criminal problem, not a medical one. Subsequent legislation was crafted through that lens, which has placed a heavy burden on patients until today.[14] Although medical understanding of OUD has advanced tremendously over the past 50 years, treatment remains siloed from mainstream medicine, even in primary care.

There is no one-size-fits-all approach to MAR, and relapse is common. Patient-specific factors and the availability of resources should be considered when designing the most individualized, advantageous plan for MAR.

Methadone

Background. Methadone has the most extensive history for treating OUD and consistently has demonstrated efficacy.[13] A meta-analysis of randomized controlled

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TABLE

Profile of medications for treating opioid use disorder[10-12]

Drug	Receptor activity	Route of administration and typical dosing[a]	Restriction on dispensing	Clinical effects	Treatment retention (number needed to treat)[b]	Precautions
Methadone	Full agonist	*Oral* Initial: 10-30 mg once daily Target: > 60 mg once daily	Limited to opioid treatment programs	Reduces withdrawal symptoms Reduces illicit opioid use Attenuates illicit opioid effects	2	Carries a risk for respiratory depression Delayed onset of peak effect
Buprenorphine[c]	Partial agonist	*Sublingual* Initial: 4-8 mg Maximum: 16-24 mg on Day 1 *Subcutaneous* 100-300 mg/mo	Prescriber enrollment required Subject to a Risk Evaluation and Mitigation Strategy[d]		4-5 (dose-dependent)	Might precipitate acute withdrawal
Naltrexone	Antagonist	*Intramuscular* 380 mg/mo	Must be administered by a health care professional	Blocks effects of illicit opioids Reduces illicit opioid use (only when given intramuscularly)	2[e]	

[a] Dosing of methadone and buprenorphine is highly individualized.
[b] Compared to nonpharmacotherapy alone.
[c] Available as buprenorphine alone and as buprenorphine–naloxone. Listed dosing is for the buprenorphine component.
[d] Subcutaneous injection formulation only.
[e] Based on the percentage of weeks abstinent, according to urine drug tests and patient self-reporting. Recommended reading: Wolfe et al, 2011.[29]

trials comparing methadone to nonpharmacotherapy alone found that methadone improved treatment retention by an absolute 57% (NNT = 2).[10]

Methadone was approved by the FDA for detoxification and maintenance treatment in the early 1970s, although the Narcotic Addict Treatment Act (NATA) of 1974 restricted dispensing of maintenance treatment to highly regulated clinics known as *opioid treatment programs* (OTPs).[14] NATA required the treating physician to register with the US Drug Enforcement Agency (DEA) and to comply with conservative dosing regimens and observed dosing.

Over time, regulations evolved to give the physician greater flexibility in developing a care plan, allowing "take-home" doses, and improving patients' access to care. Although access to methadone for the treatment of OUD remains limited to federally certified OTPs, regulations facilitate incorporation of a whole-person approach to care, including counseling, individual and group therapy, and toxicology testing.[7]

Clinical considerations. Methadone requires slow titration. For patients starting methadone as an outpatient, federal law[15] limits the initial dose to 30 mg and requires physician documentation when the first-day total dosage exceeds 40 mg. This dosing constraint makes it challenging to provide care because a daily dosage ≥ 60 mg has been found to produce, first, higher program retention (relative risk = 1.36; 95% CI, 1.13-1.63) and, second, greater reduction in illicit opioid use (relative risk = 1.59; 95% CI, 1.16-2.18) than is seen in patients who receive a lower daily dosage.[16]

Due to a prolonged elimination half-life, methadone reaches steady-state in 3 to 5 days. Patients and their families should be educated that withdrawal symptoms might not feel fully managed in the first few days of

therapy and that time is required to experience safely the regimen's full effects.

Aggressive dose-titration during methadone induction can result in drug accumulation and respiratory depression. The risk for methadone-related mortality is highest in the first 2 weeks of therapy, mostly related to overdose potential if the drug is combined with other opioids.[17]

Buprenorphine

Background. The prescribing rate for buprenorphine, particularly in primary care, is accelerating.[18] A meta-analysis of randomized controlled trials found that[11]:

- compared to placebo, buprenorphine, at any dosage, improves treatment retention by an absolute 21% to 28% (NNT = 4-5)
- patients receiving high-dose buprenorphine (≥ 16 mg/d) had fewer evident cases of illicit opioid use.

Unlike methadone, buprenorphine exerts partial agonism at the μ-opioid receptor, resulting in a so-called ceiling effect that significantly reduces the adverse effect profile, including respiratory depression and euphoria, relative to a full-agonist opioid, such as methadone.[19]

Whereas accessing methadone is limited to OTPs, buprenorphine is available for office-based treatment. By hosting OUD treatment and primary care in the same place, primary care physicians can provide comprehensive medical care including and beyond OUD, thereby improving retention and managing comorbidity.[20]

Integrated models involving support staff—eg, nurses, behavioral health providers, and pharmacists—have produced the greatest success with office-based treatment models.[21] Office-based treatment normalizes OUD as a chronic disease managed by the primary care physician, enabling concurrent harm-reduction strategies; medication reconciliation; and convenient, regular prescribing intervals (eg, every 30 days).[22] Nevertheless, access to buprenorphine is limited. Because buprenorphine is a controlled substance, the Ryan Haight Online Pharmacy Consumer Protection Act of 2008 prevents initial prescribing of buprenorphine without in-person evaluation. Telehealth consultations increased access to buprenorphine through temporary exceptions during the COVID-19 pandemic. However, revised rules and regulations for telehealth visits for these controlled substances are forthcoming from the DEA as temporary exceptions for telehealth consultations come to an end. Additionally, prescribing buprenorphine for OUD requires that the treating physician undergo specific training and obtain qualifications, which have evolved over time through federal legislation.

The Drug Addiction Treatment Act of 2000 (DATA 2000) authorized what is known as an *X-waiver*, which allows physicians to prescribe controlled substances for office-based treatment of OUD, provided that:

- they are registered to do so with the Substance Abuse and Mental Health Services Administration and the DEA
- they have had subspecialty training in addiction or completed an 8-hour training course
- they are able to refer patients to appropriate counseling and ancillary services.

DATA 2000 restricted patient panel sizes to 30 patients in the first year, expanding thereafter upon appropriate certification.

The Comprehensive Addiction and Recovery Act of 2016 (CARA) and the Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act of 2018 (the SUPPORT Act) collectively extended prescribing authority for MOUD to other qualifying practitioners (eg, advanced practice clinicians). Despite these attempts to expand access to services, the overdose death rate has continued to increase.

To further expand access to MAR, the US Department of Health and Human Services updated its practice guidelines in April 2021, allowing clinicians to bypass X-waiver training requirements by applying for a notification-of-intent (NOI) buprenorphine waiver.[a] However, clinicians are still limited to prescribing buprenorphine for 30 patients at a time. Clini-

[a] At buprenorphine.samhsa.gov/forms/select-practitioner-type.php.

Although medical understanding of OUD has advanced tremendously over the past 50 years, treatment remains siloed from mainstream medicine, even in primary care.

cians who undergo complete X-waiver training may prescribe for 100 patients in the first year and, if eligible, 275 patients thereafter.

In addition, as a component of the Consolidation Appropriations Act of 2023, Congress passed the Mainstreaming Addiction Treatment Act of 2021, or MAT 2021, and Medication Access and Training Expansion Act of 2021, or MATE 2021. MAT eliminated the X-waiver, NOI, and restrictions on the number of patients for whom a provider could prescribe buprenorphine, under federal authority; however, restrictions within one's state might limit the ability to prescribe buprenorphine. MATE 2021 is an educational requirement for licensing by the DEA (at application and renewal) that will require prescribers to complete 8 hours of training in substance use disorders starting in June 2023.

Use of the monthly injectable extended-release buprenorphine product[b] is limited by an FDA Risk Evaluation and Mitigation Strategy (REMS) program, which requires specialized training and certification by the prescriber, distributor, and administering clinician. REMS reduces buprenorphine accessibility due to time, cost, and regulatory barriers; although such restrictions have been instituted with the patient's safety in mind, any limitation to buprenorphine prescribing, apart from controlled substance licensure, serves only to limit access to a primary component of MAR.

Clinical considerations. Due to the competitive nature of buprenorphine and its high affinity for the μ-opioid receptor, the drug can displace other opioid agonists and precipitate acute withdrawal. The withdrawal experience can thereby condition fear and disfavor toward buprenorphine among patients.

It is vital, therefore, that (1) patients' expectations for treatment be managed appropriately and (2) the treating physician be prepared to provide additional buprenorphine for adequate maintenance doses and utilize adjunct comfort agents (clonidine, nonsteroidal anti-inflammatory drugs, ondansetron) to manage acute withdrawal symptoms. Newer buprenorphine dosing strategies, such as micro-induction and macro-induction, have emerged to curtail these risks.[23,24] This is an evolving area of MAR; newer low-threshold initiation strategies[25] (see "Low-threshold MOUD prescribing models," in the text that follows) and evidence that supports micro-induction[26] might eliminate the practice of requiring active withdrawal for treatment.

Regardless of the strategy for dosing buprenorphine, it's critical that patients be educated on how to initiate treatment outside a clinical setting, such as at home, where they occupy a familiar haven during a potentially uncomfortable time and can be as effective at initiation as they would be in a clinical setting, with no difference in precipitation of adverse effects.

At-home induction might be more appropriate for patients who are not yet in significant enough withdrawal while in the physician's office.[27] Guidance should be provided on dosing instructions, self-assessment of withdrawal symptoms, and, if applicable, patience with the slow-dissolving sublingual tablet or film formulation.

Patients and their families should be educated that withdrawal symptoms might not feel fully managed in the first few days of methadone therapy.

Naltrexone

Background. Naltrexone is available as an oral tablet and an extended-release, once-monthly intramuscular injection; the latter has demonstrated superiority in MAR.[28] Oral naltrexone has limited supporting evidence, is inferior to other MOUD options, and should not be used to treat OUD.[7] Altogether, approval of naltrexone for OUD is controversial, due to potentially unethical trials and approval processes,[29] although a multicenter randomized controlled trial demonstrated the drug's noninferiority with respect to treatment retention relative to buprenorphine.[30] Used over time, naltrexone does not relieve withdrawal symptoms but can reduce cravings.

Clinical considerations. There are numerous clinical barriers that limit the use of naltrexone.

First, patients should be abstinent from opioids for 7 to 14 days prior to starting therapy; usually, this means undergoing medically supervised withdrawal in a controlled environment. This is an obvious limitation for patients who are constrained financially—those who lack, or have inadequate, health insur-

[b] Sold under the brand name Sublocade.

ance or are unable to be away from their job for an extended time.

Second, because naltrexone does not address withdrawal symptoms, supportive therapies should be incorporated into the treatment plan, including:

- clonidine for hyperadrenergic symptoms (anxiety, diaphoresis, hypertension)
- nonopioid analgesics for pain
- antiemetics, such as ondansetron and metoclopramide, for nausea or vomiting
- loperamide for diarrhea
- diphenhydramine for insomnia.

Third, patients taking naltrexone have a diminished response to opioids. This complicates pain management in the event of an emergent surgical procedure.

Last, when naltrexone wears off, patients are effectively opioid-naïve, which increases the risk for overdose in those who stop therapy abruptly.[29] The increased risk for overdose should be communicated to all patients with OUD who are being treated with naltrexone.

This nonopioid option is appealing to policymakers and is often prioritized in the criminal justice system; however, the decreased efficacy of naltrexone (compared to methadone and buprenorphine), potential for overdose, and challenges in initiating treatment are concerning and limit the drug's use in many real-world settings.

Because naltrexone is not a controlled substance, regulations regarding maintaining inventory and distribution are more flexible.

Overall, the cost-effectiveness of intramuscular naltrexone is unclear. State-administered insurance programs vary in their requirements for coverage of naltrexone treatment.[31]

Comprehensive medication reconciliation is vital

Overall fragmentation of care within OTPs places patients at risk for adverse events, such as drug interactions.[32] Under Title 42 of the US Code,[33] patients must provide written consent for an OTP provider to disclose their history of a substance use disorder. Allowing the patient to decide which medical providers can access their treatment records for an OUD benefits patient confidentiality but poses numerous issues worth exploring.

All prescribed controlled substances are recorded in the prescription drug monitoring program, or PDMP, a state-level electronic database accessible to health care professionals to inform prescribing decisions and identify drug interactions. The PDMP has substantially reduced opioid overprescribing and improved identification of patients at risk for overdose or misuse of opioids.

Unlike all other controlled substances, however, prescriptions ordered by an OTP are not recorded in the PDMP (although there are recent exceptions to this scenario). Without such information, a physician might not have important information about the patient when making medical decisions—placing the patient at risk for harmful outcomes, such as drug–drug and drug–disease interactions.

For example: Methadone is associated with a prolonged QT interval,[34] increasing the risk for a fatal arrhythmia. Concurrent QT-prolonging medications, such as azithromycin and citalopram, further increase this risk.[35] Because methadone dispensing is isolated from the patient's medical record, the clinician who prescribes MOUD has an incomplete patient history and could make a potentially fatal treatment decision.

Diversion is unlikely

Health care providers often express concern about diversion in MOUD. However, misuse and diversion rates of methadone and buprenorphine have declined steadily since 2011, and, in fact, are actually lower than the diversion rate of prescription antibiotics.[36]

Regardless, diversion of buprenorphine should not be a concern for physicians prescribing MOUD. Although a prescriber might worry about manipulation of the formulation of buprenorphine for intravenous administration, addition of naloxone to buprenorphine in tablet form diminishes the potential for overdose. Additionally, the ceiling effect of buprenorphine limits the likelihood of significant respiratory depression and euphoria.

Should buprenorphine reach a patient for whom it was not prescribed, it is highly unlikely that an overdose would result. Rath-

Buprenorphine, available for office-based treatment, has a so-called ceiling effect that reduces the adverse effect profile, including respiratory depression and euphoria.

er, the medication would protect against the effects of illicit opioids and relieve withdrawal symptoms. Most people with OUD who have misused buprenorphine have done so to relieve withdrawal symptoms,[37] not to experience intoxication.

Health care deserts

So-called health care deserts in parts of the United States are an ongoing problem that disproportionately affects lower-income and segregated Black and Hispanic communities[38]—communities that shoulder the highest burden of OUD and OUD-related mortality[39] and whose populace is in greatest need of MAR. Even when health care is accessible in such a desert, some clinicians and pharmacies refuse to prescribe or dispense MOUD because of the accompanying stigma of OUD.

A MAR desert, like a pharmacy desert, is a geographic region—one without access to a MAR or an OTP provider, thereby preventing patients from reaching appropriate care; for some patients, having to travel to the nearest provider can render treatment inaccessible.[40]

Efforts are in place to identify areas at greatest need of OUD-related medical services, such as heat maps that identify areas of increased utilization of emergency medical services for opioid overdose. State-run programs have been implemented to increase access, such as the Illinois Helpline (https://helplineil.org) that provides support and resources for patients, friends, family, and providers.

Prescribing buprenorphine for OUD requires that the treating physician undergo specific training, including subspecialty training in addiction or an 8-hour training course.

Novel solutions

Key strategies to increase access to care and slow the opioid epidemic include low-threshold prescribing of MOUD and mobile OTPs.[41]

Low-threshold MOUD prescribing models. Adoption of one of these models in a medical practice that provides MAR might increase absolute enrollment. A low-threshold prescribing model involves[42]:

- same-day treatment
- leniency with respect to abstinence periods and a concomitant substance use disorder
- enhanced accessibility to MOUD through nontraditional medical settings.

Low-threshold prescribing is flexible in regard to patients' needs and bypasses many of the barriers discussed in this article. Impressive multicenter success has been achieved by the CA Bridge program in California (https://cabridge.org), including an increase in recognition of OUD, treatment initiations, and outpatient engagement.[25]

The cost-effectiveness of low-threshold MOUD prescribing programs remains to be determined.

Mobile OTPs. In July 2021, the DEA authorized a mobile component to existing OTP registrants that is permitted to dispense methadone and buprenorphine. Mobile units are physically separate from the OTP but have similar functions, depending on available space. Services that cannot be provided on the mobile unit of an OTP must be available at its brick-and-mortar location.[7] Logistically, OTP registrants no longer need a separate registration to implement a mobile unit, thus expanding care to patients in underserved or remote areas who often encounter barriers to access.[43]

Conclusion

Understanding the distinct clinical and accessibility benefits and limitations among available MOUD is essential for prescribing clinicians. Accessing treatment is limited by federal regulation, stigma, and the existence of health care deserts that limit access to necessary care for patients with OUD. Newer harm-reduction models, such as low-threshold prescribing and mobile OTPs, represent progress, but many patients remain untreated. **JFP**

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Do not use oral naltrexone to treat OUD; this route of administration has limited supporting evidence.