REVIEW

Medication-Assisted Treatment of Opioid Use Disorder: Review of the Evidence and Future Directions

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Learning Objective: After participating in this activity, learners should be better able to:
Evaluate the rationale for and current evidence supporting medication-assisted treatment of opioid use disorder.

Abstract: Medication-assisted treatment of opioid use disorder with physiological dependence at least doubles rates of opioid-abstinence outcomes in randomized, controlled trials comparing psychosocial treatment of opioid use disorder with medication versus with placebo or no medication. This article reviews the current evidence for medication-assisted treatment of opioid use disorder and also presents clinical practice imperatives for preventing opioid overdose and the transmission of infectious disease. The evidence strongly supports the use of agonist therapies to reduce opioid use and to retain patients in treatment, with methadone maintenance remaining the gold standard of care. Combined buprenorphine/naloxone, however, also demonstrates significant efficacy and favorable safety and tolerability in multiple populations, including youth and prescription opioid–dependent individuals, as does buprenorphine monotherapy in pregnant women. The evidence for antagonist therapies is weak. Oral naltrexone demonstrates poor adherence and increased mortality rates, although the early evidence looks more favorable for extended-release naltrexone, which has the advantages that it is not subject to misuse or diversion and that it does not present a risk of overdose on its own. Two perspectives—individualized treatment and population management—are presented for selecting among the three available Food and Drug Administration–approved maintenance therapies for opioid use disorder. The currently unmet challenges in treating opioid use disorder are discussed, as are the directions for future research.

Keywords: buprenorphine, medication-assisted treatment, methadone, naltrexone, opioid use disorder

Opioid use disorder (OUD) is defined by the *Diagnostic and Statistical Manual of Mental Disorders* (fifth edition)[1] as the maladaptive use of opioids, prescribed or illicit, resulting in two or more criteria that reflect impaired health or function over a 12-month period. OUD is scaled according to severity (mild/moderate/severe) and does not require physiological tolerance or dependence in order to be considered a substance use disorder. Text Box 1 summarizes core criteria and provides a mnemonic to assist clinical diagnosis and teaching.

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In the United States, rates of prescription opioid analgesic misuse rose exponentially in the preceding decade,[2] as has the treatment received for both heroin use disorder and opioid analgesic use disorder.[3] Among persons aged 12 years and older, self-reported lifetime misuse of heroin and opioid analgesics is estimated at nearly 2% and 14% of the population, respectively.[3]

Effective treatment of OUD has been identified as a national priority to reduce the rates and societal costs of individual disability associated with OUD, the infectious disease burden associated with intravenous opioid use (especially hepatitis C [HCV] and HIV transmission), and escalating rates of accidental opioid overdose deaths and pediatric opioid ingestions.[2,4–8] Prior reviews of medication-assisted treatment (MAT) of OUD provide useful guidance to clinicians,[9–12] yet algorithms for selecting medication treatment require continuous updating to remain current with the emerging evidence. The goal of this review is to succinctly provide this clinical update and to highlight unresolved challenges in treating OUD.

METHODS

All randomized, controlled trials (RCTs) with English abstracts on medical management of OUD were searched using

Text Box 1
DSM-5 Criteria for Opioid Use Disorder OUD Presented in the Author's Mnemonic

Long Time Craving Control ⇨ TRASHeD ⇨ Withdrawn
Longer use or larger amounts used than intended
Time spent obtaining opioids, using, or recovering from use
Craving opioids
Failed attempts to **control** or cut back opioid use
Opioid **tolerance**
Role failure due to opioid use
Activities reduced because of recurrent opioid use
Social problems resulting from recurrent opioid use
Health problems resulting from recurrent opioid use
Dangerous opioid use: use despite risk of physical hazard
Opioid **withdrawal** syndrome

In the above mnemonic, the satisfaction of two or more criteria in a 12-month period defines opioid use disorder. Criteria are listed in order of severity, progressing from milder criteria to those criteria that most impair function or cause distress. Severity scaling is determined by the number of criteria that are met and may be remembered by "5 or 4 is a moderate score" (2–3 = mild; ≥6 = severe).

PubMed mesh terms [opioid dependence OR opioid addiction] AND medication, yielding 502 abstracts. These articles were screened for inclusion as contributing to the evidence on MAT for OUD. The resulting set of references was supplemented, based on an examination of abstracts, to include relevant case reports, reviews, meta-analyses, and clinical trials. Finally, the Provider's Clinical Support System for Medication-Assisted Treatment website (www.pcssmat.org), which contains current practice training and educational support for opioid MAT, was reviewed to identify elements of expert consensus beyond the current evidence.

RESULTS: OVERVIEW OF MAT FOR OUD

Mu-Opioid Receptor Targeted Stabilization of OUD

The Food and Drug Administration (FDA) has approved three medications for preventing opioid relapse and for stabilization/maintenance treatment of OUD: buprenorphine, naltrexone, and methadone. All three are ligands that bind to central mu-opioid receptors as the molecular target for their therapeutic activity, yet they differ significantly in their respective intrinsic activities at the mu-opioid receptor, their pharmacokinetic and pharmacodynamic properties (with effects on efficacy and toxicity), and the mechanisms by which they confer relapse-prevention protection to treated individuals (Table 1).

In selecting MAT, the first consideration is whether an individual has OUD with physiological dependence. All three medications are FDA approved based on RCTs demonstrating efficacy and safety in OUD with historical symptoms of physiological dependence (Table 2). The addition of agonist maintenance to relapse-prevention treatment at least doubles the probability, compared to relapse-prevention treatment alone, that an individual will achieve opioid abstinence during active treatment,[24–27] and the addition of antagonist maintenance nearly doubles opioid abstinence.[23] Oral naltrexone, although FDA approved to treat OUD, is excluded from consideration here due to poor adherence rates and significant opioid-overdose mortality following medication discontinuation in clinical studies of OUD treatment outcomes.[28–31] Attempts to pair oral naltrexone with psychosocial interventions aimed at improving compliance and retention in treatment have not yet demonstrated sustained positive results.[29,32] Naltrexone implant and buprenorphine implant are not yet FDA approved for OUD, and trials to date provide insufficient evidence of safety and efficacy.[33,34]

The evidence for efficacy both in reducing opioid use and retaining patients in care is strongest for agonist treatment; methadone maintenance remains the gold standard of care for OUD.[35] The evidence for antagonist treatment of OUD remains comparatively weak, given the mortality risk and poor adherence with oral naltrexone, plus the limited RCT evidence for extended-release naltrexone (naltrexone ER). The latter includes only a trial[23] with open-label extension[19] in a Russian population without access to agonist therapy and a small trial of employment contingency to improve naltrexone ER adherence in a US cohort.[36] Also in Russia, a small RCT of employment contingency to improve adherence used a different, non-FDA-approved formulation of naltrexone ER. Efficacy in reducing opioid use (60%–70% opioid-free urines) was similar to the two above trials cited, and the employment-contingency condition improved adherence but did not affect opioid use.[37] These studies do not adequately address either safety following medication discontinuation or efficacy compared to agonist therapy, and they pose problems for generalizability. A phase 4, multisite RCT comparing naltrexone ER to buprenorphine/naloxone maintenance is currently under way, with the expectation that results will resolve safety and efficacy questions regarding naltrexone ER as a treatment for OUD (NIDA Clinical Trials Network protocol 0051 [Principal Investigator: John Rotrosen/NewYork University School of Medicine]; ClinicalTrials.gov identifier NCT02032433).

Unknown Aspects of Mu-Opioid Receptor Functional Activity in MAT

Although it is commonly accepted that the functional effects of MAT differ according to their respective intrinsic activities at central mu-opioid receptors, this view is oversimplified. The many complexities of mu-opioid receptor ligand binding and biased agonism (e.g., "functional selectivity" according to mu-opioid receptor/effector coupling and intracellular environment, and agonist-induced receptor conformational changes with prolonged agonist exposure)[38–40] are only now being

Table 1

Comparison of FDA-Approved Medications to Treat Opioid Use Disorder with Physiological Opioid Dependence

Medication	MOR intrinsic activity MOR binding	Differential pharmacology affecting MOR activation at therapeutic dose	Mechanism of relapse prevention
Buprenorphine	Partial agonist High affinity K_i* = 0.2 nM	Slow MOR dissociation allows thrice-weekly sublingual dosing and possibility of high-dose weekly formulations[13–15] Highest known MOR affinity makes rescue from overdose by naloxone less effective;[16] rapid precipitation of withdrawal if full agonists present	Reduces opioid craving, withdrawal, and stress reactivity Competitively blocks or reduces the reinforcing effects of other opioids
Methadone	Full agonist High affinity K_i* = 3.4 nM	Long terminal half-life (up to 120 hours) with delayed steady-state efficacy poses increased MOR toxicity risk during induction phase[17] Multiple drug-drug interactions pose both opioid-toxicity and withdrawal risks during treatment[18]	Reduces opioid craving, withdrawal, and stress reactivity Reduces the reinforcing effects of other opioids
Naltrexone ER	Antagonist High affinity K_i† = 0.26–0.34 nM	Lack of MOR agonism associated with delayed stabilization of opioid craving[19] Safety concern based on rodent data demonstrating chronic naltrexone exposure increases respiratory-depression risk upon opioid agonist reexposure[20]	Competitively blocks reinforcing effects of opioid agonists Reductions in craving are psychologically mediated (reduced anticipatory expectancies)

* Equilibrium dissociation constant for the test compound and relative values are from Volpe et al. (2011).[21]

† Equilibrium dissociation constant is from Yuan et al. (2013).[22]

MOR, mu-opioid receptor; ER, extended release; nM, nanomoles.

discovered, and may account for the clinical effects of these medications that remain poorly understood and that appear to vary widely among individuals. For example, little is known about why only certain individuals develop OUD following recurrent opioid exposure, although population studies in patients receiving opioid analgesics identify co-occurring substance use and mental illness as risk factors for developing OUD,[41] and a recent meta-analysis suggests that the rs1799971 polymorphism of the *OPRM1* gene may confer vulnerability to OUD following exposure to either heroin or prescription opioids.[42] Clinically, dosing needs in agonist maintenance therapies different significantly among individuals, and most patients do not develop tolerance to the relapse-prevention efficacy of buprenorphine or methadone

Table 2

Opioid-Abstinence Rates with Medication Compared to Nonmedication[a]

Medication[b]	Percentage opioid free on medication	Percentage opioid free on placebo/detoxification	Study
Naltrexone ER	36	23	Krupitsky et al. (2011)[23]
Buprenorphine/naloxone	20–50	6	Fudala et al. (2003)[24] Weiss et al. (2011)[25,c]
Buprenorphine/naloxone	60	20	Woody et al. (2008)[26,d]
Methadone	60	30	Mattick et al. (2009)[27]

ER, extended release.

[a] The randomized, controlled clinical trials summarized here paired medication maintenance with evidence-based psychosocial treatments and opioid use self-report data that were confirmed with urine toxicology. Clinical settings for treatment delivery may affect the rates of opioid use in the nonmedication control groups. The trials predominantly used adult opioid use disorder populations, with the majority being heroin dependent or having mixed dependence on heroin and prescription opioids.

[b] All medications are FDA approved.

[c] Population was prescription opioid–dependent patients.

[d] Population was youth aged 14–21 years.

maintenance. These observations suggest dynamic factors beyond ligand intrinsic activity at mu-opioid receptors. Whistler[43] has presented a helpful summary of the converging evidence that opioid agonists having both high efficacy and high propensity to produce mu-opioid receptor desensitization and endocytosis ("molecular trafficking") have lower liability for abuse and produce less tolerance than opioid agonists that induce comparatively little endocytosis. Examples of the former include endogenous opioid ligands and methadone, whereas the latter include morphine, codeine, buprenorphine,[44] and most commonly misused prescription opioids. Thus, endocytosis may help to explain the lack of tolerance observed for relapse-prevention efficacy with methadone maintenance but would not explain the same observation with buprenorphine maintenance.

Within methadone-maintained patients, pharmacogenomic studies identify variability in treatment response and pharmacokinetics associated with the variants of several genes (*OPRM1*, *ARRB2*, *KCNJ6*, *ABCB1*) and hepatic CYP450 enzymes, suggesting layers of complexity in any given individual's treatment response.[45] For example, a recently published meta-analysis demonstrates that individuals homozygous for the CYP2B6*6 polymorphism are slow metabolizers of both the R- and S-enantiomers of methadone and therefore would be expected to have lower dosing requirements.[46] The utility of pharmacogenomic screening may be especially important in future clinical practice with methadone maintenance.

Comparing MAT Tolerability and Convenience

RCTs examining methadone, buprenorphine, and extended-release naltrexone injection stabilization are all associated with acceptable adverse-effect profiles and with an acceptable level of patient tolerance.[23–27] Agonist treatment is associated most frequently with opioid-class effects such as dose-dependent sedation, constipation, sweating, neurocognitive impairment, and sexual dysfunction. Dose-dependent respiratory depression is an adverse effect mainly of methadone, a full mu-opioid agonist, whereas the partial-agonist properties of buprenorphine prevent dose-dependent respiratory depression greater than 50% reduction of baseline even at IV doses of 2 mcg/kg in opioid-naive healthy volunteers.[47] This "ceiling effect" on respiratory depression has obvious benefits for tolerability as well as for accidental or intentional overdose. Similarly, buprenorphine's partial-agonist properties have a protective "ceiling effect" that does not induce euphoria in opioid-tolerant individuals, whereas methadone-induced euphoria may be present in the early treatment of OUD but decreases with steady-state dosing stabilization.[48]

Naltrexone ER is associated most commonly with insomnia, site reactions to injection, clinically insignificant elevation of transaminases, hypertension, nasopharyngitis, and influenza.[19,23]

Patient convenience for dosing is least burdensome with monthly injections of naltrexone ER or monthly maintenance visits with office-based buprenorphine/naloxone—both modeling typical outpatient treatment for severe chronic illness. Dosing is most burdensome with required observed daily dosing in opioid treatment programs prescribing methadone or buprenorphine maintenance in the early phases of recovery.

Retention in Treatment After the Initiation of MAT

All three medications show improved retention in treatment compared to placebo or no medication.[24–27] Head-to-head comparisons are mainly available for buprenorphine versus methadone maintenance, with methadone demonstrating the highest rates of treatment retention in all studies,[35,49] including the treatment of pregnant women[50] and those with HIV.[51] One RCT conducted in Iran compared all three medications in a cohort of men dependent on intravenous buprenorphine and found that retention in treatment over a 24-week period was best with methadone followed by buprenorphine and then oral naltrexone, although it was noted that the available daily dose of buprenorphine (5 mg) was not an agonist dose equivalent to the study's daily dose of methadone (50 mg)—which likely contributed to poorer retention in the buprenorphine-treated group.[52]

Impact on HIV Risk Behaviors

In HIV-infected populations, methadone and buprenorphine maintenance significantly reduce the use of illicit opioids and the risk of HIV transmission through the use of injection drugs, though their impact is less robust on sexual risk behaviors.[53–56] In a secondary analysis using a large national cohort from a safety RCT (comparing hepatic responses to 24 weeks methadone and buprenorphine maintenance for OUD),[57] an interesting gender difference emerged: sexual risk behaviors increased among men maintained on buprenorphine but decreased in methadone-maintained men, whereas women decreased risk with either buprenorphine or methadone maintenance.[51]

Impact on Hepatitis C Risk Behaviors

Cumulative, lifetime HCV seroprevalence estimates among injection-drug users is up to 90%,[58] with high seroconversion rates attributable to both sharing syringes/needles and sharing drug preparation equipment (e.g., drug cookers and spoons, filtration cottons, vehicle fluids).[59,60] Two large, prospective cohort studies report the protective effect of methadone[61,62] and buprenorphine[62] maintenance, but not detoxification, in preventing HCV seroconversion among adult injection-drug users who are HCV negative at treatment entry.

Impact on Preventing Opioid Overdose

Several risk factors for unintended opioid overdose have been identified. They include misuse of heroin and opioid analgesics, misuse of diverted buprenorphine and methadone, increases in opioid prescribing, having four or more prescribers or pharmacies filling opioid prescriptions, being prescribed doses equivalent to more than 100 mg morphine, opioid ingestion coupled with alcohol or the use of other sedatives/

hypnotics (with synergistic effects on respiratory depression), receipt of public subsidy income providing access to drug purchase and binge drug use, suboptimal methadone-induction practices in relation to both pain management and addiction, opioid-analgesic switching, previous overdose history, loss of opioid tolerance among OUD due either to extended abstinence during incarceration or to treatment-related abstinence, and older age, with smoking status and co-occurring medical conditions likely contributing to fatalities.[2,63–71] Given that MAT reduces illicit opioid use, educates about OUD and accidental-overdose prevention, and may provide (where available) intranasal naloxone rescue kits to family and friends for use at the scene of an opioid overdose,[68,72] it is expected that MAT would be an important factor in preventing accidental opioid-overdose deaths occurring in those with OUD while they remain in active treatment. While data to date suggest that that is indeed the case for buprenorphine, methadone, and naltrexone ER,[19,63] more data are required to judge the safety of MAT following treatment dropout and planned medication discontinuation, particularly for antagonist therapies for which the preclinical[20] and clinical[28,31,73] evidence indicates increased risk for respiratory depression upon opioid agonist reexposure.

Safety Profile of MAT

Buprenorphine and methadone[57] and naltrexone ER[19,74] maintenance have favorable safety profiles, with HCV-infection being the most common predictor of mild-to-moderate increases in transaminases among adults, pregnant women,[75] and youth.[26,76] Methadone risk for QTc prolongation (associated with torsades de pointes, which has an estimated 10%–17% risk of sudden death due to cardiac arrhythmia[77]) is dose dependent, but screening baseline QTc intervals has not yet been shown to assist risk management during methadone maintenance.[78] Neither buprenorphine nor naltrexone is associated with QTc prolongation.

Drug-drug interactions are numerous with methadone, due to many cytochrome P450 isoenzymes involved in its hepatic metabolism (mainly CYP3A4, but also CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6).[12,18] Metabolic inhibitors that increase methadone peak concentrations pose a risk for sedation and respiratory depression, bowel immotility, and QTc prolongation and cardiac arrhythmia; whereas metabolic potentiators that reduce methadone peak and trough concentrations pose a risk for opioid withdrawal and relapse to opioid use. Other substances and drugs having similar adverse effects (sedation, reduced bowel motility, QTc prolongation, and reductions in heart rate, blood pressure, and respiratory rate) may pose additive and synergistic effects, even if they do not alter methadone metabolism. Common examples include alcohol and benzodiazepines (sedation and reduced respiratory drive), antipsychotics, tricyclic antidepressants, and calcium channel blockers (QTc prolongation), and psychotropics with anticholinergic effects (constipation).

By comparison, buprenorphine and naltrexone have few drug-drug interactions and a benign side-effect profile. Owing to its partial-agonist properties, buprenorphine is not associated with a significant risk for respiratory depression;[47] however, in combination with sedatives/hypnotics (especially diazepam),[79–81] it poses a risk for sedation and reduced respiratory drive. Naltrexone has no risk for reduced respiratory drive, but attempts to "override" blockade with high-dose opioid use poses a risk for accidental-overdose death (see Vivitrol® package insert). Buprenorphine is metabolized primarily by CYP3A4 and has clinically significant drug-drug interactions with rifampin (reductions in buprenorphine concentrations pose a risk for opioid withdrawal, although this effect is not observed with rifabutin)[82] and atazanavir (increased buprenorphine concentration and sedation/cognitive impairment).[83] Buprenorphine has not had confirmed, clinically significant CYP3A4 or CYP2D6 interactions with other commonly prescribed psychotropics and medications, although infrequent case reports exist; definitive human studies are lacking.[18,84] Naltrexone is not metabolized by cytochrome P450 isoenzymes; instead, it has hepatic metabolism via dihydrodiol dehydrogenase to β-naltrexol, which is then conjugated for urinary excretion.[84] Its major drug interaction is blockade of opioid analgesic efficacy.

In pregnancy, naltrexone ER has no demonstrated safety, whereas both buprenorphine and methadone maintenance are safe and effective for maintaining maternal abstinence and retention in prenatal care,[85] and are safely recommended during breastfeeding.[86,87] Buprenorphine demonstrates less peak-dosing suppression of fetal heart rate, fetal heart rate reactivity, and biophysical profile scores, and generates a milder neonatal abstinence syndrome than methadone.[88,89] Early neonatal development appears within normal limits for infants exposed to buprenorphine or methadone in utero.[90] Longer-term neurodevelopmental safety is known for infants exposed in utero to methadone[91] and is being investigated for buprenorphine-exposed infants.

Ease of Induction and Comparison of Available MAT Formulary

The MAT formulary available in the United States for treating OUD is summarized in Table 3. Naltrexone ER is available only under a brand name, whereas buprenorphine monotherapy, buprenorphine/naloxone, and methadone are all available both generically and under brand names. Oral methadone concentrates are dose-equivalent, but the differences in formulations for buprenorphine/naloxone are not reliably dose-equivalent (see, e.g., the dosing differences with buccal film). Converting between these forms of buprenorphine/naloxone requires careful attention to dosing practices (food and smoking should be avoided 30 minutes before and after dosing, and dissolved medication should be held with saliva for a full 10 minutes to optimize mucosal absorption) and to patient response. General dosing ranges for both induction

Table 3

Opioid Use Disorder Formulary in the United States

Available formulary	Dosage forms (mg)	Induction dosing (mg)	Recommended dosing range for stabilization/maintenance (mg)
Methadone (HCl oral concentrate, per ml)			
Generic	5, 10	5–10 every 4 hours up to 40 in the first 24 hours	Gradual titration with close monitoring over 2 weeks to 60–120 daily; rapid metabolizers may require higher dosing
Methadose	10		
Methadose sugar-free	10		
Methadone HCL Intensol	10		
Buprenorphine + naloxone			
Sublingual tablet			
Generic	2/0.5, 8/2	2/0.5–4/1; repeat up to 16/4 in the first 24 hours	4/1–24/6 daily
Zubsolv	1.4/0.36, 5.7/1.4	1.4/0.36–2.8/0.72; repeat up to 11.4/2.8 in the first 24 hours	2.8/0.72–17.1/4.2 daily
Sublingual film			
Suboxone Film	2/0.5, 4/1, 8/2, 12/3	2/0.5–4/1; repeat up to 16/4 in the first 24 hours	4/1–24/6 daily
Buccal film			
Bunavail	2.1/0.3, 4.2/0.7, 6.3/1	2.1/0.3; repeat up to 8.4/1.4 in the first 24 hours	2.1/0.3–12.6/2.1 daily
Buprenorphine			
Sublingual tablet (generic only)	2, 8	2–4; up to 16 in the first 24 hours	4–24 daily
Naltrexone ER			
Vivitrol	380	380 IM following agonist clearance; oral naltrexone 50 mg daily may precede or supplement initial induction	380 IM every 4 weeks; oral naltrexone may be added to supplement in weeks 3–4 as needed

ER, extended release.

and for stabilization/maintenance treatment are also listed in Table 3.

An advantage of methadone is that it can be started at any time during an overarching course of treatment. A disadvantage, however, is that it takes time to achieve a steady-state dose that is therapeutically effective in OUD, and this time period is one of high risk for treatment dropout and accidental overdose if titration is too rapid.[17,92] Buprenorphine requires the individual to be in mild-moderate opioid withdrawal prior to dosing, in order to avoid precipitating severe opioid withdrawal (due to its partial-agonist activity), but relief is achieved within 24–72 hours of induction for both monotherapy and the naloxone-combined product. The partial-agonist "ceiling effect" protects against respiratory depression, thus rendering this medication safe for rapid induction. Buprenorphine monotherapy is recommended for observed induction and for stabilizing or maintaining pregnant women or those that may respond adversely to naloxone due to allergies or co-occurring medical conditions. The combination product is buprenorphine plus naloxone in a 4:1 ratio and was designed to prevent misuse and diversion of buprenorphine among injection drug users. Buprenorphine has good bioavailability via oral mucosal absorption, whereas naloxone does not. Taken sublingually, the naloxone component has poor bioavailability, but if crushed and injected, the naloxone component is readily available to exert opioid antagonist effects, thus reducing the risk of abuse in buprenorphine treatment. Buprenorphine/naloxone is consequently the formula of choice for inductions that are not fully observed and for routine maintenance, in order to reduce product diversion and misuse. Naltrexone ER has the most complicated induction profile because of the need to complete metabolism of opioid agonists prior to dosing (typically 7–14 days), thereby avoiding severe opioid withdrawal (due to its antagonist activity).

Prolonged symptoms of opioid withdrawal during washout pose a high risk for treatment dropout and relapse. Attempts to abbreviate this period require more complex dosing algorithms as well as back-up options for environmental containment to prevent relapse to opioid use.[93]

Risk for Diversion and Negative Public Health Impact

Buprenorphine (all formulations) and methadone are known to be diverted by patients and to be commonly used illicitly,[63,94,95] resulting in further opioid misuse and overdoses, in accidental pediatric exposures,[96] and in accidental or intentional adolescent exposures.[6] Since naltrexone ER has no known diversion value, it allows for the treatment of OUD without contributing to illicit opioid use.

DISCUSSION

Factors to Consider in Selecting Treatment with MAT

MAT is recommended for adults presenting for clinical treatment of OUD with physiological dependence: it significantly augments treatment retention, reduces illicit opioid use, reduces the burden of opioid craving, and, in the case of agonist therapies, provides effective relief of the opioid withdrawal syndrome. Thus, MAT is a stabilizing addition to relapse-prevention counseling and mutual help groups (such as Narcotics Anonymous) in that it increases the effectiveness of those interventions. Longer-term, abstinence-based residential treatment without MAT shows limited effectiveness, especially among recently detoxified heroin users,[97,98] and loss of tolerance during this period of abstention poses an increased risk of fatal overdose if one relapses to opioid use upon discharge to home. Youth is a predictor of early dropout from psychosocial treatment of OUD,[99] whereas medication adherence and early opioid abstinence predict greater retention and treatment success among youth treated with buprenorphine/naloxone.[100] A 2005 Cochrane review noted that the available evidence was insufficient to support psychosocial treatment alone as effective for OUD.[101] The evidence remains insufficient, even to predict which individuals, if any, are likely to do well without MAT.

The selection of MAT can be viewed from two different perspectives: individualized treatment versus population management. An individualized treatment approach will consider many factors, in addition to the evidence base, to guide medical decisions. These factors include the following: the availability of, and patient's access to, MAT; the experience of the prescribing clinician; the clinical setting of treatment; patient and family preferences; occupational risks (see next paragraph); co-occurring medical and psychiatric illnesses; and the patient's motivation for opioid abstinence, capacity to adhere to recommended treatment, and legal status. If the risk for treatment dropout is high, the evidence regarding MAT and retention in treatment significantly favors a recommendation for agonist therapy; methadone maintenance demonstrates the highest patient retention rates in all studies comparing methadone to buprenorphine. A recommendation of methadone or buprenorphine/naloxone maintenance must also be balanced by a discussion with the patient (including informed consent) regarding both the difficulty of terminating agonist therapies (due to reexperiencing opioid withdrawal and craving) and the high rates of opioid relapse following the discontinuation of either buprenorphine[25,26] or methadone.[102,103] Unfortunately, no long-term studies have compared taper outcomes with buprenorphine versus methadone. Clinicians are encouraged to monitor taper trials closely for any evidence of patient destabilization or relapse risk that would require returning to higher-dose agonist treatment. The benefits of extended methadone or buprenorphine/naloxone maintenance delivered within an opioid treatment program (requiring daily medication monitoring during early recovery, and providing structured psychosocial interventions and integrated care options) are especially pronounced for populations with significant drug-related legal charges and drug-using social networks, for patients with co-occurring medical illness related to injection drug use, and for socially disadvantaged patients, who may receive, through the integrated structure of the program, the intensive social and medical services needed to support sustained recovery.

In some situations, the selection of MAT may reflect risk-benefit assessments unrelated to the medical factors as such. For instance, the performance of pilots, physicians, professional athletes, or those carrying firearms could be compromised and even be dangerous because of opioid agonist treatment's cognitive or sedative effects or its impact on reaction times.[104,105] No studies specific to these professions have been conducted for agonist therapy of OUD, however, so this concern is empirical rather than evidence based at this time. In such cases, antagonist therapy may be preferred for a motivated, treatment-seeking individual who desires to continue such employment, despite the comparatively weak evidence supporting antagonist versus agonist therapies. Similarly, an individual with co-occurring OUD and alcohol use disorder might benefit most from antagonist therapy, given that the FDA has approved naltrexone ER as effective in preventing relapse to alcohol use.[106,107] In all such situations, these matters should be covered in a collaborative informed consent process, and clinicians should carefully document the discussion.

A population-management approach would consider the public health impact of OUD, along with the cost-effectiveness of the available treatment options, over patient preferences and individualized selection of MAT. Primary consideration would be given to preventing opioid diversion into the community, opioid overdose deaths, and the transmission of infectious diseases (in particular, hepatitis C and HIV) through the use of injection opioids. To optimize such decisions, all three MAT options for OUD would need to be available, and prescribers would need to be trained in the appropriate use of each one. Lack of prescriber familiarity and comfort with MAT, as well as limits imposed on prescribers by managed care (e.g., dosing limits, prior authorization reviews,

and limits on toxicology), continue to be barriers to dissemination of MAT for OUD in clinical practice.[108] The availability of a regularly updated, evidence-based algorithm to assist in decision making would also contribute to the adoption of MAT in practice.[109]

An example of a simple, evidence-based algorithm for MAT selection—one designed to be flexible in relation to regional MAT availability—is outlined in Text Box 2. Failed treatment trials would result in the selection of an alternate MAT treatment or in the relocation of treatment itself—for example, from an office to a structured treatment setting with closer patient monitoring, such as an opioid treatment program, an integrated mental health care clinic, or a specialized integrated care clinic (following an integrated care model as is used for infectious diseases). In the United States, methadone maintenance must currently be delivered within a federally regulated opioid treatment program, but some evidence suggests, as a future option, that methadone maintenance can be effectively delivered within an office-based setting, especially for clinically stable patients who have achieved take-home doses.[110–112] The use and implementation of a MAT algorithm would reduce discrepancies in treatment based on regional variations, prescriber expertise, or access to specialty clinics. The main weakness of this approach, however, is that it could reduce the role of patient preferences in selecting MAT. This consideration is a serious one in framing an effective population-management approach since patient engagement in substance use treatment is essential for optimal outcomes. Service-utilization research and feedback from programs using this approach are much needed.

MAT Selection in Adolescents

The buprenorphine/naloxone combination is FDA approved for adolescents aged 16 and older and has demonstrated safety and efficacy for youth with OUD.[26] As such, it is currently the treatment of choice. Nevertheless, concern about adolescent nonadherence and the misuse and diversion of buprenorphine/naloxone has generated some support for empirical treatment with naltrexone ER. Caution is advised, however, because evidence is lacking as to the safety and efficacy of naltrexone ER in this population. In the United States, methadone maintenance is not available for the treatment of adolescents.

MAT Selection in Women of Childbearing Age

For women of childbearing age and those who are pregnant or planning pregnancy, careful discussion, along with informed consent, is required in selecting MAT. Although methadone maintenance is the current gold standard of clinical care during pregnancy, buprenorphine monotherapy (but not buprenorphine/naloxone, though early evidence suggests that the combination warrants further study)[113] is a potential alternative based on studies comparing the safety and efficacy of these treatments during pregnancy.[85] Postpartum breastfeeding mothers may

Text Box 2
Evidence-Based Medication-Assisted Treatment Selection Algorithm for Treating Opioid Use Disorder in Adults[a]

A. Threshold questions
  (1) Is the patient actively seeking abstinence from all illicit opioid use?
    YES: consider antagonist or agonist medication-assisted treatment (MAT)
    NO: consider agonist MAT to reduce risk of accidental opioid overdose death by maintaining opioid tolerance
  (2) Does the patient have significant co-occurring chronic pain?
    YES: consider agonist MAT to reduce pain-related opioid relapse
    NO: consider antagonist or agonist MAT
B. Exclusions to extended-release antagonist maintenance
  - pregnant or planning pregnancy
  - foreseeable need for opioid analgesia during treatment
  - recent opioid overdose or high risk for opioid overdose behavior
C. MAT treatment setting
  (1) office-based outpatient care
    - patients committed to abstaining from all substance use
    - no recent history of accidental or intentional substance overdose
    - no recent history of opioid diversion
  (2) structured care setting (e.g., opioid treatment program, integrated mental health care clinic)
    - recently stabilized sedative/hypnotic or alcohol use disorders
    - recent history of accidental or intentional substance overdose
    - patient is receiving agonist MAT and has recent history of opioid diversion

[a] This algorithm is flexible in that it includes local care options and is designed to reduce opioid overdose deaths and opioid diversion. Failure of one MAT trial would prompt reconsideration of other available MAT options or the relocation of treatment from an office-based practice setting to a structured clinical setting with closer patient monitoring.

be switched from buprenorphine monotherapy to combination buprenorphine/naloxone maintenance in order to prevent diversion, especially since naloxone is poorly absorbed sublingually and is unlikely to be absorbed by suckling infants.[114]

Lack of Clinical Studies for Using MAT in Nondependent OUD

No research has examined MAT in nondependent OUD, and even case reports are lacking on this topic. Such off-label use, which would require appropriate informed consent and risk-management consultation, should not be considered without careful deliberation and documentation of medical decision making. Theoretically, OUD without any history of physiological dependence would favor antagonist treatment in most cases, as maintenance on agonist therapy will induce physiological opioid dependence. In most cases, this risk would not be perceived to outweigh benefit except in the presence of an imminent risk of death by opioid overdose. Such situations include recurrent or recent near-fatal overdoses with opioids or a recent intentional opioid overdose in an impulsive individual returning to an outpatient setting. In these examples, the preserved or augmented opioid tolerance provided by agonist treatment might be considered protective against future toxic opioid use, in which case buprenorphine/naloxone would be favored over methadone because of its lower risk of opioid toxicity and fewer drug-drug interactions. Another example may be the patient with a co-occurring pain syndrome who requires intermittent opioid analgesia, satisfies criteria for OUD without physiological dependence, but misuses opioid analgesics. In this example, low-dose buprenorphine/naloxone maintenance in a divided-dosing regimen could potentially enable pain treatment and circumvent opioid misuse; indeed, studies of OUD with physiological dependence show buprenorphine/naloxone to provide a benefit in mild-to-moderate pain syndromes.[25,115] Note, however, that the above comments reflect theoretical considerations only; evidence for efficacy and safety is lacking for all three medications in relation to nondependent OUD.

Need for Development of Non-opioid Therapies to Ameliorate Acute and Protracted Opioid Withdrawal Syndromes

Opioid withdrawal is commonly misrepresented as a "flu-like" syndrome due to the constellation of physical symptoms characterizing acute hyperadrenergic rebound, along with malaise and gastrointestinal distress. This concept of opioid withdrawal is incomplete, however, in that it ignores the severe affective and cognitive distress (including treatment-resistant anxiety, dysphoria/depression, severe opioid craving, and loss of self-efficacy) that persists up to 30 days in untreated OUD abstinence[116,117] and that contributes to opioid relapse and treatment dropout, even among young OUD patients with relatively brief histories of dependence.[118]

Potential non-opioid treatments to stabilize opioid withdrawal and opioid craving may be developed through an understanding of how neurobiological circuitry interacts with opioid pathways.[119] Such treatments would be expected to relieve symptoms, improve retention in care, ease induction, and possibly increase the options for managing OUD during pregnancy. A small pilot RCT (n = 24) of buprenorphine detoxification with and without gabapentin, a GABAergic anticonvulsant, demonstrated better short-term opioid-use outcomes with gabapentin,[120] but two RCTs assessing the use of memantine, a glutamatergic antagonist, as an adjunct to naltrexone ER induction and stabilization[121] or to oral naltrexone[122] had negative results. Further research on novel pharmacotherapies to ease opioid withdrawal are warranted.[123,124]

Clinicians are encouraged to educate patients about opioid withdrawal and its presenting a risk for opioid relapse and for dropping out of treatment. A collaborative plan should be developed, in advance, for managing opioid withdrawal. For example, informed consent with agonist therapies should include a discussion both of opioid withdrawal as presenting a risk for relapse and of the future inevitability of experiencing opioid withdrawal when discontinuing agonist treatment or if doses are missed. Collaborative treatment plans that include aggressive pharmacological management of symptom relief and options for safe containment in higher levels of care (such as partial or residential treatment programs) would be expected to improve retention in care and, more generally, the patient's understanding of how to avoid relapse to opioid use.

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