Medications for Opioid Use Disorder: A Guide for Physicians

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Physicians should prescribe responsibly and hold their patients accountable. We should not enable addiction—we should promote recovery.

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Abstract

The opioid crisis shaped the national public health dialogue for some time now. A "call to action" is a strong and resounding cry from multiple disciplines. This piece intends to detail the nuts and bolts of prescribing medications used for the treatment of opioid use disorder. The underlying message here is that opioid use disorder is a chronic, treatable illness and physicians of all specialties have a responsibility to not turn a blind eye.

Forward

This article grows from the 1st Annual Larry Lewis Symposium held at Washington University School of Medicine in St. Louis, Missouri, in August 2017.[1] The symposium was a scientific forum addressing the current opioid epidemic. This is the fifth essay in this series.

Overview

Evidence clearly demonstrates that abstinence programs are not the standard of care for opioid use disorder (OUD),[2,3] and are an unacceptable recommendation from any medical professional. Abstinence-only, or no medications, when treating OUD has a higher rate of continued illicit opioid abuse and lower rate of retention in treatment. Patients on medications are less likely to die of an overdose death compared to those not taking medications.[4] Medication assisted therapy or medication for addiction treatment (MAT) uses pharmaceuticals to combat the underlying neurobiological changes that occur in opioid addiction.

An important first step is to identify a patient with OUD.[5] The DSM 5 describes OUD as a problematic pattern of opioid use leading to clinically significant impairment or distress. There are 11 criteria (Figure 1), and a patient must meet two to three criteria to qualify for a mild disorder; more than six is a severe disorder. As you might imagine, a patient may not readily reveal this information to their doctor, especially if their doctor is the one prescribing the opioids. Further, the nature of addiction comes with some denial of the problem and it is commonplace to have several attempts at initiation of treatment before a patient accepts that they need help. Notably if the patient is taking an opioid as prescribed, tolerance and withdrawal are not criteria for an OUD.

If concerned for an OUD, a physician should utilize concepts of motivational interviewing to discuss substance use with their patient. Expressing empathy builds rapport and encourages a patient to be more forthcoming regarding their struggles. In clinical practice and experience, this translates to increased identification of OUD. When a patient has an OUD, there is a discrepancy between their values or goals and their actions or behavior, i.e., what they say they want compared to what is occurring in their life or what they are doing. The role of the physician is to develop this discrepancy with the patient. In motivational interviewing, recommendations are to avoid arguments

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following occurring within a 12 month period		
1	Opioids are often taking in larger amounts or over a longer period of time than was intended	AMOUNT
2	There is a persistent desire or unsuccessful efforts to cut down or control opioid use	CRAVING
3	A great deal of time is spent in activities to obtain the opioid, use the opioid, or recover from its effects	TIME
4	Craving, or a strong desire or urge to use opioids	CRAVING
5	Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home	RELAPSE
6	Continued opioid use despite having persistent or recurrent social or interpersonal problems caused by or exacerbated by the effects of opioids	DYSFUNCTION
7	Important social, occupational, or recreational activities are given up or reduced because of opioid use	
8	Recurrent opioid use in situations in which it is physically hazardous	HARM
9	Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that's likely to have been caused or exacerbated by the substance	INSIGHT/ JUDGEMENT
10	A need for markedly increased amounts of opioids to achieve intoxication or desired effect / A markedly diminished effect with continued use of the amount of opioid	TOLERANCE
11	The characteristic opioid withdrawal syndrome / The same or a closely related substance is taken to relieve or avoid withdrawal symptoms	WITHDRAWAL

Figure 1. DSM 5 criteria for OUD[6]

or direct confrontation. Information from collateral sources is a useful tool in diagnosing OUD. Recognizing that time is limited especially for a primary care physician who has many other medical problems to address in a short appointment slot, there is certainly room for referral to addiction professionals or psychiatry for a more intense diagnostic evaluation. However, the scope of the opioid epidemic is vast; opioid overdose caused more deaths in 2016 than those caused by motor vehicle crashes.[7] As such, it is not possible for one specialty of medicine to handle this. It will require a multidisciplinary approach, and each physician needs to take ownership of their role here.[1]

After identifying and establishing a diagnosis of OUD, the next logical step is to facilitate treatment. There are currently three FDA approved medications for the treatment of OUD: methadone, buprenorphine and naltrexone. These medications are superior at reducing illicit opioid use over no medication in randomized clinical trials.[2,3,8] Buprenorphine and methadone are demonstrated to reduce mortality from opioids.[4,9–11]

With regards to each of the three medications, we shall review strategies, shall review prescribing information, and offer clinical wisdom. It should be noted that there is no "one-size-fits-all" approach to treatment, nor is there a "typical" patient. Addiction is a complex pathology with a multifactorial etiology, therefore its treatment must reflect that.

Methadone

Our "old faithful" in the treatment of OUD is methadone. Methadone is listed as a World Health Organization essential medication. It is the oldest of the three medications for OUD, and thus has the largest evidence-base, with large multi-site studies from all over the world describing its effectiveness in reduction of illicit drug use, retention in treatment, reduction of death by overdose, reduction of cellulitis, HIV and Hepatitis C infections, and reduced criminal and HIV high-risk behavior.[12]

Methadone as treatment for OUD is restricted to the setting of a federally-certified and -accredited opioid treatment program (OTP). There are approximately 1,500 OTPs in the United States.[12] It is dispensed in these settings in a liquid formulation. OTP admission criteria includes patients over age 18 and diagnosis of an OUD for at least one year. These can be waived for pregnant women and patients recently released from incarceration.

Initially, patients are required to go to the OTP daily. Importantly, methadone can be initiated in hospitalized inpatients even if the hospital is not an OTP.

Chemistry and Mechanism of Action

Methadone is a Schedule II controlled substance and is a full agonist at the mu-opioid receptor. Its bioavailability and half-life are highly variable between individuals. The average half-life is 24 hours (but can range from 8 to 59 hours).[13] Steady-state concentration is reached in about five days. The peak serum concentration is about two to four hours after the dose is administered, so it is necessary to monitor for sedation around that time. There is no ceiling effect, and it is metabolized by CYP450 3A4 enzyme. Initial dosing and dose increases are times when methadone causes respiratory depression and must be done with great caution and daily monitoring as rapid escalation can lead to respiratory depression. The goal of the first weeks of treatment is to relieve withdrawal but avoid oversedation and respiratory depression.

Risks and Adverse Effects

Of the three medications, methadone has the most potential for drug-drug interactions. 3A4 inhibitors will cause methadone accumulation. These include antacids (cimetidine), antibiotics, antifungals (erythromycin, ciprofloxacin, fluconazole) and antidepressants (fluvoxamine, sertraline, paroxetine). 3A4 inducers increase its metabolism potentially resulting in methadone withdrawal and cravings for opioids. Common side effects include constipation, nausea, sweating, sexual dysfunction, drowsiness, weight gain, and edema.

Potential contraindications include allergy, acute asthma, patients with buildup of CO_2 from lung disease, and paralytic ileus. The risk of respiratory depression is highest in patients who are older, cachectic, have COPD, or with concurrent use of benzodiazepines, alcohol, or other sedatives. In these situations, patients should be treated with lower doses and with even more caution. A black box warning for QTc prolongation and torsades de pointes was issued in 2006.[14] Intake assessment should include screening for risk factors including a family and personal cardiac history, current medications, current use of methamphetamines or cocaine (both can prolong QTc), labs (to evaluate for low potassium or magnesium) and an EKG. When the QTc is between 450-500, discuss risks and benefits with the patient. If it is over 500, do not initiate methadone. If the patient is already on methadone, consider decreasing the dose, switching to a different medication and eliminating other medications that prolong the QTc.[15]

There is a risk of misuse, diversion, and accidental overdose with methadone which is why patients are initially required to go to an OTP every day. Patients should be strongly counseled about the risks of diversion and misuse, and about safe storage to prevent accidental overdose by a child, pet, or an opioid-naïve person.

When a patient prescribed methadone through an OTP is admitted to the hospital, it is necessary to call the OTP clinic to verify that the patient is in treatment, their dose, when the last dose was administered, and whether the patient has any take-home medications. Patients should be continued on their methadone while hospitalized unless it is medically contraindicated. The OTP should also be notified upon discharge so that they are aware of the patient returning for treatment.

Buprenorphine

Buprenorphine was initially discovered in 1966 as a structurally similar compound to morphine without incorporating some of its less desirable addictive properties. However, it was not until 1978 when Janski et al. discussed the role of buprenorphine as a treatment for OUD. In his subsequent work, Janski described buprenorphine as a medication with "unique pharmacology in man" with very little risk of dependence following chronic administration.[16] He described the search for a medication to treat analgesia and addiction which culminated in the discovery of buprenorphine. Interestingly, the Food and Drug Administration did not approve buprenorphine for the treatment of OUD until 2000.[17] In order to prescribe Buprenorphine, a prescriber must undergo an eight-hour approved training followed by applying for an "X-waiver" from the Drug Enforcement Agency (DEA). However, it can be dispensed in the emergency department or hospital without a waiver.

Chemistry and Mechanism of Action

Naturally produced endorphins activate mu receptors resulting in analgesia and euphoria. Heroin and other exogenous opioids activate mu receptors resulting in similar effects in addition to respiratory and central nervous system depression. Buprenorphine is a partial agonist resulting in a submaximal ceiling effect, thereby offering a therapeutic opportunity with a safety net to mitigate the ill effects of full agonists such as heroin. This dose dependent ceiling also curtails risk

of overdose which can occur with full agonists such as methadone. Importantly, children and pets can still develop respiratory depression from buprenorphine.[18] Another important chemical property of buprenorphine is its high binding affinity to opioid receptors. This prevents the positive reinforcement and euphoria that often occurs if full agonists are used concomitantly following buprenorphine induction, i.e. the patient injects heroin while using buprenorphine. The high affinity also explains how buprenorphine can precipitate withdrawal in a patient on opioids. If the patient is still under the effects of opioids (not in withdrawal) buprenorphine will outcompete the other opioid to bind at the mu receptor. However, since it is only a partial agonist, it will activate the receptor to a lesser extent than a full agonist resulting in withdrawal. This is otherwise referred to as the antagonist effect as a full agonist is displaced by the partial agonist with stronger affinity.[12] Practice guidelines recommend that patients are in early withdrawal prior to induction to significantly reduce this risk. Buprenorphine is also a potent kappa receptor antagonist. Its effect on kappa receptors produces significant mood benefits with studies exploring the use of buprenorphine as an antidepressant.

Formulations

Sublingual formulation of buprenorphine, used in addiction comes in tablet form (Zubsolv® with naloxone and Subutex® as buprenorphine alone) and sublingual film (Suboxone® with naloxone). While Buccal films are also available, they are not currently deployed in the treatment of OUD. The choice of formulation in clinical practice is one of patient and provider preference, although the combination yields an additional benefit of protection from improper use due to the antagonistic properties of naloxone. When administered sublingually, 50% of buprenorphine is immediately absorbed while none of the naloxone is absorbed.[17] When crushed and injected or insufflated, the naloxone becomes bioavailable and can displace buprenorphine resulting in immediate withdrawal from its antagonistic effects. This effect of naloxone is the primary reason for providers to prefer the combination of the two. The exception is in pregnancy where buprenorphine alone (Subutex®) is recommended, although more recent data questions this approach.[19] While subdermal implants, transdermal and injectable formulations are available in the U.S., they are mainly used for its antinociceptive properties. However, they were recently approved for OUD.[20]

Dosing Guidelines

It is critical for patients to be in withdrawal prior to "induction" or initiation of buprenorphine in order to avoid precipitated withdrawal. The Clinical Opiate Withdrawal Scale (COWS)[21] can assist with this quantifying the patient's degree of withdrawal. A typical first dose once the COWS score is greater than 6 is 4 mg for monotherapy or 4/1mg (4 mgs of buprenorphine with 1 mg of naloxone) for combination.[12] During this period, the patient's vital signs are typically monitored and they remains under observation. One to two hours later, another 4 mg dose may be administered with a usual max dose on day 1 around 8-12 mg of buprenorphine. On day 2, the first dose is typically the maximum dose of day 1 followed by an additional 2-4 mg depending on residual withdrawal symptoms with a typical maximal dose for day 2 being around 12-16 mg. By day 3, providers typically get to a maintenance dose of 16 to 20 mg at which almost all the opioid receptors are saturated limiting need for further increasing the dose, as was the practice prior to dosing studies. Maximum daily dosing is between 24-32 mg. More recent sources may recommend a more aggressive induction strategy. Home induction is also safe in the correct patient population.[22] Patients may prefer their dose be split and administered twice a day as opposed to methadone which is generally administered once a day.

Detoxification/Maintainence

The best available evidence for long-term sobriety from opioids rest with using buprenorphine for prolonged maintenance without arbitrarily stopping therapy against the patient's wishes. Studies comparing two and four-week detoxification using buprenorphine suggest superior rates with four weeks of taper with duration of taper being the strongest predictor of success.[23] In some clinical practices it is common to use buprenorphine primarily for detoxification from opioids. In this case, the objective is to alleviate individuals from withdrawal symptoms and treatment usually lasts days if not weeks. Naltrexone is often deployed in the transition from buprenorphine with evidence suggesting that such a combination will aid in relapse prevention in the long-term.[24] However, such rapid detoxification strategies do place most patients at an elevated risk of relapse and overdose. With regards to maintenance, most studies suggest that patients are more likely to stay in treatment and reduce relapse if they are maintained on buprenorphine, long term. Here, the duration is often open ended with patient preference influencing the duration of maintenance.[25]

Naltrexone

Naltrexone works as a competitive mu opioid receptor antagonist with high affinity, blocking the effects of exogenously administered opioids. It was investigated in the 1970s before obtaining FDA approval in 1984. Randomized trials demonstrated that oral naltrexone was not superior to placebo or to no medication in the treatment of opioid use disorder.[26] This is mainly because patients are required to take the medication daily. The long-acting extended release naltrexone (XR-NTX) was approved by the FDA in 2010. The medication is encapsulated in polymer microspheres and delivers steady naltrexone concentrations for approximately a month. It is indicated for the treatment of alcohol and opioid use disorders, and was found to be superior to no medication[8] and placebo[27] in reducing return to opioid use. If a patient maintained on XR-NTX were to use opioids, naltrexone would block their effects. This theoretically could be overridden if enough opioids were used or from opioids with extremely high binding affinities such as some of the novel illicit opioids. Recent studies comparing naltrexone to buprenorphine[28,29] demonstrated that XR-NTX was not inferior to buprenorphine in rates of return to opioid use, but that there was a significant challenge in retention during naltrexone induction. In a large randomized multisite trial that took place in residential treatment programs in the United States,[28] a large portion of patients did not actually receive the naltrexone injection which was a major limitation. The major challenge is that patients require a period of abstinence from opioids prior to induction (approximately one week) which many are unable to achieve. Often this can be achieved in an inpatient or rehabilitation setting. Naltrexone will precipitate withdrawal in patients still using opioids. This is important to avoid, as it can deter patients from the medications in the future and lead them back to opioid use. Naltrexone has no abuse liability or specific regulations surrounding its prescribing.

Naltrexone undergoes renal and hepatic metabolism, but there is no CYP450 enzyme involvement and drug-drug interactions are limited compared to buprenorphine and methadone. Contraindications include allergy, current use of opioids, acute opioid withdrawal (as evidenced by urine drug screen, patient self-report or having withdrawal symptoms when given a naloxone challenge), or severe hepatic impairment. It is not recommended for patients who are pregnant. Common side effects include injection site pain, insomnia and elevated liver enzymes. Liver function tests should be monitored at baseline, six and 12 months during treatment.

Dosing Guidelines

When performing an induction of XR-NTX, physicians must ensure patients are abstinent for at least seven to 10 days (possibly longer for long-acting opioids) and can consider use of "naloxone challenge" where 0.8 mg naloxone is injected intranasal (IN), intramuscularly (IM), or IV and then the patient monitored for opioid withdrawal. Alternately, naltrexone 25mg is administered on day 1, 50mg on day 2, and if tolerated without symptoms of opioid withdrawal, patients receive XR-NTX dosed at 380mg IM q4weeks.

Patients are vulnerable to opioid overdose and death after taking XR-NTX, as their tolerance is significantly diminished. Patients should be counseled about this risk and given a naloxone kit. If a patient requires emergency pain treatment, regional anesthesia and non-opioid analgesics can be used as alternatives. If they require opioids, they will require a high dose and potentially continuous monitoring in a hospital ICU setting.[12]

Duration of Treatment

Patients can receive medications for OUD for varying periods of time. It is established that discontinuation of medication leads to relapse and short-term treatment is generally not recommended.[9] Rather, the preferred treatment approach is maintenance therapy, meaning that the patient stays on medication for as long as it provides a benefit. Medication for OUD allows patients to have time and ability to focus on their long-term recovery without experiencing withdrawal and minimizing cravings. Their lives can go from thinking short-term ("where and how can I get my next fix?") to thinking long-term (jobs, relationships, other responsibilities).

Medically supervised withdrawal (also known as detoxification) demonstrates poor results, with only 11% being retained in treatment at 14 weeks when on a detox regimen, and 66% retention with maintenance medication, in this case buprenorphine.[30] Detox patients are also at higher risk for overdose likely due to reduction in tolerance from a short period of sobriety. During a two-year follow up after discharge from a detoxification program, over a quarter of the patients reported a non-fatal overdose.[31] There should be no pre-determined duration of treatment with medications for OUD; rather we should approach OUD as a chronic disease with a chronic care model of treatment that we might use for diabetes or hypertension.

Conclusion

This article outlines key concepts for prescribers of MAT, with the intention of more and more physicians prescribing MAT in order to adequately combat the opioid epidemic. Opioid addiction is chronic and debilitating and can affect anybody including our fellow physicians. Most importantly, it is treatable and our available treatment options are effective and well-tolerated.

We end with a cautionary word that is the opinion of these writers. The need for expanding MAT in the treatment of OUD must be balanced with the need for holistic treatment for OUD. Addiction is complex and requires more than just writing a prescription. On the contrary, for many patients this problem started with a physician and a prescription pad, and we ought to be careful not to repeat that history. Physicians should prescribe responsibly and hold their patients accountable. We should take time to discuss psychosocial issues with our patients and utilize motivational interviewing. We should not enable addiction; we should promote recovery.

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Disclosure

None reported.

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