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### **Medications for Opioid Use Disorder**

**SCOPE:** This Medications for Opioid Use Disorder (MOUD) Guideline is intended to offer prescribing assistance for providers, patients and the interested general public to increase the effectiveness and safety of MOUD in the ambulatory care setting. It is not intended to be comprehensive in scope. These recommendations are not a substitute for clinical judgment, and decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual patient. References can be found in the OUD References and Further Reading.

**MOUD PHARMACOTHERAPY SELECTION:** Three medications, methadone, buprenorphine and naltrexone, are approved by the US Food and Drug Administration. The effect of each medication is through effects on the mu-opioid receptor and each agent has demonstrated health benefits including in reduction in unprescribed or cessation of opioid use. Beyond this, the agents differ in their mechanism of action and respective treatment outcomes.

The two major medications available for the treatment of OUD are buprenorphine and methadone, which have both demonstrated to reduce all-cause mortality by 50%. Choice between these agents is based on patient preference. Methadone and buprenorphine are available in Opioid Treatment Programs, while buprenorphine is available for office-based treatment and can be provided by any prescriber with a DEA license. Additional considerations include past treatment experience with MOUD, program structure and accessibility, patient medical and psychiatric co-morbidities and medications. For a list of contraindications and cautions for each agent, see Appendix 1. For buprenorphine induction methods see the section on Buprenorphine Initiation Methods

Buprenorphine and naltrexone are available as long-acting injections. Buprenorphine long-acting injectables must be obtained through a restricted distribution program (REMS) and should be dispensed directly to a member of the healthcare team.

For craving reduction and relapse prevention in a patient who is interested in a non-opioid agonist medication treatment, extended-release naltrexone injection may be an effective choice. It is important to note that oral naltrexone pills are not effective for OUD as evidence suggests they are no more effective than placebo. The main challenge to effective treatment with extended-release naltrexone injection is the long period of abstinence necessary to initiate the medication, limited effectiveness at retaining people in treatment and lack of demonstrated evidence for mortality reduction.

**OPIOID OVERDOSE TREATMENT AND PREVENTION:** Naloxone is a mu-opioid receptor antagonist that reverses the effects of opioids. In California, anyone who is at risk for experiencing or witnessing an opioid overdose can be furnished take-home naloxone for bystander administration.

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Additionally, in March 2023, the US FDA approved naloxone nasal spray for purchase over-the-counter. More than one dose of naloxone may be necessary, as might rescue breathing and CPR for trained individuals or supplement oxygen if available, especially if the opioid is combined with other central nervous system depressants.

People with OUD, both not in treatment and in treatment, should be offered a take-home naloxone kit and provided education on overdose recognition and reducing risk of opioid overdose. Non-prescribed and street drugs can contain opioids. Therefore, anyone that takes these should be offered a take-home naloxone kit and fentanyl test strips. The person's family and friends should be included in the education in order for them to be trained to identify and respond to an opioid overdose. For details on take-home naloxone, see the BHS Overdose Prevention and Naloxone guideline, BHS Recommendations for Take Home Naloxone, and the DPH Clearinghouse Naloxone Distribution Policy and Procedures. Providers may consider offering fentanyl test strips to patients who use drugs, now available via the DPH Naloxone Clearinghouse

**OPIOID WITHDRAWAL AND MANAGEMENT:** Opioid withdrawal typically does not include severe and life-threatening symptoms compared to withdrawal syndromes characteristic of other substances (e.g., alcohol and benzodiazepines). Although not life-threatening, opioid withdrawal can be uncomfortable and distressing. Patients experiencing opioid withdrawal symptoms must be treated humanely and their symptoms addressed to preserve their dignity. Failure to do so increases the chances of return to use, overdose, distrust of medical care, or abandonment of treatment.

The symptoms of opioid withdrawal are experienced as the opposite of the pharmacologic effects of opioids. The onset, duration, and intensity of withdrawal symptoms vary and are dependent upon the particular opioid used, the duration of use, and the degree of dependence and tolerance. Mood, anxiety, trauma, stress, and other factors can influence the experience of opioid withdrawal symptoms.

Opioid withdrawal management alone is not an effective treatment for OUD and should be part of a comprehensive treatment plan. When opioid withdrawal management is used alone, patients are at increased risk of return to use, overdose, and overall mortality. Patients withdrawing from opioids with severe and poorly managed co-occurring medical, psychiatric, and cognitive conditions may require close monitoring in a hospital or residential setting. Additionally, patients who are withdrawing from opioids and other substances (e.g., alcohol, benzodiazepines) may require close monitoring and additional interventions.

Medication treatment can and should be provided in all healthcare settings for interested individuals. For people who are interested in more recovery supports, linkage to appropriate services should occur as part of a patient's comprehensive treatment plan. While opioid withdrawal management alone is not considered adequate treatment, it may be included as the first of step-wise interventions that include evaluation, stabilization, and fostering readiness for and entry into treatment, consistent with the ASAM recommendation for all substance use disorders.

**BUPRENORPHINE INITIATION METHODS:** Buprenorphine can be initiated by multiple methods highlighted in the following section. In addition, Epic users can find these as an SmartSet under "Buprenorphine - MOUD Order Set". The selection of buprenorphine initiation methods should be

driven by patient choice. There are currently no randomized controlled trials to support one method over the other. Table 1 highlights some considerations when choosing buprenorphine initiation. This is not intended to replace clinical judgement.

**Table 1. Buprenorphine Initiation Method Selection**

See Appendix 4 for additional guidance

Method	Consider for	Potential Disadvantages
Sublingual traditional starts	<ul style="list-style-type: none"> <li>- Using heroin or other short-acting opioids</li> <li>- People who do not have access to full-agonist opioids or wish to stop them immediately</li> </ul>	<ul style="list-style-type: none"> <li>- Patient must be able to stop opioids long enough to be in moderate withdrawal</li> <li>- Requires longer period of cessation for people using fentanyl</li> </ul>
Sublingual overlap starts (also known as microdosing)	<ul style="list-style-type: none"> <li>- Difficulty starting buprenorphine using traditional start</li> <li>- Currently on methadone</li> <li>- Transitioning from prescribed full opioid agonists for pain to buprenorphine</li> <li>- Using fentanyl daily</li> <li>- Not interested in stopping opioids before starting buprenorphine</li> </ul>	<ul style="list-style-type: none"> <li>- Off-label dosing</li> <li>- Patients need adjunctive medications to minimize opioid withdrawal</li> <li>- Requires following a scheduled dosing regimen which may be difficult for some</li> </ul>
Sublingual macrodosing	<ul style="list-style-type: none"> <li>- Patient understanding and preference to experience opioid withdrawal for one day which may be severe</li> <li>- Able to wait until they are in moderate opioid withdrawal to start</li> </ul>	<ul style="list-style-type: none"> <li>- Off-label dosing</li> <li>- Method with most limited evidence</li> <li>- High risk for precipitated withdrawal - recommend providing adjunctive medications</li> <li>- More tolerated with longer periods since last fentanyl use (~2 days)</li> </ul>
Buprenorphine long-acting with sublingual to start	<ul style="list-style-type: none"> <li>- Patient prefers injectable medication</li> <li>- Patient prefers to initiate with sublingual buprenorphine before initiating LAI</li> </ul>	<ul style="list-style-type: none"> <li>- Starting sublingual first may be a barrier for some patients</li> <li>- Risk of injection site reactions</li> </ul>
Buprenorphine long-acting injection 2 injection Direct to Inject	<ul style="list-style-type: none"> <li>- Patient prefers injectable medication</li> </ul>	<ul style="list-style-type: none"> <li>- Off- label dosing</li> <li>- Risk of precipitated withdrawal – recommend</li> </ul>

	<ul style="list-style-type: none"> <li>- Patient prefers to initiate immediately with buprenorphine LAI</li> <li>- Patient has difficulty initiating with buprenorphine SL</li> </ul>	<ul style="list-style-type: none"> <li>- providing adjunctive medications</li> <li>- Risk of injection site reactions</li> </ul>
Buprenorphine long-acting injection 3 injection Direct to Inject	<ul style="list-style-type: none"> <li>- Patient prefers injectable medication</li> <li>- Not interested in stopping opioids before starting buprenorphine</li> <li>- Patient prefers to initiate immediately with buprenorphine LAI</li> <li>- Patient has difficulty initiating with buprenorphine SL</li> </ul>	<ul style="list-style-type: none"> <li>- Off-label dosing</li> <li>- Risk of precipitated withdrawal by possibly lower than 2 injection Direct to Inject</li> <li>- Team needs to coordinate 3 sequential injections</li> <li>- Risk of injection site reactions</li> </ul>

**SUBLINGUAL TRADITIONAL STARTS:** These starts are well established in people switching from short-acting opioids such as heroin, oxycodone, morphine, etc. They require the person to be in mild to moderate opioid withdrawal prior to starting. Patients can be instructed to wait 12 hours from last short-acting opioid use (48-72 hours for long-acting opioids such as oxycodone ER or non-pharmaceutical fentanyl) and identify 3 symptoms or signs of opioid withdrawal prior to starting. Patients that are not physically dependent on opioids may benefit from lower starting doses of 2 mg.

Day 1: Buprenorphine 2 mg SL q2h prn opioid withdrawal (up to 8-16 mg)

**OR**

Day 1: Buprenorphine 4 mg SL q2h prn opioid withdrawal (up to 24 mg)

**OR**

Day 1: Buprenorphine 8 mg SL q2h prn opioid withdrawal (up to 24 mg)

**AND**

Day 2-7: Buprenorphine 8mg BID or TID

**SUBLINGUAL OVERLAP INITIATIONS (aka MICRODOSING):** Traditional protocols for buprenorphine initiation are well established and work for many individuals with OUD. However, there are various clinical circumstances when alternative, off-label, buprenorphine initiation strategies may be desired (see Table 1). Off-label methods for dosing buprenorphine has limited but growing evidence, although they are not universally accepted. These initiation strategies aim to use very small doses of buprenorphine that are gradually increased. Given the sub-therapeutic levels of buprenorphine, it is common for patients to continue to use other full agonist opioids. This allows buprenorphine levels to build up slowly and minimizes the withdrawal patients experience. CBHS

pharmacy has developed 2 protocols which are shown below and are accompanied by patient education, counseling points, and blister packs.

*Prescribing/Dispensing Tips:*

- All take home doses for overlap starts >1 day will be blister-packed for ease of use
  - See table below for an example regimen → schedule. This should be adjusted depending on how patient tolerates the start or if they miss doses
- Buprenorphine mono-product is recommended when the tablets are being cut into quarters

**Overlap Initiation 7-day Protocol (AKA The Howard Street Method)**

<b>Buprenorphine mono-product 2 mg tablets (NDC 50383-0924-93)</b>	
<b>Blister-pack days 1-3 and dispense #2 tablets</b>	
Day 1	Dissolve ¼ of a 2 mg tablet (0.5 mg) under your tongue in the morning
Day 2	Dissolve ¼ of a 2 mg tablet (0.5 mg) under your tongue twice daily
Day 3	Dissolve ¼ of a 2 mg tablet (0.5 mg) under your tongue in the AM Then Dissolve ½ tablet (1 mg) in the afternoon and evening
<b>Buprenorphine-Naloxone or Buprenorphine mono-product 2 mg Tablets</b>	
<b>Blister-pack days 4-6 and dispense #9 tablets</b>	
Day 4	Dissolve 1 (2 mg) tablet under your tongue twice daily
Day 5	Dissolve 1 and ½ (3 mg) tablets under your tongue twice daily
Day 6	Dissolve 2 (4 mg) tablets under your tongue twice daily
<b>Buprenorphine-Naloxone or Buprenorphine Mono-Product</b>	
<b>Provider can change to films based on patient preference</b>	
Day 7 +	Custom (12-32 mg depending on clinical situation)

**Overlap Initiation 4-day Protocol**

<b>Buprenorphine mono-product 2 mg tablets (NDC 50383-0924-93)</b>	
<b>Blister-pack and dispense #7 tablets</b>	
Day 1	Dissolve ¼ of a 2 mg tablet (0.5 mg) under your tongue observed now, then every 6 hours for a total of 4 doses
Day 2	Dissolve ½ of a 2 mg tablet (1 mg) under your every 6 hours for a total of 4 doses
Day 3	Dissolve 1 (2 mg) tablet under your every 6 hours for a total of 4 doses
<b>Buprenorphine-Naloxone or Buprenorphine Mono-Product</b>	
<b>Provider can change to films based on patient preference</b>	
Day 4+	Custom (12-32 mg depending on clinical situation)

*Patient Education:*

- This is a gentle and gradual way for you to start buprenorphine that will not require you to stop using opioids until later.
- There is some discomfort during the overlap start. It is common that people feel mild anxiety, nausea, or restlessness. We will provide medications to take if you feel these symptoms. This

can feel like early withdrawal, but it is rare that someone gets fully sick when they follow the blister pack.

- We blister-pack your medication to help you stay on your dosing schedule. It is important to follow the schedule to avoid severe withdrawal.
- If you miss doses of buprenorphine, please check in with your provider to avoid getting sick (also known as precipitated withdrawal).
- Commonly, people continue to use opioids given the smaller doses of buprenorphine are not enough. You can try to cut down on your opioid use gradually over the week. However, you do not have to. This can happen later when you're on a higher dose if that is your goal.
- Do not try to quantify how much opioid that you need to decrease per day – let your body naturally cut down. As the buprenorphine builds up in your body, you will notice that the same amount of opioid does not cause the same effect, and you can begin to try less if you want at a rate that feels comfortable.
- You may not notice a decrease in opioid use or notice decreased effects from other opioids after the first few days as the buprenorphine slowly builds up.
- You may not feel 100% better right away. Your body is transitioning, and most people feel better and better with time.
- The goal of overlap starts is to avoid going through significant opioid withdrawal, though you may still notice some more mild opioid-withdrawal symptoms. Your provider may prescribe other medications to help treat these (ex. Restlessness, anxiety, trouble sleeping)
- After overlap starts, you may continue on buprenorphine at a higher total daily dose. Talk to your provider about what dose and duration is right for you.

**SUBLINGUAL MACRODOSING:** Macro dosing is a broad term used to describe starting buprenorphine at doses  $\geq 16$  mg. This method has limited evidence from patients in the Emergency Department and does not have substantial published evidence in the outpatient setting. Patients are less likely to experience precipitated withdrawal with longer periods of since last opioid use. For patients using fentanyl, it is often more well tolerated by waiting 48-72 hours since last fentanyl use. Therefore, the use should be limited to patient preference with adequate risk discussion.

Day 1: Buprenorphine 16 mg SL as needed for opioid withdrawal, then 8mg every 1-2 hours as needed for withdrawal up to 32 mg total

Days 2-7: Buprenorphine 8 mg TID

*Patient Education:*

- Severe opioid withdrawal may occur and adjunctive medications for opioid withdrawal management should be used
- Wait until you are in at least moderate opioid withdrawal prior to starting, waiting longer is associated with less precipitated withdrawal (closer to 2 days since last fentanyl use)

**BUPRENORPHINE LONG-ACTING INJECTION WITH SUBLINGUAL TO START:** There are two buprenorphine long-acting injectable (LAI) formulations. Sublocade is a monthly injection that has a long half-life which reduces the risk of overdose even after the patient misses an injection. Brixadi is available as a weekly and monthly product allowing for patients to have the choice in dosing frequencies. See Appendix 3 for a summary of buprenorphine LAI dosing. Any of the buprenorphine

sublingual starting methods can be utilized to initiate buprenorphine prior to an injection. Each LAI has recommendations for how long a patient should be take buprenorphine prior to starting the LAI (see Appendix 3).

**BUPRENOPRHINE LONG-ACTING INJECTION WITH DIRECT TO INJECT:** Direct to inject (DTI) is a term used for initiating buprenorphine long-acting injectable in people who are not currently taking buprenorphine. This initiation method may be appropriate for some patients, in particular those who prefer this method. There is a small but growing amount evidence for initiating buprenorphine via direct to inject with Brixadi (weekly). The pharmacokinetics of Sublocade and Brixadi (monthly) differ from Brixadi (weekly) in terms of time to peak levels. Therefore, direct to inject is only recommended with Brixadi (weekly) There are two protocols for initiating buprenorphine long-acting DTI that include a 2 -injection DTI and 3-injection DTI. The protocols differ in number of injections, dosing and whether the patient needs to be in opioid withdrawal prior to initiating. See the Direct to Inject Guideline for details of the protocols and patient selection.

**APPENDIX 1: MEDICATION TABLES**

**TABLE 2: MEDICATIONS FOR OPIOID Use Disorder**

Medication	Mechanism of Action	Dose & Administration	Contra-indications	Adverse Effects	Comments
<p><b>Buprenorphine</b></p> <p><b>Buprenorphine long-acting injection</b></p>	<p>Partial mu opioid agonist which reduces opioid withdrawal symptoms and cravings. The high binding affinity for the mu-opioid receptor blocks the effects of other opioids.</p>	<p><i>Patients should be in mild to moderate opioid withdrawal (COWS &gt;10) when initiating buprenorphine to prevent precipitated withdrawal</i></p> <p><b>Sublingual/buccal:</b>                      Induction 2-4 mg q2h prn opioid withdrawal symptoms up to 8 mg on Day 1. Then increase in 4-8 mg increments to a maintenance dose of 12-16 mg per day. Max 32 mg per day. To avoid precipitated withdrawal among people on fentanyl or methadone, clinicians offer low-dose buprenorphine inductions (with film</p>	<p>Use of opioid antagonists</p> <p>Known allergy to buprenorphine (rare)</p>	<p>Sedation, anxiety, constipation, nausea, vomiting, diaphoresis, headache</p>	<p>Buprenorphine was the first opioid agonist treatment available in an office-based setting. Buprenorphine can be prescribed for OUD treatment by any physician, nurse practitioner, pharmacist or physician assistant that has a DEA license. There are no regulations for treatment inclusion or exclusion or limits on number of patients one individual prescriber can treat. Partial mu opioid agonist leads to ceiling effect for respiratory depression and improved safety profile. However, when combined with additional CNS depressants the ceiling effect is mitigated although continues to be lower risk than other full agonist opioids.</p> <p>In addition to treating opioid withdrawal and cravings, maintenance treatment with buprenorphine is associated with increased treatment retention compared to detoxification.</p> <p>Buprenorphine binds with high affinity to the mu opioid receptor and can displace full opioid agonists leading to precipitated withdrawal. Therefore, an appropriate</p>

		<p>or patches) with overlap of full agonist opioid.</p> <p>A maintenance dose is established when a patient no longer experiences opioid cravings or opioid withdrawal.</p> <p><b>Injection:</b></p> <p><b>Sublocade:</b></p> <p>For patients not currently taking buprenorphine, administer a test dose of 4 mg SL when objective and clear signs are opioid withdrawal are present and observe for one hour to confirm tolerability. Recommended dose is 2 initial doses of 300 mg given as early as 1 week or up to 1 month after initial injection, followed by 100 mg monthly</p>		<p>initiation method should be discussed with patients.</p> <p>Buprenorphine can be prescribed in a co-formulated product with naloxone which was added due to block effects of buprenorphine if injected (which is exceedingly rare).</p> <p>Naloxone has minimal absorption when taken sublingually or buccally (see Hepatic Impairment for exceptions) but can result in side effects for some patients. All formulations of buprenorphine are safe and effective, regardless if they contain naloxone. The formulation should be based on patient preference and patients should not be required to use formulations co-formulated with naloxone.</p> <p>In January 2022, FDA issued a warning about the potential for dental problems in buprenorphine products that dissolve in the mouth. They recommend swishing with a large sip of water after the medication dissolved and recommend regular dental check-ups while on buprenorphine. Several professional societies called for FDA to retract this warning, stating that the FDA's findings are not based on solid research evidence and can lead to potentially harmful, stigmatizing effects that may further limit access to buprenorphine. BHS supports reducing barriers and stigma to buprenorphine access.</p>
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	<p>maintenance dose. If using this rapid initiation method, up to 8 mg SL buprenorphine could be given to manage withdrawal symptoms on induction day. Increasing the maintenance dose to 300 mg may be considered when benefits outweigh risks. Healthcare settings and pharmacies that dispense injection must be enrolled in REMS program.</p> <p><b>Brixadi:</b></p> <p>For patients not currently taking buprenorphine, administer a test dose of 4 mg SL followed by an initial dose of 16 mg of Brixadi (weekly). Administer an</p>			<p><b>Injection:</b></p> <p>Sublocade: indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. Brixadi: Indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. (1)</p> <table border="1" data-bbox="1333 730 1906 1079"> <thead> <tr> <th>Daily dose of SL</th> <th>Brixadi (Weekly)</th> <th>Brixadi (Monthly)</th> </tr> </thead> <tbody> <tr> <td>≤ 6 mg</td> <td>8 mg</td> <td>N/A</td> </tr> <tr> <td>8-10 mg</td> <td>16 mg</td> <td>64 mg</td> </tr> <tr> <td>12-16 mg</td> <td>24 mg</td> <td>96 mg</td> </tr> <tr> <td>18-24 mg</td> <td>32 mg</td> <td>128 mg</td> </tr> </tbody> </table> <p><b>Drug Interactions:</b> Metabolized by CYP3A4</p> <p><b>Monitoring:</b> Attend regular dental check ups.</p>	Daily dose of SL	Brixadi (Weekly)	Brixadi (Monthly)	≤ 6 mg	8 mg	N/A	8-10 mg	16 mg	64 mg	12-16 mg	24 mg	96 mg	18-24 mg	32 mg	128 mg
Daily dose of SL	Brixadi (Weekly)	Brixadi (Monthly)																	
≤ 6 mg	8 mg	N/A																	
8-10 mg	16 mg	64 mg																	
12-16 mg	24 mg	96 mg																	
18-24 mg	32 mg	128 mg																	

		<p>additional dose of 8 mg within 3 days of first dose to achieve 24 mg.</p> <p>Patients already taking SL buprenorphine may be converted to Brixadi (weekly) or Brixadi (monthly) at an equivalent dose. See above guidance for injection without prior SL administration.</p> <p><i>Renal impairment:</i> no adjustment</p> <p><i>Hepatic impairment:</i> Buprenorphine: decrease dose by 50% in severe impairment.</p> <p>Naloxone: avoid naloxone containing products in severe (and possibly moderate) impairment</p>			
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<p><b>Methadone</b></p>	<p>Full m opioid agonist which reduces opioid withdrawal symptoms and cravings. The high binding affinity for the m opioid receptor blocks the effects of other opioids.</p>	<p><i>Only available from a Opioid Treatment Program or as emergency treatment of withdrawal through “72 hour methadone” rules when treating OUD.</i></p> <p><b>Oral:</b> 10-50 mg PO daily titrated every 5 days to a maintenance dose of 0 – 120 mg daily or higher for people using fentanyl due to higher tolerance.</p> <p>A maintenance dose is established when a patient no longer experiences opioid cravings or opioid withdrawal and is not experiencing side effects. Of note, higher doses are expected among people who use fentanyl. Further, women who are pregnant or those deemed to be rapid</p>	<p>Contraindications: Paralytic ileus, documented Torsade de pointes (Tdp) on methadone, use of opioids antagonists</p> <p>Caution: decompensated liver disease, severe apnea, severe asthma, severe COPD, sedative-hypnotic or CNS depressant abuse, familial QTc prolongation or QTc prolongation &gt;450 msec, concomitant use of medications that prolong the QTc interval</p>	<p>Sedation, constipation, nausea, vomiting, diaphoresis, QTc prolongation, Tdp, respiratory depression</p>	<p>The use of methadone for the treatment of OUD is restricted to licensed Opioid Treatment Programs (OTP).</p> <p>In addition to reducing withdrawal and cravings, methadone for OUD has the best evidence for treatment retention, in addition to reducing unprescribed opioid use, reduced seroconversion of HIV and HCV, reduced mortality of OUD, reduced criminal behavior and improved birth outcomes.</p> <p>Methadone has a long half-life resulting in a steady-state serum levels 3-5 days after dose adjustments, therefore doses are titrated slowly to reduce toxicity.</p> <p>OTP’s have additional confidentiality requirements under Code of Federal Regulations 42; therefore, methadone will not be present on CURES.</p> <p><b>Drug Interactions:</b> Multiple drug interactions, primarily metabolized by CYP3A4, followed by CYP2B6 and CYP2C19 and, to a lesser degree by CYP2C9 and CYP2D6. Examples of medications increase methadone serum levels by CYP3A4 inhibition includes azole antifungals, macrolides, fluoroquinolones and some antidepressants</p>
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		<p>metabolizers may need split dosing.</p> <p><i>Hepatic impairment:</i> no adjustments providers in package insert</p> <p><i>Renal impairment:</i> CrCl ≥10mL/min: no dose adjustment. CrCL &lt;10mL/min: use 50-75% of normal dose</p>			<p>Medications to avoid with methadone include efavirenz, ketoconazole, rifampin</p> <p><b>Monitoring:</b> EKG monitoring practices are variable in terms of timing and dose. Expert consensus from the American Society of Addiction Medicine (ASAM) recommends EKG in patients on methadone doses &gt;120mg per day, patients with a history of QTc prolongation and in patients taking medications that prolong the QTc interval</p>
<b>Naltrexone long-acting injection</b>	mu opioid antagonist which may block the effects of opioids	<p><b>Injection:</b> 380 mg IM monthly</p> <p>Patients must not take opioids for 7-14 days before starting naltrexone, duration of opioid abstinence will depend on half-life of opioids used. Consider naloxone challenge to assess for opioid withdrawal.</p>	<p>Use with caution in patients with cirrhosis. Avoid use if acute liver injury or transaminitis. Likely safe in patients with Child's Pugh Class A or B cirrhosis. Typically not recommended for patients with Child's Pugh C or D unless benefits outweigh the risks of potential drug- induce liver injury</p>	<p>Nausea, headache, anxiety, sedation.</p> <p>Warnings of hepatotoxic effects are derived from studies using oral dosages up to 300 mg/day for obesity and dementia. No reports of hepatotoxicity at FDA</p>	<p>Naltrexone that has no required certifications to prescribe or requirements for treatment setting.</p> <p>Does not treating opioid withdrawal.</p> <p>A person must not have used opioids in 7-14 days prior to initiating naltrexone to avoid precipitated withdrawal.</p> <p><b>Monitoring:</b> Check LFTs and INR prior to initiation if concern for liver disease. Labs are not required prior to initiating treatment. When possible, monitor LFTs periodically while on treatment (annually unless signs or symptoms of hepatitis develop).</p>

			and with shared patient decision making. ,  Pregnancy: Use is not recommended. May be considered if benefits are determined to outweigh the risks and with shared patient decision making.	recommended dose.	
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**TABLE 3: MEDICATIONS FOR MANAGING SYMPTOMS OF WITHDRAWAL**

Medication	Target withdrawal symptom	Dose & Administration	Adverse Effects	Comments
Acetaminophen	Myalgias	<b>Oral:</b> 325-500 mg every 6 hours as needed	Nausea, loss of appetite	
Baclofen	Muscle cramps	<b>Oral:</b> 5-10 mg up to three times daily as needed	Drowsiness, nausea/vomiting, confusion, dizziness, hypotonia, asthenia	Use with caution with other CNS depressants as they may have additive effects with baclofen

Clonidine	Restlessness, sweating, anxiety	<b>Oral:</b> 0.1 to 0.2 mg (patients >90 kg may receive up to 0.3 mg); may repeat every 45 to 60 minutes if needed, up to a total of 4 doses until symptoms resolve, provided blood pressure and heart rate remain stable; maximum dose: 1.2 mg/day	Bradycardia, hypotension, dry mouth, dizziness, headache	Hypotension is uncommon at low doses. When possible, check blood pressure prior to starting. Use with caution if concern for hypotension or discuss symptoms to look out for with patients.
Hydroxyzine	Anxiety, insomnia	<b>Oral:</b> 25-50 mg every 6 hours as needed	Somnolence, dry mouth	
Ibuprofen	Myalgias	<b>Oral:</b> 400 mg every 6 hours as needed	Stomach upset	Take with food
Lofexidine	Restlessness, sweating, anxiety	<b>Oral:</b> 0.54-0.72 mg every 6 hours during the period of peak withdrawal symptoms (generally the first 5 to 7 days following last use of opioid) with dosing guided by symptoms and side effects. Max dose is 2.88mg/day. When discontinuing treatment, taper lofexidine by 1 tablet every 1-2 days. Adjust dose for renal and hepatic impairment (see package insert).	Orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, dry mouth	Limited efficacy seen in clinical trials <b>Drug Interactions:</b> <b>Methadone:</b> Concern for QT prolongation. ECG monitoring is recommended when used concomitantly. <b>Oral naltrexone:</b> Concomitant use may reduce efficacy of oral naltrexone. <b>CYP2D6 Inhibitors:</b> Monitor for symptoms of orthostasis and bradycardia with concomitant use. <b>Monitoring:</b> Monitor vital signs before dosing and advise patients on how to minimize risk of hypotension, bradycardia and syncope. Monitor ECG in patients at risk for QT prolongation.

Loperamide	Diarrhea	<b>Oral:</b> 4 mg then 2 mg up to four times daily as needed	Dizziness, constipation, stomach upset	
Ondansetron	Nausea	<b>Oral:</b> 4-8 mg twice daily as needed for anticipated length of withdrawal	Constipation, fatigue, headache, malaise	Check QTc in individuals with risk factors for arrhythmias
Trazodone	Insomnia	<b>Oral:</b> 50-100 mg at bedtime as needed	Dry mouth, dizziness, fatigue, blurred vision, next-day somnolence	

## **APPENDIX 2: CBHS PHARMACY BUPRENORPHINE FAQ'S FOR CBHS PRESCRIBERS**

### **What services does CBHS Pharmacy provide for buprenorphine patients?**

CBHS Pharmacy provides specialty services for buprenorphine patients including the following:

Monitoring: Patients check in with a pharmacist every time they pick up buprenorphine. If the patient appears intoxicated with a CNS depressant, patients will be assessed by the pharmacist and possibly referred to onsite providers if available to re-evaluate for appropriateness for dosing. They will be assessed if they need urgent medical care. Patients may be instructed to return when they are more alert. Providers can also order onsite urine drug screening.

Observed dosing: Providers may request observed dosing for patients at the CBHS Pharmacy dispensing window.

Frequent dosing: Providers may request dosing schedules more frequent than every 28 days, including daily dosing (except holidays).

Alternative buprenorphine induction dosing support: Upon provider request, CBHS pharmacy provides prescriber consultation, medication bubble packing, in depth patient counseling and close monitoring for patients prescribed alternative initiation protocols (i.e. "micro-dosing").

Buprenorphine extended-release injection: The pharmacy processes and dispenses prescriptions for buprenorphine extended-release injections for providers that meet REMS requirements. A provider authorized to administer the medication can pick up the medication from the pharmacy. Or the medication can be ordered in advance and delivered to the providers DEA registered address as long as the clinic meets the requirements for controlled substance storage and has arranged with CBHS Pharmacy to ensure that they meet the requirements of the REMS program.

Naloxone: Patients can be educated on the risks for opioid overdose and trained to respond to overdoses with naloxone. It can be furnished by a pharmacist, prescribed by a provider, or purchased over the counter.

Smoking cessation: Pharmacists can assess for tobacco use and furnish nicotine replacement therapy (patches, gum, or lozenges). Providers may also prescribe nicotine replacement therapy and pharmacists will provide thorough smoking cessation counseling.

Sterile injection kits: CBHS pharmacy provides sterile injection kits with syringes and sharps containers to our patients at no charge with referrals to treatment.

Fentanyl test Strips: CBHS pharmacy provides fentanyl test strips to patients at no charge with referrals to treatment. Programs can apply to stock a supply on site.

Medication and syringe disposal: Pre-paid postage medication take-away mail bags are available at the pharmacy, or medications may be dropped off at our medication take back receptacle. Used syringes can be disposed in receptacles provided in the building.

### **What is CBHS Pharmacy's policy on early or late buprenorphine pick-ups?**

First early pick-up (e.g., lost meds, vacation): CBHS pharmacy does not allow patients to pick-up their medication before their assigned pick-up date without authorization by the prescriber. One

early pick-up is allowed in a 365-day period. For example: Patient picks up a 7-day supply on a Tuesday, making the following Tuesday their next assigned pick-up date. If the patient returns any day prior to their assigned pick-up date, authorization from the prescriber will be required.

Second or subsequent early pick-ups in a 365-day period: The patient is required to have consolidated daily observed dosing until their next pick-up date with prescriber authorization. For example: If patient is taking 8 mg TID, they will take 24 mg at once daily observed until next assigned due date. Prior to next pick-up, prescriber should identify reasons for frequent early pick-ups and adjust take-home supply accordingly.

Late pick-ups: Patients that are  $\geq 30$  days late picking up from their assigned pick-up dates will require authorization from the prescriber to dispense buprenorphine. Patients  $< 30$  days late picking up will be counseled on adherence and dispensed the prescription as written.

**Does CBHS Pharmacy have any policies that may affect the buprenorphine prescription I write?**

Dispense in 7-day increments: To keep patients assigned pick-up days the same day of the week, CBHS Pharmacy will dispense in increments of 7 days unless otherwise requested by the prescriber. Example: Prescription written for a 30-day supply will be dispensed for a 28-days' supply.

**What are CBHS Pharmacy's hours of operation and location?**

CBHS pharmacy is open 7 days per week. The window is open for pick-ups weekdays 9:00am-6:30pm and weekends 9:00am-4:00pm. On weekends, the pharmacy is closed for an hour lunch break 12:00pm-1:00pm. Pharmacy staff are available by phone weekdays 8:30am-8:00pm and weekends 9:00am-5:00pm for any questions. CBHS pharmacy is located at 1380 Howard Street.

**What if my patient is due to pick-up on a holiday and CBHS Pharmacy is closed?**

If a patient's scheduled pick-up date falls on a holiday when CBHS Pharmacy is closed, the patient will be allowed to pick-up their buprenorphine one business day before the holiday without counting as an early pick-up. CBHS Pharmacy posts signs reminding patients of holidays and this policy.

**What is CBHS Pharmacy's vacation supply policy?**

Approval from the prescriber is required. Other restrictions may apply, and a prior authorization may be required by the patient's insurance.

**What is the record keeping requirements for prescribing buprenorphine?**

The DEA has additional record keeping requirements for controlled substances prescribed for office-based opioid therapy, such as buprenorphine, beyond the usual for Schedule III substances. The following are the record keeping requirements:

Buprenorphine inventory log: Prescribers must keep an inventory of buprenorphine dispensed (21 CFR Section 1304.03[b]). This log is *required* even if the prescriber does not stock buprenorphine

products. Because no BHS clinic stocks buprenorphine products, this is generally a log with a zero balance.

**Who can I contact if I have further questions regarding buprenorphine at CBHS Pharmacy?**

CBHS substance use disorder pharmacists can help! Call 628-754-9110 to request a phone consult. Or reach out by email at [druginfo.bhs@sfdph.org](mailto:druginfo.bhs@sfdph.org).

### APPENDIX 3: BUPRENORPHINE LONG-ACTING INJECTABLES (LAIS)

#### BUPRENORPHINE LONG-ACTING INJECTION (SUBLOCADE)

**Dose:** Patients not currently taking buprenorphine should receive an initial dose (e.g. 4mg) of transmucosal buprenorphine before administering the first injection. The starting dose is 300 mg IM. The second injection is 300mg and may be administered as early as 1 week and up to 1 month after the initial injection. After two injections, the maintenance dose is 100mg monthly. A monthly maintenance dose of 300mg may be considered in patients who tolerate 100mg but do not demonstrate a satisfactory clinical response.

**Administration site:** subcutaneous tissue of the abdomen, thigh, buttock, or back of the upper arm. Injection sites should be rotated between doses.

**Dosing interval:** monthly

**Dosing window:** minimum of 26 days between maintenance injections

#### Initiation

##### 1. Switching from established buprenorphine SL dose to buprenorphine LAI:

Buprenorphine Transmucosal Dose	Sublocade Dose		
	Dose 1	Dose 2	Dose 3
8-18 mg/day	300 mg	100 mg	100 mg
20-24 mg/day	300 mg	300 mg	100 mg

2. **If NOT currently receiving buprenorphine treatment:** For patients not currently taking buprenorphine, administer a test dose of 4 mg SL when objective and clear signs are opioid withdrawal are present. If no precipitated withdrawal after one hour, administer starting dose of 300 mg. Package insert recommends monitoring patients in a healthcare setting after injection for withdrawal or sedation. May receive an additional 8 mg SL buprenorphine to manage withdrawal symptoms on induction day.

**Overlap with sublingual medication:** No overlap suggested in the package insert. Continual use of sublingual PRNs requires documentation of discussion with the patient around symptoms, duration of sublingual overlap, and plan to taper off if application. Due to likely subtherapeutic blood levels with initial dosing CBHS Pharmacy supports using supplemental sublingual buprenorphine for the first 3 months when the injections are the 300mg dose or patients on 100mg with  $\leq 8$ mg/day sublingual ongoing. Beyond this duration for 300mg dose, a discussion should occur between pharmacist and prescriber to document clinical justification and plan.

**Medication supply, storage and handling:**

Supplied	Reconstitution	Refrigeration	Administration	Needle Size
Kit of prefilled syringe: 100 mg/0.5 mL 300 mg/1.5 mL	None	Yes, may be kept at room temperature for up to 12 weeks. Remove from refrigerator for at least 15 minutes prior to injection.	Do not remove from foil pouch until patient has arrived for injection. Do not attach needle until time of administration. Remove air bubble prior to injection. Pinch the skin and lift to avoid injecting into muscle and inject at a 45-90 degree angle to avoid dermal administration. Do not rub the injection site after.	19G 5/8 inch

**Pharmacokinetics:**

Half-life	Time to maximum concentration	Time to steady state
43-60 days	24 hours after injection	4-6 months

**REMS Program:** The medication can only be purchased by a REMS certified pharmacy or healthcare setting. The REMS program is to mitigate risks of patients obtaining the medication and injecting it intravenously. A requirement of the REMS is that the medication is only provided to licensed healthcare providers and administered by healthcare providers. The medication can only be delivered to a healthcare providers location where their DEA license is registered. Certified programs can not distribute, transfer, loan, or sell the medication.

## **BUPRENORPHINE LONG-ACTING INJECTION (BRIXADI)**

**Dose:** Target weekly dose is 24 mg and can go up to a maximum of 32 mg weekly. Doses for monthly injection range between 64-128 mg.

**Dosing interval:** weekly or monthly

### **Initiation:**

**1. If NOT currently receiving buprenorphine treatment (package insert guidance):**

Administer 4 mg of SL buprenorphine as test dose when there are signs of mild-moderate withdrawal. If no precipitated withdrawal after 1.5 hours, administer Brixadi 16 mg weekly. Administer an additional Brixadi 8 mg weekly dose within 3 days of 1<sup>st</sup> dose to achieve the recommended dose of 24 mg weekly. If needed, can administer an additional Brixadi 8 mg dose for a total weekly dose of 32 mg.

**Off-label:** Providers may consider initiating Brixadi at 24 mg weekly in cases for patients with higher tolerances or high buprenorphine doses in the past.

**2. If on SL buprenorphine, can convert to either weekly or monthly injection:** Transition to either weekly or monthly injection based on SL dose equivalent in table below.

<b>Daily dose of SL buprenorphine</b>	<b>Brixadi (weekly)</b>	<b>Brixadi (monthly)</b>
≤ 6 mg	8 mg	--
8-10 mg	16 mg	64 mg
12-16 mg	24 mg	96 mg
18-24 mg	32 mg	128 mg

**3. Direct to Inject:** See page 6 for rationale regarding this initiation method. In certain scenarios, Brixadi (weekly) can be initiated at 24 mg when patient is in mild-moderate withdrawal without a SL test dose.

**Dose adjustments:** An additional 8 mg injection may be administered based on clinical judgement during a dosing interval up to a maximum of 32 mg per week or 128 mg per month. Consider using sublingual supplemental as an alternative for ease of use and access.

**Overlap with sublingual medication:** No overlap suggested in the package insert. Continual use of sublingual PRNs requires documentation of discussion with the patient around symptoms, duration of sublingual overlap, and plan to taper off if application. Due to likely subtherapeutic blood levels with initial dosing CBHS Pharmacy supports using supplemental sublingual buprenorphine for the first four injections (weekly or monthly) and up to the equivalent of 32mg/day sublingual ongoing. Beyond this duration, a discussion should occur between pharmacist and prescriber to document clinical justification and plan.

**Administration site:** subcutaneous into tissue of buttock, thigh, abdomen, or upper arm. For those not currently on buprenorphine treatment, Brixadi (weekly) should not be injected into upper arm until steady state is reached (after 4 consecutive doses). Brixadi (monthly) does not require

injection site rotation. For Brixadi (weekly), the same site of injection should not be used for at least 8 weeks.

**Dosing window:** +/- 2 days for weekly injection and +/- 1 week for monthly injection to avoid misses doses, it should not be administered more frequently than weekly for the weekly or monthly for the monthly as an ongoing order.

**Transitioning from Brixadi:** Patient may be transition from weekly to monthly or from monthly to weekly dosing of Brixadi based on clinical judgement based on dose equivalencies. If patient continues to report opioid cravings and a dose escalation is needed, consider checking a buprenorphine plasma level or switching to Sublocade which can provide a higher plasma level.

**Medication supply, storage and handling:**

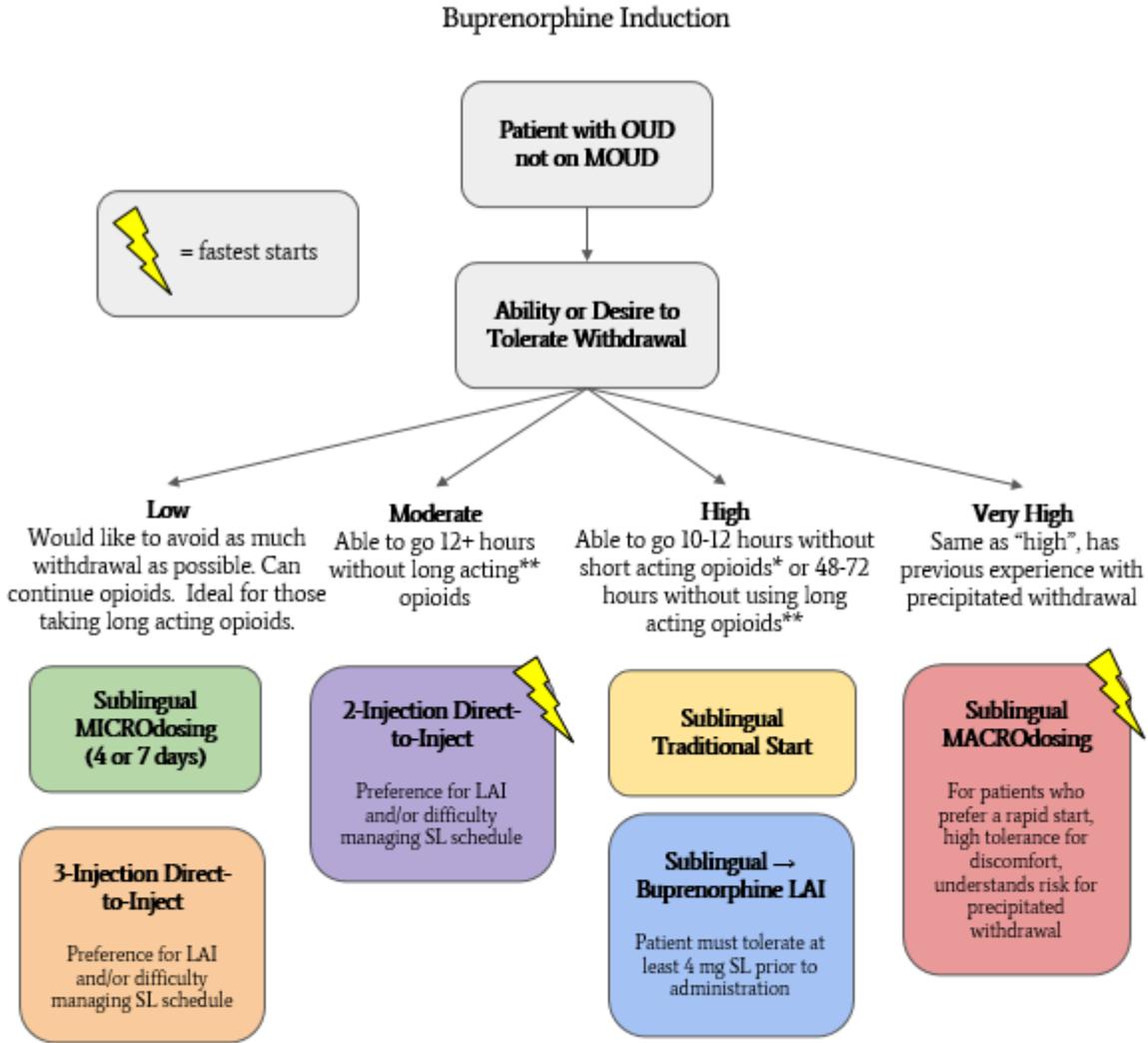
Supplied	Reconstitution	Refrigeration	Administration	Needle Size
Pre-filled syringes  <u>Weekly:</u> 8 mg/0.16 mL 16 mg/0.32 mL 24 mg/0.48 mL 32 mg/0.64 mL <u>Monthly:</u> 64 mg/0.18 mL 96 mg/0.27 mL 128 mg/0.36 mL	None	Not required. Store at room temperate	Insert plunger into body of syringe and rotate clockwise until attached to stopper. Pinch skin at injection site and insert needle at 90° angle and inject medication until plunger pressed fully down. Hold for two seconds and then pull needle out of skin while keeping the plunger depressed. Once needle out of skin, slowly lift thumb off plunger and allow syringe guard to cover needle.	23G ½ inch needle

**Pharmacokinetics:**

	Half-life	Time to maximum concentration	Time to steady state
<b>Weekly</b>	3-5 days	24 hours	4 consecutive doses (4 weeks)
<b>Monthly</b>	19-26 days	6-10 hours	4 consecutive doses (4 months)

**REMS Program:** The medication can only be purchased by a REMS certified pharmacy or healthcare setting. The REMS program is to mitigate risks of patients obtaining the medication and injecting it intravenously. A requirement of the REMS is that the medication is only provided to healthcare providers and administered by healthcare providers. The medication can be delivered to a healthcare providers location where their DEA license is registered. Certified programs can not distribute, transfer, loan, or sell the medication.

**APPENDIX 4: BUPRENORPHINE INDUCTION DECISION TREE**



Always offer options to patients. If multiple unsuccessful attempts with buprenorphine, consider methadone clinic referral. Utilize SUD warm line for further guidance - (855) 300-3595

\*Short acting opioids include heroin, oxycodone IR, hydrocodone, tramadol, codeine and morphine  
 \*\*Long acting opioids include non-pharmaceutical fentanyl (due to lipophilic properties) and methadone.