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SUPPLEMENT TO
THE JOURNAL OF
**FAMILY
PRACTICE**[®]

VOL 70, NO 9 | NOVEMBER 2021 | MDEDGE.COM/FAMILYMEDICINE



**MANAGEMENT OF
OPIOID USE
DISORDER
IN PRIMARY CARE**

Management of Opioid Use Disorder in Primary Care Settings With a Focus on Long-Acting Medication Formulations

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doi: 10.12788/jfp.0293

LEARNING OBJECTIVES

After participating in the activity, PCPs should be able to:

- Assess a patient with possible signs and symptoms of opioid use disorder
- Identify criteria necessary to make a diagnosis of opioid use disorder
- Recognize factors that should be considered to tailor treatments for patients with opioid use disorder
- Select the best treatment option for patients with opioid use disorder

TARGET AUDIENCE

This activity is intended for primary care physicians (PCPs).

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SPONSORSHIP

Supported by an independent educational grant from Alkermes, Inc.

INTRODUCTION

Opioid use disorder (OUD) is a chronic, relapsing disease of the brain characterized by uncontrolled opioid (prescription opioids, heroin, or other illicit opioids) use despite negative consequences to the individual.¹ It is recognized as a serious national public health crisis that has reached epidemic proportions. Approximately 2 million individuals ages 12 or older met the criteria for OUD in the United States in 2018, including 1.7 million with an OUD related to painkillers (defined as the use of prescription opioids in any other way than as directed by a prescriber), and 0.5 million with heroin use disorder. In addition, an estimated 10.3 million individuals have problem use of opioids, including 9.9 million who have problem prescription pain reliever use and 808,000 who used heroin.²

Untreated OUD is associated with significant mortality and morbidity. Mortality for patients with untreated OUD is 10- to 20-fold higher than in the general population and is mainly due to overdose, infectious diseases from injection drug use (hepatitis C virus, HIV), trauma, and suicide.^{3,4} In 2018, there were approximately 46,800 opioid-overdose deaths in the United States (ie, 128 deaths per day).⁵ The risk of fatality is due to the pharmacologic property of opioids to suppress respiration with a narrow therapeutic window, and overdose may be inadvertent in patients taking illicit opioids (eg, heroin) where the dose being taken is unclear. The higher risk of overdose death is amplified by the infiltration of illicit fentanyl into the heroin supply. The morbidity associated with OUD is related to adverse health and social consequences, including infectious diseases, hospitalizations, unemployment, family disruptions, homelessness, and incarceration. The mortality and morbidity associated with OUD casts a heavy economic burden, which was estimated at \$504 billion in 2015, or 2.8% of the gross domestic product for that year.⁶

Despite these somber statistics and dire consequences, OUD is a medical condition that is highly responsive to medications. Three FDA-approved medications—the full μ -opioid receptor agonist methadone, the partial agonist buprenorphine, and the antagonist naltrexone—are available with demonstrated efficacy in reducing opioid cravings, reducing risk of relapse, reducing risk of overdose, and supporting long-term recovery.⁷ However, medications for OUD (MOUDs) are underutilized.⁸

Underutilization of MOUDs is partly due to lack of access to treatment. At present these medications are available mainly through specialized addiction treatment programs, and many communities in the United States do not have such programs at all or do not have enough of them.⁹

Even in facilities that provide opioid treatment, there is underutilization. Data from national surveys conducted in 2016 indicate that only 6% of treatment facilities offered all 3 medications, and only 36% provided any of the approved medications.¹⁰ Further, only about 20% of individuals with OUD received medical treatment at a specialty facility in 2018.² On the other hand, buprenorphine and naltrexone can be prescribed out of primary care, mental health, and a broad range of medical settings. Therefore, there is an imperative for treatment of OUD with these medications to be broadly adopted as part of the standard of care across our health systems and settings.

Underutilization of MOUDs is also due to factors inherent to the disorder itself as patients with OUD have high dropout rates from treatment settings where medications are not provided or even when medications are provided.¹¹⁻¹³ For example, a recent study showed that the proportions of patients discontinuing MOUDs within 30 days or less after treatment initiation was 52% for individuals treated with injectable naltrexone, 70% for those treated with oral naltrexone, 31% for those treated with sublingual or oromucosal buprenorphine/naloxone, 58% for those treated with sublingual buprenorphine, and 51% for those treated with transdermal buprenorphine. Adherence to the medications is crucial as patients with OUD do best with consistent dosing and with long-term treatment.¹⁴

The advent of long-acting injectable (LAI) formulations of naltrexone (a once-monthly naltrexone LAI) and buprenorphine (a once-monthly buprenorphine LAI and a 6-month buprenorphine subdermal implant) is a new development that has the potential to help improve treatment adherence and reduce dropout from treatment. Naltrexone and buprenorphine are also available as tablets or films for daily administration^{8,14}; they are effective for many patients, but for others adherence to a daily regimen can be a challenge. Daily adherence can be a challenge for any medical problem, let alone opioid use disorder.) Further, economically disadvantaged patients may be tempted to sell their buprenorphine to generate income, and diversion of buprenorphine is a significant problem. For example, worldwide surveys of patients enrolled in outpatient opioid agonist programs have shown that between 18% to 28% of patients sold or gave away their medication.¹⁵ Long-acting injectable formulations circumvent the problem of daily adherence, as well as the diversion problem, since the injections are only handled and administered by clinicians.

Primary care providers (PCPs) are often the first point of contact for individuals with problem opioid use or with developed OUD and are in a good position to intervene,

TABLE 1. **Drug-Use Terminology**^{17,19}

Tolerance	The need for a higher dose of a substance to achieve the desired effect
Physical dependence/withdrawal	A state in which unpleasant symptoms emerge when a substance to which the body has adapted is withdrawn
Withdrawal	The negative physical and psychological effects of opioid discontinuation that are felt to be intolerable by the opioid user and which lead to continued opioid use despite causing impairment or distress
Addiction	A chronic condition in which a substance is sought and used compulsively despite harmful physical effects or detrimental life consequences

providing integration of both primary care and care for the addiction.¹⁴ PCPs are able to prescribe buprenorphine (after taking a brief training and obtaining an “X-waiver” certification) and naltrexone. As such, they are in a pivotal position to help alleviate the OUD crisis. PCPs should thus have adequate knowledge of OUD and be prepared to screen, diagnose, discuss treatment options including long-acting formulations, implement early treatment intervention, refer patients for higher levels of care, provide support, and monitor patients.

UNDERSTANDING OUD

Exogenous opioids bind to the μ opioid receptor in the brain, indirectly stimulating the dopaminergic system (as well as other systems) to release dopamine at the nucleus accumbens, which is associated with pleasurable feelings, and thereby rewarding the drug-taking behavior.^{17,18} Dopamine is a neurotransmitter that under normal circumstances is released to reward healthy behaviors (exercise, eating, sexual activity, etc). Exogenous opioids, however, result in the release of more dopamine than in a normal healthy reward response. Initially, this overstimulation of the reward system can produce euphoric effects, but overtime patients often report continued use to feel normal or to avoid/remove negative feelings and withdrawal symptoms. With chronic opioid use, the brain adapts to the elevated levels of dopamine and noradrenalin by making changes to its neuronal structure and signaling that increase the threshold for dopamine and noradrenalin release, ie, more of the opioid is needed to achieve the same level of pleasure (TABLE 1).^{17,19} When this happens, the individual has developed physical dependence and tolerance to the opioid. The neuronal changes result in a hypersensitization of the brain reward system such that in the absence of opioids, the individual experiences craving, which can occur independent of withdrawal symptoms. Withdrawal symptoms are the negative physical and psychological effects of opioid discontinuation, associated with decreased production of dopamine and increased

TABLE 2. **The “4Rs” and “4Cs” Screening Tool for Substance Use Disorder in Clinical Practice**²⁴

The 4Rs	The 4Cs
<ul style="list-style-type: none"> • Role failure • Relationship trouble • Risk of bodily harm • Repeated attempts to cut back 	<ul style="list-style-type: none"> • Control (loss of it) • Craving • Compulsion to use • Consequences of use

noradrenaline, resulting in craving and continuous drug use, compulsive drug-seeking behavior, and the related adverse consequences as a result of this behavior.²⁰ The neuronal changes caused by chronic opioid use are long-lasting changes that retain the vulnerability to relapse and facilitate craving for months to years after the patient has undergone successful withdrawal management, hence the typical need for long-term treatment to support the patient’s recovery.²⁰

SCREENING

Screening provides an opportunity for early identification of patients with, or at risk, for OUD. The Substance Abuse and Mental Health Services Administration (SAMHSA) recommends universal screening for OUD.⁷ Likewise, the US Preventive Services Task Force (USPSTF) recommend routine screening of adolescents and adults for illicit drug use, including nonmedical use of prescription drugs.²¹ In addition, screening is also included on sports preparticipation physical exam questionnaires.

In primary care settings, screening can be effectively performed in the first instance with a single-question screener, “How many times in the past year have you used an illegal drug or a prescription medication for non-medical reasons?”²² An adapted version of this question forms the National Institute on Drug Abuse (NIDA) Quick Screen.²³ A positive screen (an answer other than zero) has a 100% sensitivity and 73.5% specificity for the detec-

TABLE 3. Components of Comprehensive Assessment for OUD and Other Substance Use Disorders^{14,27}

Note: Comprehensive assessment should be completed at some point during the early stages of patient management; however, completion of assessments should not delay treatment initiation.

Standard Clinical Assessments
Physical exam; medical history; family medical history; current medications; social history; allergies
Psychiatric/Other Comorbid Information
Mental status exam; psychiatric diagnoses and treatments; other comorbid diagnoses and treatments
Substance Use History
Past/present substance use and/or addictive disorder or behavior, treatments, and response to treatments; withdrawal potential
Patient's Readiness to Engage in Treatment
Potential to relapse; recovery environment; facilitators and barriers to treatment engagement
Diagnostic formulation(s)

OUD, opioid use disorder.

tion of a drug use disorder.²² Alternatively, the “4Rs” and “4Cs” may also be a quick and useful tool in screening for substance use disorders in the clinical setting (TABLE 2).²⁴ A positive initial screen is followed by further assessments with the use of a validated screening tool for OUD, such as the Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS) Tool for Substance Use Screening in Primary Care Patients.^{25,26} The NIDA Quick Screen and the TAPS are also available online.^{24,25}

ASSESSMENT

Comprehensive assessment of a patient with OUD is of critical importance for determining the appropriate level of care, treatment planning, and gauging the extent of patient engagement and is recommended by the American Society on Addiction Medicine (ASAM) (TABLE 3).^{14,27} The extent of assessment depends on whether the PCP will be offering or referring the patient for treatment.⁷ If the PCP intends to refer the patient, assessment is focused on medical assessment, making a diagnosis of OUD, and patient safety. If the PCP intends to treat the patient, the focus should be on comprehensive assessment, as outlined in TABLE 3,^{14,27} which should be completed at some point during the initial stages of patient management. These assessments do not necessarily have to occur during the first visit, and their completion should not delay treatment initiation.¹⁴

DIAGNOSIS

OUD is diagnosed based on 11 criteria outlined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* that “describe a problematic pattern of opioid use leading to clinically significant impair-

ment or distress” (TABLE 4).¹ At least 2 of the 11 criteria need to be met within a 12-month period for a diagnosis of OUD, and the 2 criteria cannot be only tolerance and withdrawal. Severity of OUD is categorized based on the number of symptoms present. Patients presenting with 2 to 3 symptoms are categorized as having mild disease, 4 to 5 symptoms as having moderate disease, and 6 or more symptoms as having severe disease.¹

TREATMENT OF OUD

ASAM recommends a combination of medication and psychosocial treatments as the standard of care in the treatment of OUD.¹⁴ Yet, medication is the foundation of treatment. It is effective by itself with no psychosocial intervention, other than the doctor-patient relationship (which should not be underestimated).^{28,29} Medication reduces patients’ cravings and withdrawal symptoms, thus supporting the patient to make changes to their lives, including addressing psychosocial factors associated with OUD. The medications, at adequate doses, also block or attenuate the pharmacologic effects of opioids, including both rewarding effects that drive addiction and dangerous effects such as respiratory depression. Some patients also obtain psychosocial treatment, such as psychotherapy, counselling, or social work service, to address the psychosocial factors associated with OUD, and psychosocial treatment should be offered to interested patients. However, psychosocial support is not required for medications for OUD to be effective, so these medications should be offered regardless of whether patients with OUD engage in other recovery activities. A Cochrane review of randomized controlled trials concluded that the addition of psy-

TABLE 4. **DSM-5 Criteria for OUD¹**

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least 2 of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period of time than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused by or exacerbated by the effects of opioids.
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.
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.
10. Tolerance,* as defined by either of the following:
 - a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
 - b. A markedly diminished effect with continued use of the same amount of an opioid.
11. Withdrawal,* as manifested by either of the following:
 - a. The characteristic opioid withdrawal syndrome
 - b. The same—or a closely related—substance is taken to relieve or avoid withdrawal symptoms

*Individuals who are taking opioids solely under appropriate medical supervision will not meet the OUS criteria.

Severity Classification:

Mild: Presence of 2 to 3 symptoms

Moderate: Presence of 4 to 5 symptoms

Severe: Presence of 6 or more symptoms

OUD, opioid use disorder.

chosocial treatment to medication does not change the effectiveness of retention in treatment or opiate use during treatment, compared with medication alone.³⁰

ASAM recommends that treatment of OUD should be tailored to the individual's needs and based on shared decision-making.¹⁴ Factors to consider include patient's openness/willingness to embrace medications, medication options vs no medication, patient's preference with regards to treatment setting (office-based opioid treatment [OBOT] or opioid treatment program [OTP]), patient's access to medications and treatment settings, and patient's understanding of the treatment options including efficacy and safety.¹⁴

Medications

Oral/Sublingual Formulations

Methadone

Methadone is a synthetic, full agonist of the opioid mu receptor that reduces cravings, prevents withdrawal symptoms, and blunts the effects of other opioids (**TABLE 5**).^{14,31,35}

At adequate doses, it does not generally produce euphoria in patients with OUD but rather induces tolerance, leading to blockade of the effects of other opioids and protection against overdose (**FIGURE**).³¹

Methadone has the longest history of use for the treatment of OUD. It has been used to treat heroin addiction since the 1960s and remains an effective treatment option for OUD. Methadone treatment is associated with a decrease in mortality,³² and decreases in HIV risk behaviors.³³⁻³⁴

Methadone is taken orally and can only be administered in federally licensed OTPs in the United States and under limited circumstances in acute care settings (ie, hospitals).¹⁴ Take-home doses are allowed in patients who have demonstrated treatment progress and are judged to be at low risk for diversion. Although methadone cannot be prescribed in primary care settings for the treatment of OUD, PCPs can be tasked with supporting these patients by providing referral and follow-up care. PCPs can also transition patients from methadone to buprenorphine or naltrexone LAI. As such, a basic knowledge of methadone is necessary for PCPs.

TABLE 5. **Oral/Sublingual Treatments for OUD**^{14,31,35}

Parameter	Methadone	Buprenorphine	Naltrexone
Pharmacologic action	Full opioid mu receptor agonist	Partial opioid mu receptor agonist; opioid delta and kappa receptor antagonist	Opioid mu receptor antagonist
Route of administration	Oral	Monoproduct: sublingual tablet Combination product with naloxone: sublingual tablet or film	Oral
Adverse effects/risk of overdose	Constipation, nausea, drowsiness, sweating, sexual dysfunction, weight gain, edema, amenorrhea, and prolonged QT interval at higher doses; higher risk of overdose than with buprenorphine	Constipation, vomiting, insomnia, sweating, blurred vision, oral hypoesthesia (oral numbness), glossodynia (tongue pain), oral mucosal erythema, palpitations, poor attention span; lower risk of overdose than methadone except if taken with central nervous system depressants (eg, benzodiazepines or alcohol)	Insomnia, hepatic dysfunction, nasopharyngitis, sedation; may increase risk of overdose if return to use because of decreased tolerance
Implications for practice	<ul style="list-style-type: none"> • Treatment must be administered in an OTP facility or be dispensed to inpatient hospitalized for another diagnosis • Patients do not require withdrawal from opioids for treatment initiation • Initially, patients must be seen daily at a licensed treatment center, which can interfere with lifestyle flexibility 	<ul style="list-style-type: none"> • Patients can receive prescriptions from a physician, NP, or PA • Prescriber must have a DEA waiver or be providing addiction treatment incidental to hospitalization for another diagnosis • Prescribers need to comply with the REMS requirements to ensure safe use of the medications • Patients need to be in mild to moderate withdrawal for treatment initiation, usually 8 to 48 hours of abstinence • Patients may need to be seen 1 to 2 times per week initially; can typically be spaced to monthly visits 	<ul style="list-style-type: none"> • Patients can receive prescriptions from a physician, NP, or PA • There are no restrictions on prescribing • Patients must completely withdraw from opioids before treatment initiation, usually 7 to 10 days of abstinence • Treatment does not alleviate withdrawal symptoms • Not widely used to treat OUD owing to lack of efficacy and low adherence rate

DEA, Drug Enforcement Administration; NP, nurse practitioner; OTP, opioid treatment program; OUD, opioid use disorder; PA, physician assistant; REMS, Risk Evaluation and Mitigation Strategy.

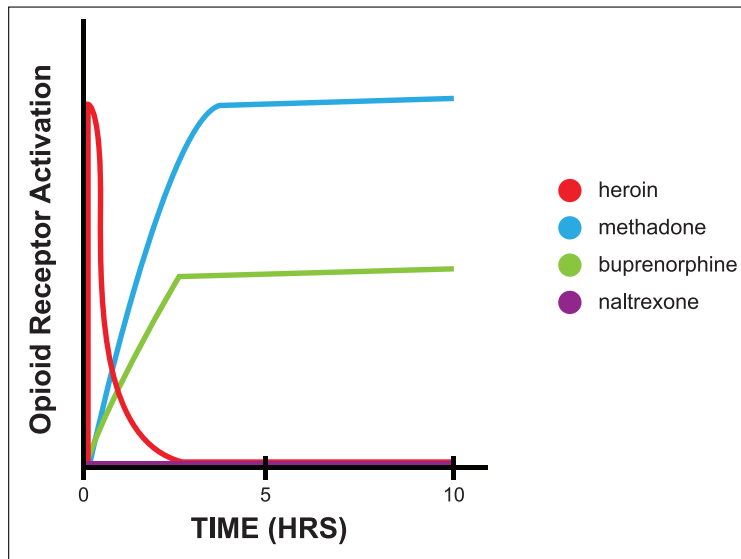
Buprenorphine

Buprenorphine is a partial agonist with very high binding affinity for the opioid mu receptor, an antagonist with high binding affinity for the delta and kappa opioid receptors, and an agonist at the ORL1 (opioid receptor-like) receptors (TABLE 5).^{14,31,35} At increasing doses, buprenorphine reaches a ceiling effect where it only partially stimulates the mu-opioid receptor (FIGURE),³¹ which minimizes opioid effects such as sedation and euphoria. While occupying most receptors with high affinity, it prevents other opioids (such as heroin, if taken) from binding and protects significantly against respiratory depression and overdose.³⁵ Similar to methadone, buprenorphine reduces opioid cravings and withdrawal symptoms and promotes abstinence from opioids.

Buprenorphine is available in several formulations specifically indicated and FDA approved for OUD—a sublingual tablet monoprodukt, sublingual tablet or film combination products with naloxone,⁷ a long-acting monthly injection, a long-acting weekly or monthly injection,³⁶ and a long-acting subdermal implant.¹⁴ Naloxone is an opioid receptor antagonist that is added as an abuse deterrent to prevent patients from crushing the tablet or film and injecting buprenorphine.³

Buprenorphine sublingual formulations are effective over a wide range of doses, typically in the range of 2 mg to 24 mg. The effective dose is individualized and is determined based on clinical indication. Dosages of at least 16 mg per day are successful at reducing illicit opioid use, and any doses above 2 mg are effective for treatment

FIGURE. **Opioid Receptor Activity**³¹



HRS, hours.

Heroin (red line) activates opioid receptors fully and quickly. Methadone (blue) is also a full agonist, but the activation is much slower and longer lasting. Buprenorphine (green) activates the receptors partially, with a similar time course to methadone. Naltrexone (purple) is an opioid receptor antagonist and therefore prevents receptor activation.

retention.³⁷ Retention in buprenorphine or methadone has been associated with reductions in the risk of all cause and overdose mortality³⁶, although some evidence suggests meth-

adone is associated with less dropout from treatment.³⁷ Patients transitioning from methadone to buprenorphine should be in mild to moderate withdrawal before the first dose of buprenorphine. Withdrawal symptoms include dysphoric mood, nausea or vomiting, muscle aches, fever, diarrhea, and insomnia. This typically occurs 24 to 72 hours after the last methadone dose and allows for sufficient time to reduce the risk of precipitated withdrawal after the first buprenorphine dose.¹⁴

Buprenorphine can be prescribed in office-based treatment settings specifically for the treatment of OUD. However, physicians wishing to treat more than 100 patients in their first year must complete an 8-hour training session to receive a Drug Addiction Treatment Act of 2000 (DATA-2000) waiver from the Drug Enforcement Administration to prescribe buprenorphine. Physician assistants and nurse practitioners need to complete 24 hours of training to obtain the waiver.⁴⁰ Clinicians can obtain their waiver without cost through the Providers Clinical Support System (PCSS) website⁴¹ or ASAM’s waiver website.⁴² In addition to the waiver, prescribers have to comply with the FDA-approved Risk Evaluation and Mitigation Strategy (REMS) for buprenorphine-containing

TABLE 6. **Obtaining a Buprenorphine “X Waiver” and Requirements for Risk Evaluation and Mitigation Strategies (REMS) Certification**^{40-44,49}

Steps for obtaining a buprenorphine “X waiver”	Explanation	Cost
1. Qualified practitioners must submit a Notification of Intent (NOI) form Note: Practitioners must also have a valid medical license and an active Drug Enforcement Agency (DEA) number to apply for the waiver	This form must be submitted in order to prescribe buprenorphine An alternative NOI form is available for clinicians who wish to treat up to 30 patients a year to forego training requirements, as well as certification to counselling and other ancillary services (such as psychosocial services) Practitioners utilizing this training exemption are limited to treating no more than 30 patients at any one time Forms can be submitted at: http://buprenorphine.samhsa.gov/forms/select-practitioner-type.php	None
2. Complete training and send training certificate	Qualified practitioners* who wish to treat more than 100 patients in the first year (see below for conditions) must complete the required training: <ul style="list-style-type: none"> • For physicians: 8 hours of training are necessary to receive the waiver • For nurse practitioners, physician assistants, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse-midwives: <ul style="list-style-type: none"> ○ 24 hours of training are necessary to receive the waiver ○ Certificates can be submitted electronically to: infobuprenorphine@samhsa.hhs.gov 	Providers Clinical Support System (PCSS) offers waiver training courses free of charge

CONTINUED

TABLE 6. **Obtaining a Buprenorphine “X Waiver” and Requirements for Risk Evaluation and Mitigation Strategies (REMS) Certification**^{40-44,49} (*cont'd*)

Steps for obtaining a buprenorphine “X waiver”	Explanation	Cost
3. Allow 45 days for CSAT to review your waiver notification form	Notification of completion is sent within approximately one week after course completion	N/A
4. If approved, SAMHSA will email a letter confirming the waiver and includes the prescriber’s identification number	If it has been longer than 45 days, please contact CSAT an email at: infobuprenorphine@samhsa.hhs.gov, or call 866-287-2728 for more information Physicians will receive and “X” number from the DEA via email, which will need to be included on all buprenorphine prescriptions; the practitioner’s regular DEA number will not change	N/A

Under the Drug Addiction Treatment Act of 2000 (DATA 2000), qualified practitioners may treat 100 patients in their first year, if they meet one of the two following conditions:

1. The practitioner is Board certified	The practitioner holds a board certification in addiction medicine or addiction psychiatry by the American Board of Preventive Medicine or the American Board of Psychiatry and Neurology
2. The practitioner provides medication-assisted treatment (MAT) in a “qualified setting”	A “qualified setting” is a practice that: <ul style="list-style-type: none"> • Provides professional coverage for patient medical emergencies during hours when the practitioner’s practice is closed • Provides access to case management services for patients, including referral and follow-up services for programs that provide, or financially support, the provision of services such as medical, behavioral, social, housing, employment, educational, or other related services • Uses health information technology systems such as electric health records • Is registered for their State prescription drug monitoring program where operational, and in accordance with Federal and State law • Accepts third-party payment for costs in providing health services, including written billing, credit, and collection policies and procedures, or federal health benefits

Steps for Risk Evaluation and Mitigation Strategies (REMS) certification

1. Designate authorized representative	The authorized representative will ensure that the dispensing location that meets the REMS requirements will be permitted to purchase, receive, and dispense buprenorphine
2. Review REMS materials	Review the buprenorphine REMS program materials, including the REMS program fact sheet on how to obtain buprenorphine, the prescribing information, and the medication guide
3. Complete the enrollment process	Complete, sign, and submit the enrollment form; only one form is needed per healthcare setting
4. Implement the REMS program	Establish processes and procedures to verify that buprenorphine is dispensed directly to a healthcare provider for administration to a patient; buprenorphine should never be directly dispensed to a patient Implement the necessary staff training and processes to comply with the buprenorphine REMS program requirements

*Qualified practitioners include physicians, nurse practitioners, physician assistants, clinical nurse specialists, certified registered nurse anesthetist, and certified nurse-midwives. CSAT, Center for Substance Abuse Treatment; DATA 2000, Drug Addiction Treatment Act of 2000; DEA, Drug Enforcement Administration; MAT, medication-assisted treatment; NOI, Notice of Intent; PCSS, Providers Clinical Support System; REMS, Risk Evaluation and Mitigation Strategy; SAMHSA, Substance Abuse and Mental Health Services Administration.

medications for OUD to ensure the benefits of prescribing these medications outweigh the risks of accidental overdose, misuse, and abuse (**TABLE 6**).^{40-44, 49}

Naltrexone

Naltrexone is an opioid receptor antagonist, with similar mu opioid receptor binding affinity to buprenorphine

TABLE 7. **Long-Acting Formulations for the Treatment of OUD**^{36,46,53,56}

Parameter	Buprenorphine Monthly LAI	Buprenorphine Weekly/Monthly LAI	Buprenorphine Subdermal Implant	Naltrexone LAI
Pharmacologic action	Partial opioid mu receptor agonist; opioid delta and kappa receptor antagonist	Partial opioid mu receptor agonist; opioid delta and kappa receptor antagonist	Partial opioid mu receptor agonist; opioid delta and kappa receptor antagonist	Opioid mu receptor antagonist
Route of administration	Subcutaneous injection in the abdominal region	Subcutaneous injection in the buttock, thigh, abdomen, or upper arm	Subdermal implant placed in the inner side of the upper arm	Intramuscular gluteal injection
Frequency of administration	Monthly	Weekly or monthly	One dose for 6 months; a second dose for an additional 6 months may be administered	Monthly
Dose	300 mg followed by 100 mg	Weekly: 8, 16, 24, or 32 mg Monthly: 64, 96, or 128 mg	320 mg (four 80 mg implants)	380 mg
Adverse effects	Constipation, headache, nausea, injection site pruritus, vomiting, fatigue, and injection site pain	Injection site pain, headache, constipation, nausea, and injection site pruritus and erythema	Implant site pain, pruritus, and erythema; headache, depression, constipation, nausea, vomiting, back pain, toothache, and oropharyngeal pain	Injection site pain, nasopharyngitis, insomnia, hepatic enzyme abnormalities, and toothache
Implications for practice	Patients can receive prescriptions from a physician, NP, or PA Prescriber must have a DEA waiver LAI can only be obtained through a restricted distribution REMS program Patients must have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days prior to LAI initiation	Patients can receive prescriptions from a physician, NP, or PA Prescriber must have a DEA waiver LAI can only be obtained through a REMS program Patients must have initiated treatment with a single dose of transmucosal buprenorphine product or are already being treated with buprenorphine	Patients can receive prescriptions from a physician, NP, or PA Prescriber must have a DEA waiver Implants can only be obtained through a closed distribution REMS program Prescriber must have received training to insert or remove the implants Patients must have achieved and sustained prolonged clinical stability on low to moderate doses of a transmucosal buprenorphine (ie, no more than 8 mg per day) before treatment initiation	Patients can receive prescriptions from a physician, NP, or PA Prescribers have no restrictions on prescribing Patients must completely withdraw from opioids before treatment initiation, usually 7 to 10 days of abstinence LAI does not alleviate withdrawal symptoms

LAI, long-acting injection; NP, nurse practitioner; OUD, opioid use disorder; PA, physician assistant; REMS, Risk Evaluation and Mitigation Strategy.

(TABLE 5).^{14,31,35} By blocking opioids from binding to the mu opioid receptor (FIGURE),³¹ naltrexone prevents euphoria and relapse. Naltrexone is available in 2 formulations—an oral tablet and a LAI. Evidence to date indicates that oral naltrexone is a less effective treatment for OUD compared to injectable naltrexone due to poor adherence with the oral formulation.¹⁴ A meta-analysis reported the lack of

superiority of oral naltrexone in treatment retention or preventing return to illicit opioid use compared with placebo or no treatment.⁴⁵

Long-Acting Formulations

Buprenorphine LAIs

A monthly formulation of buprenorphine is currently avail-

able and a weekly formulation of buprenorphine is under FDA review.

Monthly LAI

Buprenorphine monthly LAI is approved for use in patients with moderate to severe OUD (**TABLE 7**).^{36,46,53,56} It is administered by subcutaneous injection in the abdominal region and forms a solid lump. Eligible patients should initiate treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a recommended minimum of 7 days, prior to being treated with the LAI.⁴⁶

Efficacy of the monthly injection was demonstrated in a phase 3, randomized, placebo-controlled trial (BUP-XR) vs placebo. Abstinence from opioid use was significantly higher in patients who received monthly injections.⁴⁷ Further, an observational study (RECOVER) reported sustained abstinence over 12 months of treatment with the monthly injection, with improvements in psychosocial and employment outcomes; thus, demonstrating the benefits of long-term treatment for OUD.⁴⁸

Buprenorphine monthly LAI is available through a restricted distribution REMS program because of the risk of serious harm or death that could result from intravenous self-administration.⁴⁹ The program is easy to navigate and requires that (1) all healthcare settings and pharmacies that dispense the monthly LAI must be certified in the REMS program; (2) healthcare providers, healthcare settings, and pharmacies must obtain the monthly LAI through a restricted distribution program; and (3) the monthly LAI should never be dispensed directly to a patient. For the healthcare setting or pharmacy to become certified in the REMS program, (1) an authorized representative need to be designated; (2) REMS materials reviewed; and (3) the enrollment process completed. Once certified, prescribers can obtain the buprenorphine LAI for their patients in 2 ways: through a certified pharmacy for a named patient or by ordering directly through a distributor (**TABLE 6**).^{40-44,49} Note that as for other formulations of buprenorphine for OUD, the prescriber has also to be DATA 2000-waivered to be able to prescribe the LAI.⁴⁹

Weekly/Monthly LAI

Buprenorphine weekly/monthly LAI is similar to the monthly version described above and is tentatively approved by the FDA for the treatment of moderate to severe OUD (**TABLE 7**).^{36,46,53,56} It is administered weekly or monthly by subcutaneous injection in the buttock, thigh, abdomen, or upper arm and forms a soft gel.⁵⁰ Patients who have initiated treatment with a single dose of transmucosal buprenorphine product or who are already being

treated with buprenorphine will be eligible for treatment with this LAI.³⁶

In the pivotal phase 3 trial, the weekly/monthly LAI met the primary endpoint of noninferiority for responder rate (defined as having no evidence of illicit opioid use for at least 8 of 10 prespecified points during the study period) vs treatment with sublingual buprenorphine/naloxone and demonstrated superiority for the secondary endpoint of the percentage of negative opioid assessments from week 4 through 24. There were no opioid overdoses in patients receiving the LAI during the trial.⁵¹ Further, a long-term, phase 3, open-label, observational study demonstrated high treatment retention rates, with 73.6% of patients completing the treatment period, and low levels of illicit opioid use (81.5% of patients self-reported no illicit opiate use at the end of the study) with the buprenorphine LAI over a 48-week period.⁵²

Similar to the monthly LAI, the weekly/monthly LAI requires a REMS to ensure the benefits of the drug outweigh the risk of serious harm or death that could result with intravenous self-administration.³⁶

Buprenorphine Subdermal Implant

Buprenorphine subdermal implant is indicated for the treatment of OUD in patients who have achieved and sustained prolonged clinical stability on low to moderate doses of a transmucosal buprenorphine (ie, no more than 8 mg per day) (**TABLE 7**).^{36,46,53,56} Implants are inserted subdermally in the upper arm for 6 months of treatment and are removed by the end of the sixth month.⁵³ Efficacy of the subdermal implant was best demonstrated in a randomized double-blind, double-dummy study where treated patients successfully maintained clinical stability with no evidence of illicit opioid use throughout the 6 months that was comparable to control patients treated with sublingual buprenorphine.⁵⁴

PCPs are required to complete the FDA-approved buprenorphine REMS program to prescribe the implants.⁵⁵ Modest surgical skills are needed but within the range of most primary care physicians. PCPs must successfully complete a live training program and demonstrate procedural competency prior to inserting or removing the implants. Distribution of the subdermal implant is available only through a closed distribution under the REMS program to help prevent abuse, misuse, and diversion and to ensure that only REMS qualified providers are accessing the product.

Naltrexone LAI

Long-acting injectable naltrexone is indicated for the prevention of relapse to opioid dependence, following opioid

withdrawal management (**TABLE 7**).^{36,46,53,56} A minimum of 7 to 10 days of opioid abstinence is recommended before initiation of naltrexone LAI to avoid precipitation of opioid withdrawal.⁵⁴ Patients who have contraindications to buprenorphine or methadone, such as hypersensitivity to buprenorphine, or patients with severe liver impairment, should be considered for naltrexone LAI treatment. Furthermore, patients who were not successfully treated with buprenorphine and methadone modalities, who are highly motivated to taper off their current agonist therapy, or who do not want to be treated with an agonist, are also candidates for naltrexone LAI treatment.¹⁴

Naltrexone LAI is administered by deep intramuscular injection into the gluteal muscle. It should not be administered intravenously or subcutaneously. The injection consists of polymer microspheres that dissolve slowly, releasing naltrexone at levels in the blood adequate for blocking the effects of exogenous opioids.⁵⁶ The injection is administered once every 4 weeks, but more frequent dosing (eg, every 3 weeks) may be needed in rapid metabolizers of naltrexone or in those who experience breakthrough cravings or are able to overcome the opioid receptor blockade at some point within the month.¹⁴

The efficacy of naltrexone LAI has been demonstrated in several trials. In the pivotal trial that led to its approval, naltrexone LAI (in combination with bi-weekly sessions of individual drug counselling) was shown to significantly increase opioid abstinence, decrease craving, and increase treatment retention over a 24-week period compared with placebo.⁵⁷ Further, these improvements were sustained to 76 weeks in an open-label period.⁵⁸ Naltrexone LAI has better adherence for patients with OUD as compared with oral naltrexone.⁵⁹ Unlike methadone and buprenorphine, naltrexone has not been sufficiently studied to show a reduction in all-cause or opioid-related mortality.⁶⁰ Comparative effectiveness trials of naltrexone LAI versus sublingual buprenorphine suggest they are similar in effectiveness, with the exception that naltrexone is more difficult to initiate, as patients must be fully detoxified prior to starting treatment.^{61,62} Claims-based data show that naltrexone LAI is less utilized and associated with high dropout rates, although dropout from buprenorphine is also high.^{12,13} This suggests that the type of attentive medical management offered as part of clinical trials may be important to the effectiveness of these medications. Primary care is well suited to provide this type of management, for example by utilizing nurse care managers.⁶³

Naltrexone injection can be prescribed by any licensed clinician, in any treatment setting, without the

need for separate special training or certification.⁷ The requirement for complete withdrawal of opioids before treatment initiation limits the use of naltrexone LAI as high drop-out rates and poor adherence can occur during the initiation phase.⁶² However, when successfully initiated, naltrexone LAI is associated with similar retention and prevention of relapse rates as buprenorphine-naloxone.⁶² Options for initiation of naltrexone in the outpatient setting have been developed that require relatively intensive monitoring, but can be effective, with success rates that are comparable to inpatient induction.^{64,65}

Oral/Sublingual Medications vs Long-Acting Formulations

Oral/sublingual medications have the advantage of ease of administration (**TABLE 8**).¹² Patients can self-administer sublingual buprenorphine in the convenience of their home, although patients receiving treatment with oral methadone need to attend OTP clinic. The disadvantage of oral/sublingual medications is that they need to be taken daily, which may lead to adherence issues. Based on data from a nationally representative claims-based database (Truven Health MarketScan) of commercially insured individuals in the United States, approximately one-third of individuals treated with sublingual or oromucosal buprenorphine/naloxone and approximately 60% of individuals treated with sublingual buprenorphine discontinue their treatment within 30 days or less after initiation.¹²

Long-acting formulations have the advantage of less frequent dosing, which is expected to increase treatment adherence. If a patient misses their appointment, there is a short grace period to get a patient in for the next injection, since the medication levels in the system are wearing off slowly. In a randomized trial, patients receiving naltrexone LAI had twice the rate of treatment retention at 6 months compared with those taking oral naltrexone (57.1% vs 28.1%).⁵⁹ However, the same claims-based database study above reported that half of all individuals treated with naltrexone LAI or transdermal buprenorphine discontinued treatment within 30 days or less after initiation. That trial supplied relatively intensive outpatient management and counseling to all patients.¹² Nonetheless, the real-world opinion of users of LAIs is that these medications have the potential to make life easier for them by freeing-up time for preferred activities because of less frequent dosing.⁶⁶

Long-acting formulations can also reduce the stigma associated with visiting addiction facilities, as they can be administered in any physician's office. Patients also appear

TABLE 8. **Advantages/Disadvantages of Oral/Sublingual vs Long-Acting Formulations**¹²

Factors	Oral/Sublingual	Long-Acting Formulations
Administration	Methadone: OTP Stigma associated with visiting addiction facilities Buprenorphine: patient self-administered at home Convenience	Physician administered (office based) Reduces stigma associated with visiting addiction facilities Eliminates behavioral component of addiction by eliminating choice element and self-administration element from patients Minimizes diversion and misuse Patient preference
Dosing frequency	Daily May decrease treatment adherence	LAIs: monthly (or weekly/monthly) Subdermal implant: every 6 months for up to 1 year May increase treatment adherence Frees up time for other activities

LAI, long-acting injection; OTP, opioid treatment program.

TABLE 9: **Key Points for the Use of Buprenorphine Monthly LAI**⁴⁶

<p>Administer buprenorphine monthly LAI only in patients initiated on sublingual buprenorphine, followed by dose adjustment for a minimum of 7 days</p> <p>Initiation of Sublingual Buprenorphine:</p> <ul style="list-style-type: none"> • Do not start sublingual buprenorphine until the patient is in at least mild withdrawal • Instruct the patient to stop taking all opioids • Ensure patient is in mild to moderate withdrawal • Initiate sublingual buprenorphine at a dose of 2 mg to 12 mg, individualized to the patient • Adjust sublingual buprenorphine dose from Day 2 as needed <p>Transitioning to Buprenorphine Monthly LAI:</p> <ul style="list-style-type: none"> • Transition to the monthly LAI after a minimum of 7 days on sublingual buprenorphine • Initiate the LAI at a starting dose of 300 mg/month for 2 consecutive months • Administer the LAI on the abdomen in the subcutaneous space; avoid the muscle <p>Maintenance and Follow-Up Care:</p> <ul style="list-style-type: none"> • After first 2 doses, maintain patient on a dose of 100 mg monthly <p>At each visit:</p> <ul style="list-style-type: none"> • Examine the injection site for signs of infection, evidence of tampering, or attempts to remove the depot • Assess for treatment effectiveness, illicit drug use, and overall patient progress • Continue treatment long-term
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LAI, long-acting injection.

to favor an office-based treatment. In one study, 50% to 80% of OUD patients reported being “highly satisfied with office-based opioid treatment.”⁶⁷ Physician administration also eliminates the element of daily decision-making to take the medication which can be a barrier for some, as well as the need to take something every day, as aspect of the behavioral component of addiction. Further, medication diversion is less likely with long-acting medications

parenterally administered in a medical setting.

Long-acting formulations provide sustained release of active medication over a monthly duration in the case of the injections and over a 6-month period in the case of subdermal implants. This ensures sustained therapeutically effective levels of the medication over the intended duration, eliminating peaks and troughs that can mimic drug-taking effects.

TABLE 10. **Opioid Withdrawal Signs and Symptoms**¹⁴

A. Presence of either of the following:	
<ul style="list-style-type: none"> • Cessation of (or dramatic reduction in) opioid use that has been heavy and prolonged • Administration of an opioid antagonist after a period of opioid use 	
B. The following signs and symptoms develop within minutes to several days after either event in section A	
<ul style="list-style-type: none"> • Dysphoric mood • Nausea or vomiting • Muscle aches • Lacrimation or rhinorrhea • Pupillary dilation, piloerection, or sweating 	<ul style="list-style-type: none"> • Diarrhea • Yawning • Fever • Insomnia

BEST PRACTICES WITH LONG-ACTING FORMULATIONS IN PRIMARY CARE

Treating patients with long-acting formulations can be highly successful. However, sound knowledge of proper administration techniques, appropriate patient follow-up, and supportive care increases the comfort and competence of physicians to use these formulations and thus increase the likelihood that patients will continue to use their LAIs.

Buprenorphine Monthly LAI

Buprenorphine monthly LAI is administered in patients who have been initiated on treatment with sublingual buprenorphine, followed by dose adjustment for a minimum of 7 days (TABLE 9).⁴⁶

Initiation of Sublingual Buprenorphine

PCPs initiating sublingual buprenorphine should instruct the patient to wait for physical symptoms of opioid withdrawal prior to taking their first dose of sublingual buprenorphine.¹⁴ Precipitated withdrawal is caused by the high binding affinity of the partial agonist buprenorphine for the mu opioid receptor, displacing the full agonist opioid, in which the change from full to partial agonist binding is experienced as withdrawal by the patient. It typically takes a patient 6 to 12 hours from their last use of a short-acting opioid to be in mild withdrawal. If a patient takes methadone, a longer window (24 to 72 hours) must pass before beginning buprenorphine treatment.¹⁴ Once the patient is in mild to moderate withdrawal, which can be determined by the presence of 3 or more opioid withdrawal symptoms listed in TABLE 10¹⁴, buprenorphine is self-administered sublingually. The starting dose and titration should be individualized per patient, and usually ranges from 2mg to 4 mg; maintenance doses can range from 4 mg to 24 mg.¹⁴

Transitioning to Buprenorphine Monthly LAI

Patients may only be transitioned to buprenorphine monthly LAI after a minimum of 7 days on sublingual buprenorphine per the package insert.⁴⁶ Before administering buprenorphine monthly LAI, remove it from the refrigerator and allow it to reach room temperature, which takes at least 15 minutes. Assemble the syringe and needle per the package instructions by screwing on the needle to the prefilled syringe. The syringe contains the prefilled dose. The recommended starting dose is 300 mg/month for 2 consecutive months.

The injection is administered on the abdomen between the transpyloric and transtuberular planes. When selecting an injection site, ensure the selected site has adequate subcutaneous tissue that is free of skin conditions (eg, nodules, lesions, excessive pigment) and the skin is not irritated, reddened, bruised, infected, or scarred. Pinch the skin around the injection area and lift it to separate the adipose tissue from the underlying muscle to prevent accidental intramuscular injection. The needle is inserted into the subcutaneous space with the patient in the supine position. To avoid irritation at the injection site, a different site between the transpyloric and transtuberular planes should be selected for the next dose. Keeping a record of the sites injected will help ensure that the same site is not used consecutively.⁴⁶

Maintenance and Follow-Up Care

After the initial 2 doses, the patient is often continued on a dose of 100 mg monthly.⁴⁶ However, the number of 300 mg doses can vary based on patient response, since some patients may report excessive sedation and others may benefit from continuation at this dose. At each visit, the injection site should be examined for signs of infection, evidence of tampering, or attempts to remove the depot as well as for treatment effectiveness, illicit drug use, and overall patient progress. Illicit drug use should

be assessed with a urine drug test, the frequency of which is individualized depending on the stability of the patient.⁴⁶ Currently, there is no recommended duration for buprenorphine monthly LAI treatment. Duration of treatment is dependent on the response of the individual patient, the patient's individual circumstances, and clinical judgment.

Buprenorphine Weekly/Monthly LAI

Patients should only be administered buprenorphine weekly/monthly LAI after they have been initiated on a single dose of a transmucosal buprenorphine product or have been treated with buprenorphine.^{36,50} This buprenorphine LAI forms a soft gel and should be administered subcutaneously in the buttocks, thighs, abdomen, or upper arms by a healthcare professional (with a DEA waiver and registered in the REMS program) in a healthcare setting; it should not be administered intravenously or by the patient.⁵⁰ The injection will be available in pre-filled syringes at varying doses. The weekly injection will be available in 4 doses (8 mg, 16 mg, 24 mg, or 32 mg) and the monthly injection in 3 doses (64 mg, 96 mg, 128 mg, or 160 mg).⁵⁰⁻⁵²

Buprenorphine Subdermal Implants

Buprenorphine subdermal implants are indicated for the treatment of OUD.⁵³ They should only be used in patients who are clinically stable on low to moderate doses of a transmucosal buprenorphine-containing product (ie, doses of up to 8 mg per day). Patients should have been on the stable dose for 3 months or longer without any need for supplemental dosing or adjustments. Patients should not be tapered to a lower dose of transmucosal buprenorphine for the purpose of transitioning to the subdermal implants.⁵³ The implants are not appropriate for patients who are treatment naive or who are transitioning to transmucosal buprenorphine.

Insertion of Subdermal Implants

Only healthcare providers (HCPs) who have undergone training can insert or remove the implants.⁵¹ Each dose consists of 4 implants. Each implant is 26 mm in length, 2.5 mm in diameter, and contains 74.2 mg of buprenorphine (equivalent to 80 mg of buprenorphine hydrochloride). The implants are inserted subdermally in the inner side of 1 upper arm. After completion of insertion, the incision is cleaned and closed with liquid adhesive.⁵³

Follow-Up Care After Subdermal Implant Insertion

Patients should be seen 1 week after insertion to examine

the insertion site for signs of infection and wound healing problems, including implant extrusion. Thereafter, patients are seen monthly for continued counseling and psychosocial support. Patients should not normally require supplemental buprenorphine during this period, although occasionally they may do so. If there is a need for continual supplemental buprenorphine, this is indicative of inadequate buprenorphine dosing from subdermal implants. For these patients, alternative buprenorphine medications should be considered for maintenance treatment of OUD.⁵³

Removal of Subdermal Implants

Subdermal implants are removed at the end of the sixth month after implantation, which is a limitation compared to the injections which simply dissolve gradually over time. Prior to removal, the exact location of each implant should be verified by palpation. For non-palpable implants, alternative methods such as ultrasound or magnetic resonance imaging should be utilized to locate them.⁵³

To remove an implant, inject the local anesthetic just beneath the implants to effectively lift the implants toward the skin. The tissue around the implant is released, and the implant is grasped in the center and gently retracted. If the implant is encapsulated, the capsular tissue is shaved, and the tissue around the implant is dissected to release the implant, which can then be removed.⁵³

After ensuring that all implants have been completely removed, the incision is cleaned and closed by sutures. An adhesive bandage and a pressure bandage are applied and removed, as before. The removed implants should be properly disposed per facility procedure for a Schedule III drug product.⁵³

Follow-Up Care After Subdermal Implant Removal

For patients who desire additional dosing, at the time of removal of the first set of implants, new implants can be inserted subdermally in the inner upper side of the contralateral arm. If new implants are not inserted on the same day as the old implants are removed, the patient must be placed on their previous transmucosal buprenorphine dose at the time when they were transitioned to subdermal implants. After 1 insertion in each arm, additional treatments are not recommended per the product package insert. Patients who require continued treatment should be transitioned back to a transmucosal buprenorphine-containing product.⁵³

Naltrexone LAI

Prior to the administration of naltrexone LAI, a minimum of 7 to 10 days' opioid abstinence is required per

TABLE 11. **Key Points for the Use of Naltrexone LAI**^{1,14,56}

Naltrexone LAI should only be administered after a minimum of 7 to 10 days of opioid abstinence
Detoxification Strategies for Opioid Abstinence: <ul style="list-style-type: none"> • Follow 1 of 2 strategies: <ul style="list-style-type: none"> ○ Gradual opioid agonist taper ○ Naltrexone-assisted detoxification
Administration of Naltrexone LAI: <ul style="list-style-type: none"> • Mix naltrexone LAI, supplied as a microsphere powder containing 380 mg of naltrexone, into a diluent to form a suspension before injection • Inject into the gluteal muscle • Administer naltrexone LAI once a month • Alternate the buttocks for each subsequent injection
Follow-Up Care: <ul style="list-style-type: none"> • Monitor the patient for injection site reactions • Continue treatment long-term • Advise patients who wish to discontinue: <ul style="list-style-type: none"> ○ Of the risk of opioid overdose and overdose death if they return to illicit opioid use ○ Of overdose prevention with naloxone ○ Of alternative treatments

LAI, long-acting injection.

the package insert to avoid precipitation of opioid withdrawal (**TABLE 11**).^{1,14,56} In general, the ASAM recommends a 6-day period of abstinence from short-acting opioids. Because abrupt opioid cessation leads to withdrawal symptoms, which can be unbearable, withdrawal management strategies are used to assist patients to safely complete withdrawal and transition to naltrexone LAI.¹⁴

Withdrawal Management Strategies

There are 2 main withdrawal management strategies for naltrexone LAI: (1) gradual opioid taper and (2) more rapid discontinuation with use of adjunctive nonopioid medications. The former strategy involves substitution of a long-acting agonist (eg, methadone) or a high-affinity partial agonist (eg, buprenorphine), followed by a gradual taper. The latter strategy uses little or no opioid agonists and relies on nonopioid medications to alleviate withdrawal.⁶⁸

In clinical practice, buprenorphine-assisted withdrawal management can be safely performed using the following protocol, which was tested in a clinical study.⁶⁴ On day 1, the patient is asked to abstain from all opioids for 12 to 24 hours. On day 2, the patient should be in mild withdrawal. From day 2 to day 7, the patient is prescribed decreasing daily doses of buprenorphine from 8 mg to 1 mg. This is followed by a 7-day washout period. On day 15, naltrexone LAI is administered. If it is uncertain that the patient remained opioid free during the wash-

out period, a naloxone challenge is performed prior to administering naltrexone LAI. For the naloxone challenge, 0.4 to 0.8 mg of naloxone is administered intramuscularly, and the patient is monitored for precipitated withdrawal symptoms.^{14,64}

The same clinical study also tested a naltrexone-assisted withdrawal management strategy.⁶⁴ On day 1, the patient is instructed to abstain from all opioids as for the buprenorphine-assisted withdrawal management protocol. On day 2, patients with a Clinical Opiate Withdrawal Scale (COWS) score of 6 received an initial buprenorphine dose of 2 mg, with subsequent 2 mg doses given every 1 to 2 hours if the treatment was well tolerated, titrating up to a total dose of 8 mg. On day 3, standing doses of clonidine (0.1 to 0.2 mg every 4 hours up to 1.2 mg) and clonazepam (1.0 mg every 6 hours up to 2 mg) are administered and continued until day 8. On day 4, after pretreatment with 10 mg of prochlorperazine 10 mg, oral naltrexone was initiated at a dose of 1 mg, with increasing daily doses given through day 7 (3 mg, 6 mg, 12 mg, and 25 mg). On day 8, after having tolerated 25 mg of naltrexone on the previous day, the patient is administered an intramuscular injection (380 mg) of naltrexone LAI.

Of note, while both the buprenorphine-assisted withdrawal management and the naltrexone-assisted withdrawal management protocols are effective, the latter protocol was found to be more effective in the above-men-

tioned withdrawal management clinical study. Patients who underwent naltrexone-assisted detoxification were significantly more likely to be successfully inducted to naltrexone LAI compared with patients who underwent buprenorphine-assisted withdrawal management (56.1% vs 32.7%) and receive the second naltrexone LAI at 5 weeks (50% vs 26.9%).⁶⁴ Physicians need to have access to a compounding pharmacy in order to provide small doses of oral naltrexone. Other multi-site trials found no difference between rapid methods with or without buprenorphine or low-dose oral naltrexone.^{65,69} Clinically, use of ancillary meds to manage withdrawal (clonidine and other medications for symptoms) is very helpful.

In summary, there are 2 main ways to start someone with active opioid use on naltrexone: 1) inpatient withdrawal management and/or residential treatment, where a gradual opioid taper can be accomplished; 2) outpatient withdrawal management and naltrexone initiation, for which protocols exist as described above, but for which more monitoring and management are required.

Administration of Naltrexone LAI

Naltrexone LAI is a suspension containing 380 mg of naltrexone in a microsphere formulation in a single-dose vial that is refrigerated. Before use, remove the vial from the refrigerator and allow the suspension to reach room temperature, which takes about 45 minutes. The drug is supplied as a microsphere powder that is mixed into a diluent to form a suspension before injection. A properly mixed suspension will be milky white, will not contain clumps, and will move freely down the walls of the vial, per the manufacturer's instructions. Once prepared, withdraw 4.2 mL of the suspension into the syringe and inject into the gluteal muscle using 1 of 2 needles provided: a 1.5 inch or 2-inch needle. A deep intramuscular injection is used, and the choice of needle is dependent on the patient's body habitus. The buttocks are alternated for each subsequent injection.⁵⁶

Follow-Up Care

Patients should be monitored for injection site reactions, including pain, tenderness, induration, swelling, erythema, bruising, or pruritus.⁵⁶ Patients' liver function should also be monitored because cases of hepatitis and clinically significant liver dysfunction have been reported. Patients should immediately notify their physician if they develop signs or symptoms of liver disease.⁵⁶

There is no recommended duration of treatment with naltrexone LAI, but as with other medications for OUD, risk of relapse is high when medication is discontinued.^{70,71}

For many patients, medication should be thought of as a long-term treatment strategy. Should patients wish to discontinue naltrexone LAI, PCPs should advise patients of the increased risks associated with opioid overdose, especially the increased risk of overdose death, if they return to illicit opioid use because of their diminished tolerance to opioids after being treated with naltrexone. Overdose prevention with naloxone as well as the need for alternative treatments should be discussed with patients.

CONCLUSION

OUD is a chronic medical illness that can be effectively managed with medications in primary care settings. PCPs, as the first line of medical care contact for most patients with OUD, are well positioned to diagnose OUD, initiate medication for OUD, and manage continuity of care for patients with OUD. To achieve successful outcomes, treatment needs to be continued indefinitely in most patients, as treatment discontinuation increases the risk of relapse. Daily dosing of medications is one barrier to the continuity of long-term treatment, and the availability of once-monthly injectable and other long-acting formulations may help mitigate the risk of discontinuation. ●

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