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

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ABSTRACT

Opioid use disorder (OUD) is a chronic medical illness characterized by uncontrolled opioid use despite negative consequences that has resulted in a public health crisis in the United States. OUD is a medical condition highly responsive to three approved medications: methadone, buprenorphine, and naltrexone. All three medications can reduce opioid cravings, reduce risk of relapse, and support long-term recovery of patients, but they are underutilized. Underutilization is partly due to regulatory barriers including requirements for daily observed dosing of oral and sublingual medications within opioid treatment programs and limited access to these medications within typical primary care/healthcare settings. Long-acting formulations are available and could potentially facilitate patient access to these treatments. Primary care providers, who are often the first point of contact for individuals with problem opioid use or with OUD, are in a pivotal position to treat patients with medications for OUD which improves health outcomes for these patients. This review provides information about FDA-approved medications for OUD with a focus on long-acting formulations to support primary care physicians' treatment of OUD to reduce the impact of the opioid crisis.

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. [American Psychiatric Association 2013] It is recognized as a serious national public health crisis that has reached epidemic proportions. Approximately 2 million individuals aged 12 or older met the criteria for OUD in the United States in 2018, including 1.7 million with a prescription pain reliever use disorder and 0.5 million with heroin use disorder. [SAMHSA 2019] In addition, an estimated 10.3 million individuals have problem use of opioids, including 9.9 million who have problem pain reliever use and 808,000 who used heroin.

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, and sepsis), trauma, and suicide. [National Academies of Sciences, Engineering, and Medicine 2019; Hser 2017] In 2018, there were approximately 46,800 opioid-overdose deaths in the US (i.e., 128 deaths per day). [Wilson 2020] The risk of overdose is due to the pharmacological property of opioids to suppress respiration with a narrow therapeutic window, and the risk is greater among patients taking illicit opioids (e.g. heroin) where the dose being taken is unclear. This has been amplified by the infiltration of illicit fentanyl into the heroin supply. The morbidity associated with OUD is also 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. [Council of Economic Advisers 2017]

Despite the above somber statistics and dire consequences, OUD is a medical condition 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. However, medications for OUD (MOUDs) are underutilized.

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. [Grimm 2020] Methadone for treatment of OUD is restricted at present to specially licensed clinics and more such clinics are needed. 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. [Mojtabai 2019] Further, only approximately 20% of individuals with OUD received medical treatment at a specialty facility in 2018. On the other hand, buprenorphine and naltrexone can be prescribed readily 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 [Williams 2019; Morgan 2018; Wakeman 2020]. Adherence to the medications is crucial as patients with OUD do best with consistent dosing and with long-term treatment. [ASAM 2020] Thus, a wider uptake of MOUDs is crucial to mitigate the public health crisis of OUD.

The advent of long-acting injectable (LAI) formulations of naltrexone (a once-monthly naltrexone LAI) and buprenorphine (a once-monthly buprenorphine LAI, a once weekly or 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, which 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. 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, providing integration of primary care and care for the addiction. [Lagisetty 2017] Primary care providers 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. [Camí 2003; Brown 2020] 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, i.e., more of the opioid is needed to achieve the same level of pleasure (**Table 1**). [National Institute on Drug Abuse 2018] 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, by downregulated production of dopamine and upregulated noradrenaline, that are emotionally and physically intolerable by the opioid user and which leads to continued opioid use despite causing impairment or distress. 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.

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. [SAMSHA 2020] Likewise, the U.S. Preventive Services Task Force (USPSTF) recommends routine screening of adults 18 years and older for unhealthy use of prescription or illegal drugs. [U.S. Preventive Services Task Force 2020]

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 nonmedical reasons?" [Smith 2010] An adapted version of this question forms the National Institute on Drug Abuse (NIDA) Quick Screen. [NIDA Drug Screening Tool] A positive screen (an answer other than zero) has a 100% sensitivity and 73.5% specificity for the detection of a drug use disorder. [Smith 2010] 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**). [Curtis 2019] 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. [TAPS Screening Tool; McNeely 2016] The NIDA Quick Screen and the TAPS are available on-line at https://archives.drugabuse.gov/nmassist/ [NIDA Drug Screening Tool] and http://www.drugabuse.gov/taps [TAPS Screening Tool], (respectively).

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**). [American Society on Addiction Medicine Standards of Care 2020] The extent of assessment depends on whether the PCP will be offering or referring the patient for treatment. [SAMSHA 2020] 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**, which should be completed at some point during the early stages of patient management. Completion of assessments, however, should not delay treatment initiation. [ASAM 2020]

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 impairment or distress" (**Table 4**). [American Psychiatric Association 2013] 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 2-3 symptoms are categorized as having mild disease, 4-5 symptoms as having moderate disease, and 6 or more symptoms as having severe disease.

TREATMENT OF OUD

ASAM recommends a combination of medication and psychosocial treatments as the standard of care in the treatment of OUD. [ASAM 2020] 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). [Weiss 2015; Weiss 2017] Medication reduces patients' cravings and withdrawal symptoms, thus supporting the patient to make changes, including addressing psychosocial factors associated with OUD, to improve their lives. The medications, at adequate doses, also block or attenuate the pharmacological effects of opioids, including both rewarding effects that drive addiction and dangerous effects such as respiratory depression. Some patients also obtain psychosocial treatments to address the psychosocial factors associated with OUD, and psychosocial treatments should be offered to patients interested in these treatments. 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 psychosocial treatment to medication does not provide additional benefits compared with medication alone. [Amato 2011]

ASAM recommends that treatment of OUD should be tailored to the individual's needs and based on shared-decision making. [ASAM 2020] Factors to consider include patient's openness/willingness to embrace medications, medication options versus 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.

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**). 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 1**) [National Institute on Drug Abuse 2018].

Methadone has the longest history of use for the treatment of OUD. It has been used to treat heroin addiction since the 1960's and remains an effective treatment option for OUD. Methadone treatment is associated with a decrease in all-cause mortality, [Leshner 2019] decrease in HIV risk behaviors, [Sorensen 2000] decrease in the incidence of hepatitis C viral infections, and reduced use of nonprescribed opioids. [Fullerton 2014]

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 (i.e. hospitals). [ASAM 2020] 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.

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 [Gudin 2020] (**Table 5**). At increasing doses, buprenorphine reaches a ceiling effect where it only partially stimulates the mu-opioid receptor (**Figure 1**), [National Institute on Drug Abuse 2018] 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. 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 monoproduct, sublingual tablet or film combination products with naloxone, a long-acting monthly injection, a long-acting weekly or monthly injection, and a long-acting subdermal implant. [US FDA 2018] 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. [ASAM 2020] When combination buprenorphine/naloxone medications are taken sublingually as prescribed, the naloxone passes through the gastrointestinal system largely unabsorbed, but if these medications are insufflated or injected, the introduced naloxone induces opioid withdrawal symptoms. Similarly, the non-LAI formulation may also precipitate withdrawal symptoms if injected to a patient actively intoxicated with a full agonist opioid because of buprenorphine's preferential binding affinity to opioid receptors that displaces the binding of full agonist opioids.

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 as effective as methadone at reducing illicit opioid use and all-cause mortality and for treatment retention [Mattick 2014; Sordo 2017], although some evidence suggests methadone is associated with less dropout from treatment [Hser 2014]. Patients should be in mild to moderate withdrawal before receiving the first dose of sublingual buprenorphine, usually 8 to 48 hours of abstinence depending on the pharmacokinetics of opioids in their system, to reduce the risk of precipitated withdrawal. [National Institute on Drug Abuse 2018]

Buprenorphine can be prescribed in office-based treatment settings specifically for the treatment of OUD. However, physicians must complete an eight-hour training session to receive a Drug Addiction Treatment Act of 2000 (DATA-2000) waiver from the Drug Enforcement Administration to prescribe buprenorphine. [SAMSHA 2020b] Physician assistants and nurse practitioners need to complete 24 hours of training to obtain the waiver. Clinicians can obtain their waiver without cost through the Providers Clinical Support System (PCSS) website (https://pcssnow.org/medications-for-addiction-treatment/) [PCSS] or ASAM's waiver website (http://elearning.asam.org/buprenorphine-waiver-course) [The ASAM e learning]. In addition to the waiver, prescribers have to comply with the FDA-approved Risk Evaluation and Mitigation Strategy (REMS) for buprenorphine-containing medications for OUD to ensure the benefits of prescribing these medications outweigh the risks of accidental overdose, misuse, and abuse [US FDA 2018a; US FDA 2020a].

Naltrexone

Naltrexone is an opioid receptor antagonist, with similar mu opioid receptor binding affinity to buprenorphine (**Table 5**). [ASAM 2020] By blocking opioids from binding to the mu opioid receptor, (**Figure 1**) [National Institute on Drug Abuse 2018] naltrexone prevents euphoria and relapse. Naltrexone is available in two 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. [Minozzi 2011] 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.

Long-Acting Formulations

Buprenorphine LAIs

Two formulations of buprenorphine LAIs will be available at the time of publication – a monthly formulation and a weekly or monthly formulation.

Monthly LAI

Buprenorphine monthly LAI is approved for use in patients with moderate to severe OUD (**Table 6**). [Sublocade PI] It is administered by subcutaneous injection in the abdominal region that 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.

Efficacy of the monthly injection was demonstrated in a phase 3, randomized, placebo-controlled trial (BUP-XR) vs placebo. [Haight 2019] Abstinence from opioid use was significantly higher in patients who received monthly injections. 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. [Ling 2020]

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 [US FDA 2020b]. 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 two ways: through a certified pharmacy for a named patient or by ordering directly through a distributor. 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.

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. [US FDA 2018b] (**Table 6**). It is administered weekly or monthly by subcutaneous injection in the buttock, thigh, abdomen, or upper arm and forms a soft gel. [Ling 2019] 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. [US FDA 2018b]

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) versus treatment with sublingual buprenorphine/naloxone and demonstrated superiority for the secondary endpoint of the percentage of negative opioid assessments from week 4 through 24. [Lofwall 2018] There were no opioid overdoses in patients receiving the LAI during the trial. Further, a long-term, phase 3, open-label, observational study demonstrated high treatment retention rates and low levels of illicit opioid use with the buprenorphine LAI over a 48-week period. [Frost 2019]

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. [US FDA 2018b]

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 (i.e., no more than 8 mg per day) (**Table 6**). [PROBUPHINE PI] Implants are inserted subdermally in the upper arm for 6 months of treatment and are removed by the end of the sixth month. 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. [Rosenthal 2016]

PCPs are required to complete the FDA-approved buprenorphine REMS program to prescribe the implants [US FDA 2018c]. 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 6**). [VIVITROL PI] A minimum of 7-10 days of opioid abstinence is recommended before initiation of naltrexone LAI to avoid precipitation of opioid withdrawal. Patients who have contraindications to buprenorphine or methadone, for whom buprenorphine and methadone were not successful treatment modalities, who are highly motivated to taper off their current agonist therapy, or who do not want to be treated with an agonist are candidates for naltrexone LAI treatment. [ASAM 2020]

Naltrexone LAI is administered by deep intramuscular injection into the gluteal muscle. [VIVITROL PI] 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. 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. [ASAM 2020]

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 psychosocial support) was shown to significantly increase opioid abstinence, decrease craving, and increase treatment retention over a 24-week period compared with placebo. [Krupitsky 2011] Further, these improvements were sustained to 76 weeks in an open-label period. [Krupitsky 2013] Naltrexone LAI has better adherence for patients with OUD as compared with oral naltrexone. [Sullivan 2019] Unlike methadone and buprenorphine, naltrexone has not been sufficiently studied to show a reduction in all-cause or opioid-related mortality [Larochelle 2018]. 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 [Tanum 2017; Lee 2018]. Claims-based data show that naltrexone LAI is less utilized and associated with high dropout rates, although dropout from buprenorphine is also high [Morgan 2018; Wakeman 2020]. 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 [LaBelle 2016].

Naltrexone injection can be prescribed by any licensed clinician, in any treatment setting, without the need for separate special training or certification. [ASAM 2020] 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. [Lee 2018] However, when successfully initiated, naltrexone LAI is associated with similar retention and prevention of relapse rates as buprenorphine-naloxone. Options for initiation of naltrexone to address the initiation hurdle include hospitalization or residential treatment to secure abstinence, or outpatient initiation procedures have been developed which require relatively intensive monitoring but can be effective [Sullivan 2017; Bisaga 2018].

Oral/Sublingual Medications vs Long-Acting Formulations

Oral/sublingual medications have the advantage of ease of administration (**Table 7**). 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 on a daily basis, 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 a 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. [Morgan 2018]

Long-acting formulations have the advantage of less frequent dosing, which is expected to increase treatment adherence. There is also a grace period to get a patient in for the next injection, if a patient misses their appointment, 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%). [Sullivan 2019] However, the same claims-based database study above reported than 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. [Morgan 2018] 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. [Gilman 2018]

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 to favor an office-based treatment. In one study, 50%-80% of OUD patients reported being "highly satisfied with office-based opioid treatment". [Gunderson 2008] 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.

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 they will be used.

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 [SUBLOCADE PI] (**Table 8**).

Initiation of Sublingual Buprenorphine

PCPs initiating sublingual buprenorphine should instruct the patient to stop taking all opioids from all prescription and non-prescription sources. [ASAM 2020] Buprenorphine should not be started until the patient is in at least mild withdrawal to prevent iatrogenic precipitated withdrawal. 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 6-12 hours from their last use of a short-acting opioid to be in mild withdrawal. If a patient takes methadone, a longer window (24-72 hours) must pass before beginning buprenorphine treatment. Once the patient is in mild to moderate withdrawal, which can be determined by presence of three or more opioid withdrawal symptoms listed in **Table 9**, [American Psychiatric Association 2013] buprenorphine is self-administered sublingually. The patient should place buprenorphine under the tongue until fully dissolved, which is usually in less than five minutes. The starting dose and titration should be individualized for the patient, but is typically between 2 mg to 12 mg. On Day 2 and onward, patient should take the total dose from the day prior, with dose increases as needed based on the presence of opioid cravings and withdrawal symptoms and dose decreases if side effects (such as headache and upset stomach) become problematic. The dose for the second day and onward usually does not exceed 24 mg although in some cases the patient may require up to the maximum recommended dose of 32 mg daily.

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. [SUBLOCADE PI] However, patients can often be transitioned once they are clinically stable on sublingual buprenorphine, which may be less that the 7 days utilized in clinical trials. Clinical stability is clinician dependent and may be based on several indicators, including abstinence from illicit drugs, participation in psychosocial treatment, and other recovery-based activities, and productive occupational and social functioning. [ASAM 2020]

Before administering buprenorphine monthly LAI, remove it from the refrigerator and allow it to reach room temperature, which takes at least 15 min. [SUBLOCADE PI] 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 two consecutive months. The injection is administered on the abdomen between the transpyloric and transtubercular planes. When selecting an injection site, ensure the selected site has adequate subcutaneous tissue that is free of skin conditions (e.g., 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 transtubercular 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.

Maintenance and Follow-Up Care

After the initial two doses, the patient is often continued on a dose of 100 mg monthly. 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. 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

As mentioned above the weekly/monthly injection will likely be available at the time of publication of this paper, but as of now the package insert is not available. Nonetheless, some key administration points are known based on available information in the public domain.

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. [US FDA 2018] 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. [Ling 2019] The injection will be available in pre-filled syringes at varying doses. The weekly injection will be available in 4 doses (8mg, 16mg, 24mg, or 32mg) and the monthly injection

in 3 doses (64 mg, 96mg, or 128mg). The range of doses allows flexibility in dosing that can be tailored to individual patient needs. Buprenorphine weekly/monthly LAI will not require refrigeration, which could simplify storage and administration logistics.

Buprenorphine Subdermal Implants

Buprenorphine subdermal implants are indicated for the treatment of OUD. [PROBUPHINE PI] They should only be used in patients who are clinically stable on low-to-moderate doses of a transmucosal buprenorphine-containing product (i.e., doses of up to 8 mg per day). Patients should have been on the stable dose for three 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. The implants are not appropriate for patients who are treatment naïve 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. [PROBUPHINE PI] Each dose consists of four implants. Each implant is 26 mm in length and contains 74.2 mg of buprenorphine (equivalent to 80 mg of buprenorphine hydrochloride). The implants are inserted subdermally in the inner side of one upper arm. After completion of insertion, the incision is cleaned and closed with liquid adhesive.

Follow-Up Care After Subdermal Implant Insertion

Patients should be seen one week after insertion to examine the insertion site for signs of infection and wound healing problems, including implant extrusion. [PROBUPHINE PI] Thereafter, patients are seen on a monthly basis 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.

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. [PROBUPHINE PI] 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.

To remove an implant, the skin above the implant is lifted, the tissue around the implant is released, and the implant is grasped in the center and gently retracted. In the event that 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.

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.

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. [PROBUPHINE PI] 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 one 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.

Naltrexone LAI

Prior to the administration of naltrexone LAI, a minimum of 7-10 days opioid abstinence is required per the package insert to avoid precipitation of opioid withdrawal [VIVITROL PI] (**Table 10**). The ASAM recommends in general, a 6-day period of abstinence from short-acting opioids. [ASAM 2020] 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.

Withdrawal Management Strategies

There are two main withdrawal management strategies: (1) gradual opioid taper and (2) more rapid discontinuation with use of adjunctive nonopioid medications. [Sigmon 2012] 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.

In clinical practice, buprenorphine-assisted withdrawal management can be safely performed using the following protocol, which was tested in a clinical study. [Sullivan 2017] On Day 1, the patient is asked to abstain from all opioids for 12-24 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 washout period, a naloxone challenge is performed prior to administering naltrexone LAI. For the naloxone challenge, 0.4-0.8 mg of naloxone is administered intramuscularly and the patient is monitored for precipitated withdrawal symptoms. [ASAM 2020; Bisaga 2018]

The same clinical study also tested a naltrexone-assisted withdrawal management strategy. [Sullivan 2017] On Day 1, the patient is instructed to abstain from all opioids as for the buprenorphine-assisted withdrawal management protocol. On Day 2, the patient receives a single-day dosing of buprenorphine of 8 mg. On Day 3, standing doses of clonidine (0.1-0.2 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, oral naltrexone was initiated at a dose of 1 mg, with increasing daily doses given through Day 7 (3 mg, 12 mg, and 25 mg). On Day 8, after having tolerated 25 mg of naltrexone on the previous day, the patient is administered 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 mentioned withdrawal management clinical study. [Sullivan 2017] 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%). 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 [Bisaga 2018; Comer 2020]. Clinically, use of ancillary meds to manage withdrawal (clonidine and meds for symptoms) is very helpful.

In summary, there are two 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, or 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 stored refrigerated. [VIVITROL PI] 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 the suspension is taken up into the syringe and injected into the gluteal muscle using one of two needles provided—a 1.5 inch- or 2-inch needle. The choice of needle is dependent on the patient's body habitus. The buttocks are alternated for each subsequent injection.

Follow-Up Care

Patients should be monitored for injection site reactions, including pain, tenderness, induration, swelling, erythema, bruising, or pruritus. [VIVITROL PI] Patients' liver function should also be monitored because cases of hepatitis and clinically significant liver dysfunction have been reported. Because this is rare, the FDA has removed the black box warning since there is little evidence of liver irritation by naltrexone except at high doses. A baseline alanine aminotransferase or aspartate aminotransferase assessment should be done before administering naltrexone LAI.

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 [Williams 2017; Nunes 2018]. 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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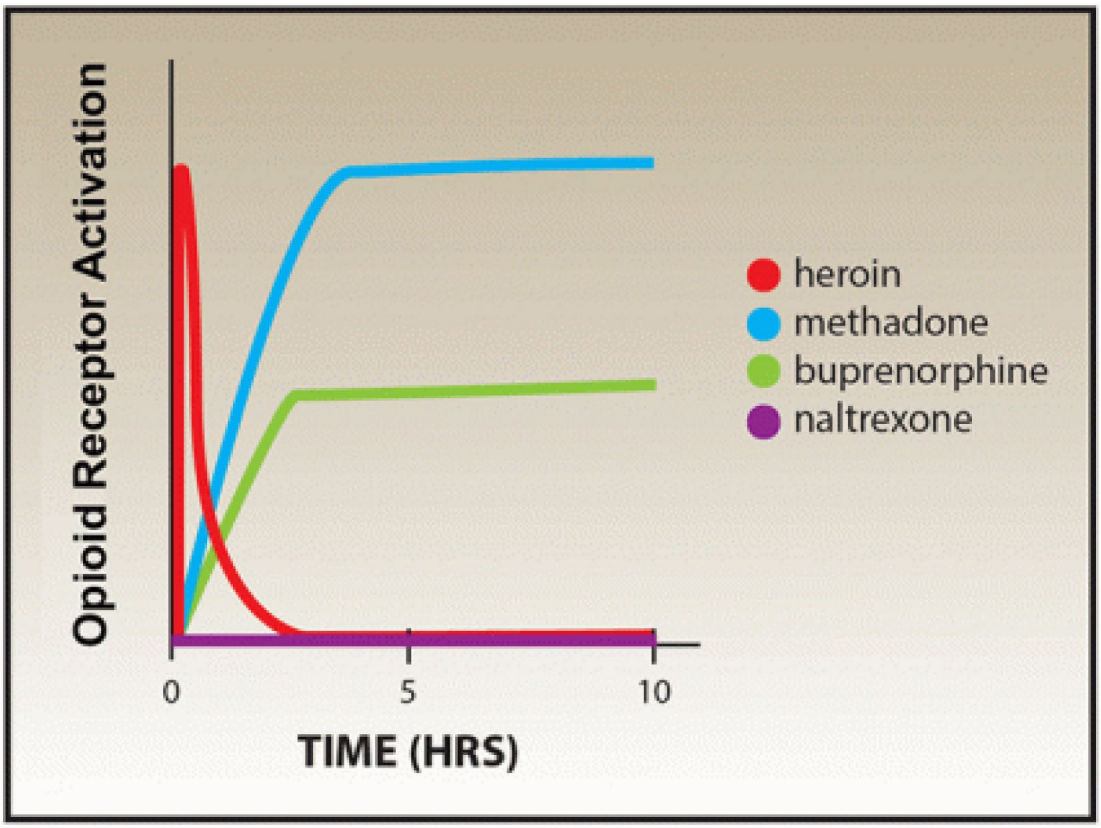
FIGURES

Figure 1. Opioid receptor activity. [National Institute on Drug Abuse 2018]



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.

TABLES

Table 1. Drug Use Terminology [National Institute on Drug Abuse 2018]

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 leads 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

Table 2. The "4R's" and "4C's" Screening Tool for Substance Use Disorder in Clinical Practice. [Curtis 2019]

The 4R's	The 4 C's
• Role failure • Relationship trouble • Risk of bodily harm • Repeated attempts to cut back	• Control (loss of it) • Craving • Compulsion to use • Consequences of use

Table 3. Components of Comprehensive Assessment for OUD and other substance use disorders [American Society on Addiction Medicine Standards of Care 2020] *[**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)

Table 4. DSM-5 Criteria for OUD [American Psychiatric Association 2013]

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 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 role 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
*This criterion is not met for individuals taking opioids solely under appropriate medical supervision.
Severity Classification:

Mild: Presence of 2-3 symptoms
Moderate: Presence of 4-5 symptoms
Severe: Presence of 6 or more symptoms

<<**Tables 5 and 6, please see end of document as they are in landscape format.**>>

Table 7. Advantages/Disadvantages of Oral/Sublingual versus Long-Acting Formulations

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

LAIs = long-acting injections; OTP = opioid treatment program.

Table 8: Key Points for the Use of Buprenorphine Monthly LAI

Administer Buprenorphine monthly LAI only in patients initiated on sublingual buprenorphine followed by dose adjustment for a minimum of 7 days
Initiation of Sublingual Buprenorphine: • 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
Transitioning to Buprenorphine Monthly LAI: • 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 two consecutive months • Administer the LAI on the abdomen in the subcutaneous space; avoid the muscle
Maintenance and Follow-Up Care: • After first 2 doses, maintain patient on a dose of 100 mg monthly • At each visit o Examine the injection site for signs of infection, evidence of tampering, or attempts to remove the depot o Assess for treatment effectiveness, illicit drug use, and overall patient progress

- Continue treatment long-term

Table 9. DSM-V Criteria for Opioid Withdrawal [American Psychiatric Association 2013]

<table>
<tr><td colspan="2">A. Presence of either of the following:

1. Cessation of (or reduction in) opioid use that has been heavy and prolonged (i.e., several weeks or longer)

2. Administration of an opioid antagonist after a period of opioid use</td></tr>
<tr><td colspan="2">B. Three (or more) of the following developing within minutes to several days after Criterion A:</td></tr>
<tr><td>1. Dysphoric mood

2. Nausea or vomiting

3. Muscle aches

4. Lacrimation or rhinorrhea

5. Pupillary dilation, piloerection, or sweating</td><td>6. Diarrhea

7. Yawning

8. Fever

9. Insomnia</td></tr>
<tr><td colspan="2">C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning</td></tr>
<tr><td colspan="2">D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance</td></tr>
</table>

Table 10. Key Points for the Use of Naltrexone LAI

Naltrexone LAI should only be administered after a minimum of 7-10 days of opioid abstinence

Detoxification Strategies for Opioid Abstinence:
• Follow one of two strategies:
  ○ Gradual opioid taper
  ○ Naltrexone-assisted detoxification

Administration of Naltrexone LAI: • 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:
• Monitor the patient for injection site reactions
• Continue treatment long-term
• Advise patients who wish to discontinue:
  ○ Of the risk of opioid overdose and overdose death if they return to illicit opioid use
  ○ Of overdose prevention with naloxone
  ○ Of alternative treatments

Table 5. Oral/Sublingual Treatments for OUD

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	Constipation, nausea, drowsiness, sweating, sexual dysfunction, weight gain, edema, amenorrhea, and prolonged QT interval at higher doses, higher risk of overdose than 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 (e.g. benzodiazepines or alcohol)	Insomnia, hepatic dysfunction, nasopharyngitis, sedation, may increase risk of overdose if return to use because of decreased tolerance

Implications for practice	• 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	• 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 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

		• Patients may need to be seen one to two times per week initially, can typically be spaced to monthly visits	

DEA = Drug Enforcement Administration; NP = nurse practitioner; OTP = opioid treatment program; OUD = opioid use disorder; PA = physician's assistant.

Table 6. Long-Acting Formulations for the Treatment of OUD

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,	Injection site pain, nasopharyngitis, insomnia, hepatic enzyme abnormalities, and toothache

			toothache, and oropharyngeal pain	
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,	• 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	• 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

	followed by dose adjustment for a minimum of 7 days prior to LAI initiation		doses of a transmucosal buprenorphine (i.e., no more than 8 mg per day) before treatment initiation	

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