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Medication-Assisted Treatment for Opioid-Use Disorder

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Abstract

The United States is in the midst of a national opioid epidemic. Physicians are encouraged both to prevent and treat opioid-use disorders (OUDs). Although there are 3 Food and Drug Administration-approved medications to treat OUD (methadone, buprenorphine, and naltrexone) and there is ample evidence of their efficacy, they are not used as often as they should. We provide a brief review of the 3 primary medications used in the treatment of OUD. Using data from available medical literature, we synthesize existing knowledge and provide a framework for how to determine the optimal approach for outpatient management of OUD with medication-assisted treatments.

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In the early 1800s, the German chemist Friedrich Sertürner isolated the active ingredient of the opium poppy, calling it *morphium* after the Greek god of dreams. Although the opium poppy had been used medicinally and recreationally by humans for thousands of years, this event marked the beginning of the modern era of medicinal opioids.[1] By the 1850s, the full chemical formula was well established, and—in combination with the invention of the hypodermic needle—morphine became the medicinal choice for a host of ailments. However, its use became problematic when a lack of good surgical and medical options led to overuse. By the early 1900s, there was full-scale international recognition of the potential lethality and morbidity of opioid addiction. Subsequently, in 1912, the United States and many other countries signed the International Opium Convention, which controlled the import, manufacture, and sale of morphine, drastically reducing its consumption.[1,2]

Many believe that the modern opioid epidemic started in the 1990s,[3,4] with a tenacious movement to improve the evaluation and treatment of non-cancer pain.[5-7] At the height of the movement, the Joint Commission revamped their pain-management standards requiring organizations to perform regular systematic assessments of pain (ie, pain on a 10-point scale).[8] Shortly thereafter, Center for Medicare and Medicaid Services (CMS) began reimbursing physicians and hospitals directly or indirectly on pain control. These factors were compounded by the aggressive advertisement of new types of opioids, ultimately leading to a 4-fold increase in prescription opioid sales in the United States from 1999 to 2014.[3,9,10] Consequently, overdose deaths involving prescription opioids rose by a factor of 5 during the same time period.[11] At present, the United Nations attributes 76% of addiction-related deaths worldwide to opioids, singly or in combination with other drugs.[12]

The United States has long led the world in opioid consumption with 66.5 opioid prescriptions per 100 people.[13] Opioid prescriptions are a dominant risk factor for developing substance-use disorders,[14] with almost 30% of patients prescribed opioids for chronic pain misusing them and up to 12% developing opioid-use disorders (OUDs).[15] Almost 80% of people in the United States who went on to use heroin regularly (an injectable opioid associated with significant potency, comorbidity, and

lethality) started their addictions with prescription opioids.[16]

An OUD is defined by 11 diagnostic criteria, occurring over a 12-month period. Symptoms include taking more of the opioid than intended; failed attempts to stop the opioid; excessive time spent obtaining the opioid; cravings for opioids; failure to fulfill obligations; repetitive interpersonal conflicts; giving up important things for the opioids; using opioids in hazardous situations; and using opioids despite knowing the substance is causing significant emotional or physical consequences, tolerance, and withdrawal. Relative severity (mild, moderate, and severe), is defined by the relative number of symptoms that an individual has.[17]

Certain factors increase the risk that an individual started on an opioid will develop an OUD.[18] This can be difficult to predict, but prescribers can use tools such as the Opioid Risk Tool[19] to help them identify a patient's risk level prior to and during opioid therapy. Opioid Assessment for Patients with Pain (SOAPP) (PainEDU, Inflexxion, Inc., Costa Mesa, CA) can also be used before initiation of long-term opioid therapy to predict which patients may exhibit aberrant medication behaviors. The Current Opioid Misuse Measure (COMM) (PainEDU, Inflexxion, Inc., Costa Mesa, CA) may serve as a useful tool to identify patients currently on long-term opioid therapy who may be exhibiting behaviors associated with misuse/abuse of opioid medications.[20]

An OUD can be difficult to diagnose in general practice settings. Even when it is diagnosed, it can be unclear what the next best treatment option should be. Screening, Brief Intervention, and Referral to Treatment (SBIRT) training can be helpful in the referral process.[21,22] Even without formal SBIRT training, it is recommended that a provider refer individuals suspected of having OUDs to addiction programs for a complete assessment. However, a medical provider's role should not end there. After a referral, Centers for Disease Control and Prevention (CDC), National Institute of Drug Abuse (NIDA), and Substance Abuse and Mental Health Services Administration (SAMSHA) have all indicated that providers have an important role in augmenting psychotherapeutic/psychosocial interventions by expanding medication-assisted treatment (MAT) for OUDs.[23] Despite broad recognition of the importance of MAT, it is estimated that only 11% of patients with an opioid use disorder are prescribed Food and Drug Administration (FDA)-approved medications for the disorder. Three medications for treatment of OUDs are approved by the FDA.[24,25] Each of these medications has advantages and disadvantages compared with the others. This article will help providers better understand MAT options for OUDs and how to use these options most effectively.

NALTREXONE

Background

Naltrexone (N-cyclopropylmethylnoroxymorphone) was synthesized by Blumberg et al in 1965.[26] Synthetically derived from the opium poppy, it acts as a blocking (antagonist) agent rather than an activating (agonist) agent. Furthermore, it has a longer duration of action, greater potency, and more oral bioavailability than naloxone, the other clinically available opioid antagonist, which makes it ideal as an opioid blocking agent for the treatment of OUDs.[27] Naltrexone was unique in that it was brought to market through a public/private partnership as one of the first official actions of NIDA.[28] It is FDA approved for the treatment of opioid and alcohol dependence and for the blockade of the effects of exogenously administered opioids in adults.[29-32]

Benefits

Some argue that because naltrexone blocks opioid receptors it works primarily as a deterrent to further use rather than as an anticraving medication. A study by Sullivan et al showed that some individuals maintained sobriety even better after "testing" the blockade.[33] Medication-benefit studies have shown that, if taken as intended, it does increase the chance of sobriety and decreases risk of overdose.[34-36] Therefore,

motivation for abstinence appears to be a key component. This is further evidenced by improved rates of compliance in highly motivated upper middle-class individuals,[37] health care professionals,[38,39] and inmates on work release.[40] Naltrexone has no abuse potential, no street value, and neither tolerance nor dependence develops.[41] Naltrexone is thought to be relatively safe for long-term treatment but can cause elevations in liver enzymes. However, it can still be used with close monitoring even with liver impairment.[42-44]

Challenges

One of the biggest challenges with naltrexone is getting patients to take it regularly enough to have it be effective.[35] A Cochrane review in 2011 showed no significant improvements in opioid abstinence or reincarceration rates for individuals using oral naltrexone.[31] This poor assessment was largely driven by poor compliance with the medication. Naltrexone study results have always been beleaguered by low adherence to the medication and poor retention in treatment. Some believe this to be related to the nonreinforcing nature of the medication and lack of incentives to continue a medication that primarily blocks the effects of opioids.[45-48] This theory is supported by the fact that there are even lower naltrexone retention rates for patients who used re-enforcing medications, such as buprenorphine and methadone, before naltrexone.[49]

Prescriptions/Administration

Naltrexone has a high affinity to mu (μ)-opioid receptors. Common dosing strategies for opioid use disorder include 50 mg per day (can start with 25 mg daily for a few days to mitigate side effects).[30,31] A typical daily dose (50 mg) will block the pharmacologic effects of 25 mg intravenous (IV) heroin up to 24 hours, with increasing doses extending the duration.[50] Peak levels of naltrexone and its major metabolite 6 beta (β)-naltrexol are reached 1 hour after the first dose.[32]

In an effort to improve compliance, there has long been a push to develop long-acting "depo" formulations. Once-monthly–dosed injectable extended-release naltrexone (Vivitrol, Alkermes Corp., Dublin, Ireland) has been FDA approved for the treatment of OUDs.[51] Initial studies were quite promising, showing superiority in patient sobriety over oral naltrexone.[52-54] Its primary benefit over oral naltrexone is that it eliminates the need for daily compliance to a structured medication regimen. It is injected once a month (typically in a clinic) and provides a relatively constant level of bioavailable naltrexone to the patient.[55] A recent study (Extended-Release Naltrexone vs Suboxone Trial [X:BOT]) directly compared long-acting injectable naltrexone with buprenorphine/naloxone (suboxone) and showed injectable naltrexone appears to be as efficacious at 6 months as buprenorphine after patients have been successfully detoxified. The study points out that early drop rates are much worse with naltrexone than buprenorphine/naloxone, but it appears that, once fully implemented, injectable naltrexone is beneficial. When both medications were taken as prescribed, days abstinent, negative urine tests, and time-to-relapse were comparable.[56]

However, a recent meta-analysis of extended-release injectable naltrexone concluded that "Many individuals intending to start extended-release naltrexone (XR-NTX) do not and most that do start XR-NTX discontinue treatment prematurely, 2 factors that limit its clinical utility significantly. XR-NTX appears to decrease opioid use but there are few experimental demonstrations of this effect."[57] Somewhat counter to this assessment, is a study comparing insurance data that showed, in a real-world clinical setting, injectable naltrexone, buprenorphine, and oral naltrexone had similar rates of discontinuation 30 days after starting treatment.[24] Authors of the X:BOT study speculated that difficulties in extended-release naltrexone inductions could be driven by the need for complete detoxification off opioids before naltrexone use. This necessity is an inherent limitation related to the blocking effects of the medication.[56] Conversely, buprenorphine can be used to assist with opioid detoxification (alleviating withdrawal

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symptoms), allowing earlier inductions. However, there may also be a role in use of low-dose naltrexone to assist with the induction of long-acting naltrexone.[58] Indeed, it appears that if buprenorphine induction and extended-release naltrexone induction are both implemented around the same time frame after complete detoxification, they have similar rates of implementation success.[58-60]

Naltrexone implants are a newer way of increasing compliance. Although not yet available in the United States, clinical trials have shown superior treatment retention with a naltrexone implant compared with oral naltrexone and a placebo implant,[61,62] with reported abstinence rates of 74% to 79% after 12 weeks.[63]

BUPRENORPHINE

Background

Buprenorphine hydrochloride (HCl), can be derived from thebaine. It is a semisynthetic opioid, characterized as a partial agonist at the μ receptor and a full antagonist at the kappa (κ) receptor. At the μ receptor, it has low activity but high affinity.[64,65] Buprenorphine was discovered in 1966, by John Lewis, a doctoral student of Sir Robert Robinson, Nobel Prize-winning discoverer of the structure of morphine.[65,66] Because of its high receptor affinity, buprenorphine acts as both a stimulator and a blocker of the μ opioid receptor. This blockade appears to be dose dependent and can be overcome with increased doses of other opioids.[67,68]

Benefits

The clinical efficacy of buprenorphine for the treatment of OUD has been well established.[69-72] Buprenorphine compliance is quite high and is associated with improved rates of sobriety, decreased criminal activity outcomes, and reduction in accidental overdoses.[34,72]

Challenges

Despite its relative safety and efficacy in the treatment of OUDs, its widespread use continues to be relatively modest. This may be due to some restrictions on administration. The induction process (getting started on buprenorphine) can sometimes be a hurdle for patients and primary care providers because induction typically requires office-based dosing and then monitoring with a same-day return appointment. However, home-based induction options have been explored with some success.[73,74]

Another challenge with buprenorphine is the length of time needed for treatment. Indeed, there is no clear discontinuation time frame, and evidence suggests that individuals do not do well after tapers.[75]

Another concern has been the potential for abuse of buprenorphine, which is increasing with the increasing use of buprenorphine. Research has demonstrated that buprenorphine does exhibit positive-reinforcement properties (which encourages compliance) similar to other opioids, and its reinforcing effects are especially prominent when injected.[76] However, in countries where opioid addiction is more common, studies suggest the majority of diverted buprenorphine is used for "therapeutic" purposes such as alleviating withdrawal and reducing the use of other opioids.[77,78] On the other hand, it appears that in countries with less access to opioids in general, buprenorphine can become the dominant opioid of abuse.[79] In Australia, 32% of opioid addicts had injected buprenorphine in the past 3 months. In Finland, 68% of opioid addicts had injected buprenorphine; 73% were also using it to "treat" their addictions. In Sweden, 89% reported illicit use of buprenorphine, with 43% admitting IV use for intoxication and 87% for alleviation of opioid withdrawal (some using for both purposes). In the United States, 49% reported illicit use in the past; however, 97% of those who used illicitly reported that it was mainly to relieve opioid withdrawal.[77]

Preparation/Administration

Buprenorphine's unique chemical properties increase its safety profile. For example, administration of 32 mg buprenorphine produces no greater respiratory depression than 16 mg buprenorphine.[64] However, when combined with respiratory depressants,

such as benzodiazepines and alcohol, there appears to be an increased risk of overdose and death.[80,81] The average dose of buprenorphine is 16 mg daily, with 24 mg per day as the most common maximum dose. It comes in several formulations (most commonly in films and dissolvable tablets). Buprenorphine has poor bioavailability when taken orally and must be dissolved sublingually. This allows coadministration with naloxone (not absorbed sublingually) to prevent the buprenorphine from being injected (an abuse deterrent).[82]

In 2000, Congress established the Drug Addiction Treatment Act of 2000 (DATA 2000), which established legal permission for physicians to prescribe buprenorphine for the treatment of OUDs (under certain conditions). The act dictated that prescribers must meet certain educational requirements and then must apply for a special designation on their Drug Enforcement Administration (DEA) license (known as an "X" number) to prescribe buprenorphine for addiction treatment. During the first year following the date of notification of this designation, physicians may treat up to 30 patients; during the second year, they may treat up to 100 patients. After prescribing buprenorphine for 100 patients over a year or longer, a physician may apply to the DEA for permission to increase the prescription limit to 275 (per recently amended guidelines). SAMHSA has laid out guidelines for the administration of the buprenorphine. Patients are typically provided a 1-week supply of medications for a designated period of time and then a 2-week supply. After demonstrating trustworthiness and sobriety, patients can receive monthly supplies of the medication. This process is much less restrictive than the daily administration required through methadone programs.[83]

Several new forms of buprenorphine are now available, including implantable and injectable formulations. Both have shown promise in improving compliance and efficacy comparable with sublingual dosing. Furthermore, they have the potential to eliminate diversion and abuse.[84]

METHADONE

Background

In 1964, Vincent Dole began a research program at Rockefeller University to pilot the use of methadone to treat opioid addicts.[85,86] Fully aware of the addictive properties, they emphasized the "harm-reduction" effects of the medication describing it as "block[ing] the normal reactions of addicts to heroin and permit[ting] them to live as normal citizens in the community."[87] In 1966, the university committee overseeing his work concluded that a "significant number of patients through methadone maintenance management have attained a reasonable degree of social rehabilitation. Their dependence has not been ameliorated nor has it been treated, but it may have been "controlled;" thus, the patient and society have gained."[88] This ultimately led to the Narcotic Addict Treatment Act of 1974, in which methadone was approved for opioid addiction treatment under the strict supervision of opioid treatment centers (methadone treatment clinics).[89,90]

Benefits

Methadone administered in methadone maintenance programs reduces the use of illicit opioids, overdose death rates, criminality, and allows patients to improve their health and social productivity.[91] In addition, enrollment in methadone maintenance reduces the transmission of infectious diseases, such as hepatitis and HIV, associated with heroin injection.[90,92] The principal effects of methadone maintenance are to relieve narcotic craving, suppress the withdrawal syndrome, and block the euphoric effects associated with heroin.[90] Since implementation, it has been shown to be the most successful long-term treatment option for severe OUD.[89] Furthermore, supervised administration of methadone has been shown to improve retention in chemical dependency (CD) treatment programs and may even reduce suicidality in comorbidly depressed addicts.[92-95] Methadone maintenance through formal

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methadone clinics has been found to be relatively safe (safer than illicit use).[34,96]

Challenges

There is significant controversy around the idea of giving a potent long-acting opioid to an opioid addict.[90,91] Because of its full opioid agonist properties, abuse is possible, and with its long half-life, it carries a higher safety-risk profile than other MAT options. Individuals have been reported to take their methadone at their clinics and then add illicit opioids to the methadone throughout the day, which increases the risk of death.[97] Methadone alone can be deadly with a lethal dose considered to be 70 mg to 75 mg for nontolerant individuals (average maintenance doses 80 mg to120 mg),[98] and it has an increased risk for accidental overdoses compared with other medications that treat OUDs.[34] Treatment length is for an "indefinite" period of time, as methadone maintenance is a "corrective but not a curative" intervention for opioid addiction.[91] Methadone continues to have a relatively high street value[99] and therefore may be diverted even when prescribed as a part of methadone clinic treatment.[100]

Preparation/Administration

Methadone is a synthetic μ-opioid receptor agonist, typically administered as a racemic mixture of (R)- and (S)-methadone, with the (R)- form primarily responsible for most biological effects. Methadone has a very slow onset of action and a long elimination half-life (24 to 36 hours).[101] At a given dose, methadone plasma levels can vary extensively among individuals.[102] Methadone can activate the NMDA receptor and inhibit serotonin and norepinephrine reuptake (similar to antidepressants).[102] Methadone comes in several preparations. It is most commonly prescribed as a tablet for pain but can be administered IV.[103] Liquid formulation is the most common and cheapest dose strategy for methadone clinics, and tablet formulations are the most common prescription formulations in pain clinics. A majority of patients require 80 mg per day to 120 mg per day of methadone or more to achieve the desired effects, with lower doses shown to be typically less effective.[90,91]

Levomethadyl acetate (LAAM) is a longer-acting derivative of methadone, which allows 3-times-a-week dosing. It is no longer sold in the United States owing to cardiac concerns (prolonged QTC interval)[104] despite some direct comparison data indicating few differences in LAAM and methadone on safety outcomes.[105,106]

Methadone clinics attempt to circumvent the abuse potential and safety risk through strict structure and regulation of administration. For the first 3 months of treatment, patients are typically required to present at the methadone treatment program 6 days a week (with 1 take-home dose). Once they have established their intent to participate in the program faithfully, they are eligible for 3-day-a-week clinic dosing and 4 take-home doses. After 1 year, patients can get 6 home doses, presenting to the clinic only 1 day a week. Throughout their treatment, these patients undergo supervised urine drug screenings and breathalyzer tests at each visit. It appears that these safety regulations are at least somewhat effective, as more methadone overdose deaths are associated with illicit methadone use than prescribed or methadone clinic use.[107] Programs may vary in their efficacy, depending on dosage of prescribed methadone. They can also vary in efficacy, based on use of support services, monitoring of the use of nonprescribed drugs, diversion of methadone, and opportunities for treatment of co-occurring disorders.[90,91]

COMPARISON

All 3 FDA-approved medications for the treatment of OUDs (naltrexone, buprenorphine and methadone) appear to offer some evidence of efficacy (Table).[108] Long-term data are somewhat limited for the 3 medications, but 1 study of individuals randomly assigned to either methadone or buprenorphine/naloxone showed that 33.2% had achieved 5-year abstinence from heroin. Unfortunately, only 20.7% had remained abstinent from both heroin and other opioids. The 2 treatment groups were compared, and it was shown

TABLE. Comparison

Parameter (characteristic)	Buprenorphine	Methadone	Naltrexone
Pharmacologic action	Partial agonist at the μ-opioid receptors and an antagonist at κ-opioid receptors	Full opioid agonist	Full opioid antagonist
FDA-approved clinical indication	Opioid-use disorder, pain	Opioid-use disorder, pain	Opioid-use disorder, alcohol-use disorder
Route of administration	Buccal film, subcutaneous extended-release injection, subdermal implant, transdermal patch	Oral, parenteral	Oral, intramuscular
Therapeutic dose	Orally: 8 to 16 (max 24) mg; subcutaneously monthly: 100 mg to 300 mg; subdermal implant: 74.2 mg every 6 months; transdermal patch: maximum 20 μg/h; replace every 7 days	80 mg to 120 mg daily	Orally: 50 mg daily or 100 mg orally every other day; or 150 mg orally every third day
Frequency of administration	Orally: daily, every other day, 3 times a week; subcutaneously: monthly; patch: weekly; implant: every 6 months	Daily	Orally: daily, every other day or every third day; intramuscularly: monthly
Protein binding	96%	85% to 90%	21%
Bioavailability	Buccal film: 46% to 65%; transdermal: 15%	Oral: 36% to 100%	5% to 40%
Half-life elimination	Buccal film, subdermal implant; transdermal patch: 24 to 48 hours; subcutaneous extended-release injection: 43 to 60 days	8 to 59 hours	4 to 13 hours
Onset of action	10 to 30 min	30 to 60 min	Up to 3 day; following 100-mg oral doses for 3 days (96% on day 1, 87% on day 2, 46% on day 3)
Duration of action	6 hours	5 to 8 hours	50 mg: 24 hours; 100 mg: 48 hours; 150 mg: 72 hours; intramuscularly: 4 weeks

Adapted from *Medications for Opioid Use Disorder. Treatment Improvement Protocol (TIP) Series 63.*[108]

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that, after 5 years, opioid use at follow-up was higher among participants randomized to buprenorphine relative to methadone. This discrepancy was attributed largely to less CD treatment participation among participants randomized to buprenorphine than methadone. However, both were better than with the no-treatment group, and mortality was not different between the 2 groups.[93,94] Five-year outcome data for naltrexone are not available, with most studies focused on data over a 6-month period[57,94,109] with a few studies looking up to a year showing some positive retention in the right populations with the right support.[110,111] Research demonstrated an association of naltrexone injections with long-term recovery among nurses (2 years), but, again, this group was highly motivated, a generally higher socioeconomic status cohort, and heavily involved in a structured professional monitoring program.[112] Given such robust response rates by this nursing cohort, it raises the question why this level of oversight and support is not more broadly used in the treatment community.[113] Generally speaking, all 3 medications offer some benefit in maintaining sobriety, and each offers some advantages over the others.

Naltrexone, for example, has no discernible addiction potential. Therefore, it could be considered for individuals who have struggled with methadone and buprenorphine abuse in the past. It also could be considered an option for patients who have not tolerated the side effects of methadone and buprenorphine. Compliance with daily naltrexone is a challenge, which can be somewhat overcome by injectable formulations. As noted, it appears that naltrexone is most effective in highly motivated populations.

Buprenorphine is associated with higher levels of compliance than naltrexone, leading to improved outcomes, and, if given at consistent dosing (greater than 16 mg per day), the compliance/retention rate is similar to methadone.[71,114,115] This is likely because of its opioid receptor partial agonism, which is not only reinforcing while taking but leads to withdrawal symptoms if missed. Therefore, buprenorphine offers an advantage in a modestly motivated population. Unfortunately, this partial agonist property can also lead to potential for abuse. Furthermore, buprenorphine can only be prescribed through physicians with specific DEA registration numbers. Access to buprenorphine-waivered prescribers can be a challenge in some areas of the country, which could limit its accessibility. Buprenorphine will cause withdrawal symptoms if discontinued. Therefore, it can be more difficult to discontinue than naltrexone. However, it is thought to be easier to withdraw from than full agonists such as methadone.[116] Although the office-based buprenorphine visits allow for autonomy over methadone clinics, risk associated with overdose in conjunction with other substances should be considered. American Society of Addiction Medicine (ASAM) recommendations indicate that buprenorphine may not be a good option for patients with active alcohol-, sedative-, hypnotic-, or anxiolytic-use disorders. They also recommend extreme caution when prescribing these substances to individuals taking buprenorphine.[70]

Methadone has the greatest evidence for long-term sustained abstinence, as it has been available the longest. However, it requires the most structure such as daily administration; counseling; basic medical testing; and access to vocational, medical, and psychiatric resources; and is generally recommended for individuals who would benefit the most from that structure.[70,117] As noted, daily administration can be a burden for individuals.[118] Despite the burden, methadone appears to have the best treatment retention of the 3 medications.[119] However, methadone's full agonist properties offer the greatest abuse potential of the three medications (which is only somewhat ameliorated by the structure of the methadone clinic program). Finally, methadone appears to be the most expensive to administer from a societal standpoint of the 3 options because of the amount of support required in its administration.[60] However, total health care costs (medication, inpatient, outpatient, and pharmacy costs) are significantly lower for patients who receive a medication for opioid dependence vs patients who do not.[60]

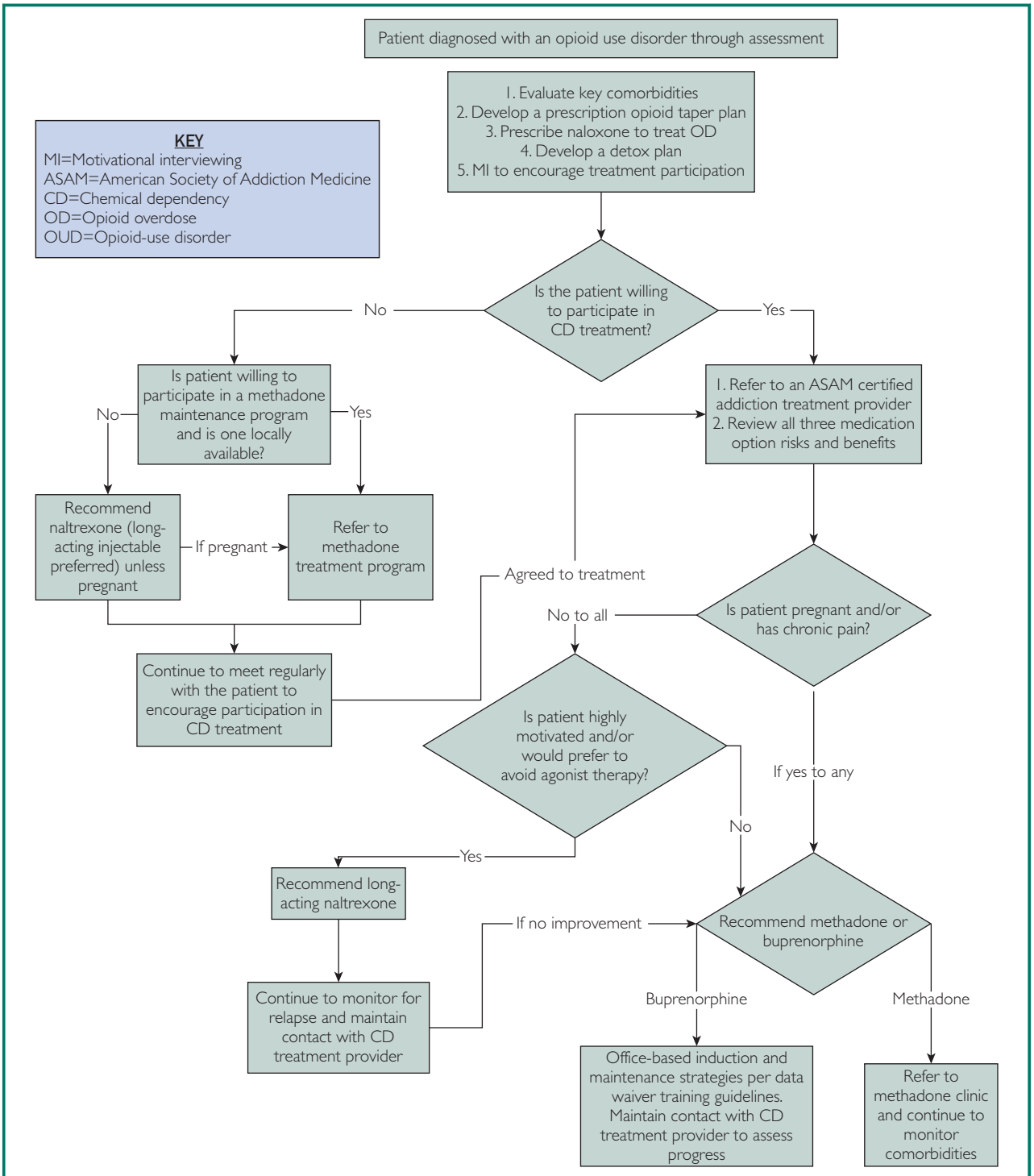

FIGURE. Patient diagnosed with an opioid-use disorder through assessment.

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ALGORITHMIC APPROACH TO CHOOSING THE OPTIMAL THERAPY

When choosing the right medication for your patient with OUD, special considerations should be given to availability of treatment options, safety and side effect profiles of each medication, and previous patient/provider experience. You should also consider the need for a close structured psychosocial support system; patients' preferences for treatment location, such as concerns about methadone clinics and associated stigma; patients' detoxification needs; and pain control in patients with comorbid chronic pain. The accompanying Figure contains an algorithm with recommendations based on clinical experience and current evidence cited in this paper. First, a clear diagnosis of a moderate-to-severe OUD, based on DSM 5 criteria[17] is important to establish. If there are any doubts about diagnoses, patients should be referred to more intensive evaluation (by addiction specialists) or CD treatment programs for multidisciplinary formal assessment. Once the diagnosis is made, we recommend an office visit focused on evaluating key comorbid conditions including, but not limited to, cardiovascular disease risk, head trauma, sexual-physical-emotional trauma, neuropsychiatric conditions, infectious disease, and comorbid substance use disorders. Developing a prescription opioid taper plan, if they are currently prescribed opioids, is also essential. If the patient needs opioid detoxification, developing a detoxification plan using local detoxification resources or office-based ambulatory detoxification through supportive medications is warranted. All patients on opioids, or with OUDs, should have, in their possession, naloxone to treat potential opioid overdoses. This prescription and recommendation should also be extended to their families, friends, and significant others. An appointment focused on the brief intervention and referral to treatment portions of SBIRT should be initiated. Ongoing use of motivational interviewing strategies should be implemented to encourage participation in treatment. If the patient is willing to participate in formal CD treatment, a referral to treatment should be made, and all medication options should be discussed. If the patient is willing to fully detoxify off opioids and is highly motivated or would prefer to avoid agonist therapy for personal/professional reasons, long-acting injectable naltrexone treatment should be considered. The decision between buprenorphine and methadone should be discussed thoroughly with the patient. If the patient has chronic pain and/or is pregnant, methadone or buprenorphine should be the first consideration. Both have advantages and disadvantages, as noted here, and good compliance with either option can often be predicated on patient preference. If the patient is unsuccessful with one or the other medication, the alternative medication should be tried. If the patient is initially unwilling to participate in an office-based or other CD treatment program, naltrexone (long-acting injectable) should be considered, along with ongoing motivational interviewing to encourage participation in CD formal treatment. If the patient is not successful on naltrexone or is pregnant, the patient should be referred to a methadone treatment program with ongoing visits to assess comorbidities and motivational interviewing to encourage formal treatment. If a patient returns to use after initial success (relapse), this algorithm can be repeated as often as necessary starting with referral for CD treatment and recommendation for reinitiation of previously successful medications or use of alternative medications. If a patient has struggled with buprenorphine side effects, dropped out or abused it, or continued to use opioids while on it, then methadone treatment through a methadone maintenance program should be strongly encouraged. If a patient has succeeded with MAT, the medication should be continued for as long as necessary. Successful use of sublingual buprenorphine is generally a good prognostic sign for injectable/implantable buprenorphine, and these formulations should be strongly considered given their decreased potential for abuse. Some patients, for myriad reasons, may prefer to try to

detoxify off opioid agonists and continue with psychosocial treatment plus injectable naltrexone. Patients requesting to taper off their MAT should be closely monitored. Providers should assist with the safe and gradual taper off medications and be prepared to assist with reinitiation of medications, if necessary.

SPECIAL CONSIDERATIONS

Pregnancy

Naltrexone is typically not recommended during pregnancy because of detoxification concerns and an unknown safety profile in pregnancy. Opioid detoxification in pregnancy is not recommended because of associations of fetal exposure to fluctuating levels of opioids with repeated withdrawal that can harm placental function, with subsequent decreased neonatal birth weight, preterm labor, fetal convulsions, and even fetal death, as well opioid drug-use relapse and resumption of high-risk behaviors such as intravenous drug use and criminal activity.[120,121] The standard of care for pregnant women with OUD is to initiate MAT with either methadone or buprenorphine.[122] Buprenorphine monoproduct was recommended over the buprenorphine/naloxone formulation because of risks of naloxone exposure and withdrawal from misuse, but these have not been supported by the available data.[122,123] Buprenorphine as a single agent has been shown to have shorter treatment duration, less medication needed to treat neonatal abstinence syndrome (NAS) symptoms, and shorter hospitalizations for neonates compared with methadone.[123] However, methadone remains the primary suggested treatment for severe OUD during pregnancy.[124] In 2013, the American Academy of Pediatrics cited well-established data confirming minimal transmission of methadone and buprenorphine in breast milk. Subsequently, they asserted that appropriate medically monitored use of methadone and buprenorphine should not impair breast feeding if the mother so desires.[60,125,126] Despite good evidence of their efficacy, and no nefarious long-term fetal consequences,[127] both buprenorphine and methadone are, unfortunately, still underused during and after pregnancy.[124]

Adolescence

Adolescents with severe OUD are recommended to receive MAT by the American Academy of Pediatrics; however, research on these medications in adolescents is sparse.[128-130] Owing to regulatory issues, most methadone treatment programs do not accept patients younger than 18 years of age. Naltrexone is certainly an option but is limited by compliance. Furthermore, there are very few data supporting its efficacy in this population.[131] Buprenorphine is FDA approved for opioid addiction in persons 16 years and older. Several studies have shown benefit in adolescents with severe OUD.[132-134]

Perioperative Use

Recommendations related to surgery while on medications to address OUD typically suggest discontinuation of oral naltrexone use 72 hours before elective surgery and continuation of methadone with adjunctive opioids as needed. Treatment with buprenorphine tends to be a bit more complicated, given its agonist/antagonist properties. Options include continuing a home regimen, daily or in divided doses (3 or 4 times a day), with additional buprenorphine doses for breakthrough pain; stopping buprenorphine at 5 to 3 days preoperatively and converting to a traditional opioid; or continuing buprenorphine while using traditional opioids as needed, while maximizing nonopioid co-analgesics and regional anesthesia. A recent literature review suggests continuation of buprenorphine through surgery.[135]

Pain

Naltrexone has no indication for pain. However, methadone and buprenorphine are both FDA approved for the treatment of

pain. It is important to note that restrictions associated with buprenorphine and methadone prescriptions (ie, special DEA number and treatment in special clinics) are specific to use of these medications for treatment of OUDs, not pain. Both medications can be prescribed without restrictions for pain. Patients with opioid addiction who receive prescription opioids for treatment of chronic nonmalignant pain present a therapeutic challenge. In one study, 54 patients with chronic pain and opioid addiction were randomized to receive methadone or buprenorphine/naloxone. At the 6-month follow-up, both groups reported improvements in pain with methadone showing slightly better results.[136]

CONCLUSIONS

We are currently in the midst of an opioid epidemic caused by many factors including overzealous use of medications, availability of potent opioids (both legal and illegal), and pervasive social expectations that all pain can be eliminated. We clearly cannot medicate our way out of the problem, but we have the opportunity to mediate the problem through more judicious use of prescription opioids. For those patients who develop OUDs, the research shows that MAT can help, but it is currently underused. Along with drug counseling, naltrexone, buprenorphine, and methadone all have a place in the treatment armamentarium for opioid addiction. The current opioid crisis is an opportunity to change the way we think and do things, moving beyond a medication-only approach to a future when we will establish a generalizable framework that uses the full repertoire of responses and resources we have at our disposal.

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Abbreviations and Acronyms: **CD** = chemical dependency; **FDA** = Food and Drug Administration; **IM** = intramuscularly; **IV** = intravenously; **MAT** = medication-assisted treatment; **NIDA** = National Institute of Drug Abuse; **OUD** = opioid-use disorder; **SBIRT** = screening, brief intervention, and referral to treatment; **SAMSHA** = Substance Abuse and Mental Health Services Administration; **X:BOT** = extended-release naltrexone vs suboxone study; **XR-NTX** = extended-release naltrexone

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