Protocol for Buprenorphine/Naloxone (Suboxone®) for Opioid Use Disorder in Outpatient Settings

BACKGROUND: Buprenorphine is an FDA approved treatment for Opioid Use Disorder (OUD). It is a high-affinity, partial agonist at the mu opioid receptor and suppresses opioid withdrawal and craving, reduces illicit opioid use and blocks exogenous opioid effects including respiratory depression. People with OUD are 50% less likely to die when they are being treated long term with methadone or buprenorphine. (National Academies Press, 2019).

Since the passage of the Consolidated Appropriations Act of 2023, any physician or nurse practitioner with a DEA registration certificate can prescribe buprenorphine. There is no longer a cap limiting how many patients a practitioner may treat with buprenorphine. DEA licensed prescribers are required to have 8 hours of training on managing of patients with opioid use disorder. PCSS offers free trainings for Physicians and RNPs.

Telemedicine Evaluations: Since March 2020, the DEA allows prescribing of controlled substances, including buprenorphine, through telemedicine. There is currently NO requirement for in-person medical evaluation to start or continue buprenorphine prescriptions. These flexibilities currently are set to expire on December 31, 2025, but may continue pending legislative changes.

CLINICAL SUPPORT/CONSULTATION:

- IMAT team 650-573-2735 (9 AM TO 9PM, 7 days a week, voicemail available after hours) or by email.
- Residential Treatment Team (RTX): send referrals by email at HS_BHRS_RTXTEAM@smcgov.org.
- BHRS Interface Team.
- UCSF National Clinician Consultation Center for Substance Use Treatment: 855-300-3595 (Monday through Friday 6 AM to 5 PM, voicemail available after hours).
- CA Bridge Project Direct Line :1-415-643-3257 (24/7 clinical support).

INITIAL ASSESSMENT:

- Complete a comprehensive evaluation for opioid, alcohol and other substance use.
- Confirm diagnosis of opioid use disorder using DSM-5 criteria checklist:

DSM-5 Criteria for Opioid Use Disorder Severity: **Mild**: 2-3 symptoms, **Moderate**: 4-5 symptoms, **Severe**: 6 or more symptoms	
	Opioids are often taken in larger amounts or over a longer period of time than intended.
	There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
	A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
	Craving, or a strong desire to use opioids.
	Recurrent opioid use resulting in failure to fulfill major role obligations at work, school or home.
	Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
	Important social, occupational or recreational activities are given up or reduced because of opioid use.
	Recurrent opioid use in situations in which it is physically hazardous.
	Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.
	Tolerance, as defined by either of the following: (a) a need for markedly increased amounts of opioids to achieve intoxication or desired effect (b) markedly diminished effect with continued use of the same amount of an opioid.
	Withdrawal, as manifested by either of the following: (a) the characteristic opioid withdrawal syndrome (b) the same (or a closely related) substance are taken to relieve or avoid withdrawal symptoms.

- Review CURES Prescription Drug Monitoring Program (PDMP) to detect unreported use of controlled substances.
- Review relative contraindications. **Pts who may not be appropriate for buprenorphine include:**

    - Allergy to buprenorphine or naloxone.
    - Severe CNS depression, intoxication or withdrawal from other substances (acute alcohol intoxication or delirium tremens), medically unstable.
    - Use of other substances is **not** a contraindication, but may warrant additional monitoring.
    - Moderate to Severe Hepatic Impairment.
        - Patients with transaminase levels less than five times normal, including those with HepC, tolerate buprenorphine well. If LFTs are at or above five times normal, consider risks and benefits and monitor transaminases frequently.
        - Moderate hepatic impairment (Child-Pugh Score 7-9): avoid combination product (naloxone). Monitor closely for signs of buprenorphine toxicity or overdose.
        - Severe hepatic impairment (Child-Pugh Score 10-15): avoid combination product (naloxone) and consider 50% dose reduction (initial & titration doses) with the monoproduct. Monitor closely for signs of buprenorphine toxicity or overdose.
- Patients starting buprenorphine in the outpatient setting will pick up medication from the pharmacy and start the medication at home on their own. In-person monitoring in the office is not required.
- Patients who are actively in moderate-severe withdrawal and need immediate dosing and supportive measures may be sent to the SMMC ED for buprenorphine initiation.
    - In this situation, call the ED to notify them a patient is on the way, AND call the IMAT team (650-573-2735), who are onsite at SMMC and can help advocate for patients.
- Seek consultation for complex patients, for example:
    - Patients transitioning to buprenorphine from methadone maintenance treatment.
    - Patients with multiple previous failed attempts to start buprenorphine in the outpatient setting.
    - Patients who are pregnant and wanting to start buprenorphine.
- Counsel the patient on other FDA-approved treatments for OUD. These include:
    - Methadone: referral to BAART can be facilitated through IMAT team at 650-573-2735.
    - XR-Naltrexone: requires 7-10 days off of opioids prior to initiation.
    - See SAMHSA TIP 63 Medications for Opioid Use Disorder or ASAM National Practice Guideline for the Treatment of OUD 2020 for additional information.
- Prescribe naloxone and provide training on how to use (video) or (handout) to all patients who have OUD, take high dose opioids for pain, have overdosed, or have a period of abstinence (including incarceration).
    - Naloxone kits can be provided directly to patients – request through your supervisor or IMAT Team.
- Order labs. Results not required to initiate treatment.
    - Urine Drug Screen, **including** Fentanyl and Buprenorphine
    - Comprehensive Metabolic Panel (CMP)
    - Urine Pregnancy Test
    - Hepatitis B Virus screening (HBsAg, anti-HBs, anti-HBc)
    - Hepatitis C Virus Antibody with reflex to HCV RNA quantitative PCR
    - HIV screening
- Encourage counseling & ancillary services, including peer-led recovery (e.g. Narcotics Anonymous; Medication-Assisted Recovery Anonymous; Dual Recovery Anonymous) and residential and outpatient treatment programs (available through RTX referral). Additional services are NOT required to prescribe buprenorphine.

TREATMENT PLANNING:

After completing assessment and shared decision-making with client to proceed with starting buprenorphine, provide patient education and obtain informed consent.

- Provide Patient Education:
    - Give a handout with buprenorphine self-start/induction instructions and a copy of the Subjective Opioid Withdrawal Scale (SOWS). Review these together with the patient.
        - Handouts: Option 1 (includes the SOWS), Option 2.

    - Coach patient on how to correctly administer: Do NOT swallow. Start with a moist mouth, avoid acidic drinks like coffee or fruit juice. Avoid smoking. Place film or tablet under the tongue and leave there for at least 15 minutes. Do not swallow or talk until fully dissolved.
    - Emphasize the importance of correct administration and timing of first doses so as to minimize the risk of precipitated withdrawal.
    - Patients should ideally plan to start/induce buprenorphine on a Monday, Tuesday or Wednesday during business hours so that they can reach the clinic in case of issues.
    - Review safe storage of medication (protected from theft/loss; locked away from children).
- Review adverse effects and precautions.
    - Common side effects of concern:
        - Constipation, abdominal pain, nausea, drowsiness, orthostatic hypotension.
    - FDA Warnings/Precautions:
        - Dental caries and tooth decay, including tooth fracture/loss for sublingual products. Can advise patients to swish mouth with water after medication is completely dissolved.
        - Precipitated withdrawal (PW) during start/induction of treatment. Counsel patient on importance of correct timing and administration of medication to reduce risk of PW.
        - Addiction, abuse and misuse: monitor for diversion and schedule regular follow up.
        - Respiratory depression: prescribe naloxone. Caution with elderly patients, those with hepatic impairment, and when patients are also using or being prescribed other CNS depressants.
        - Opioid withdrawal with abrupt discontinuation.
        - Risk of overdose death in opioid naïve individuals and children. Store in secure location.
        - Risk of hepatitis and hepatic events. Monitor liver function tests.
        - Neonatal Withdrawal Syndrome: alert provider if pregnant or planning pregnancy. Consult for additional guidance. (consider buprenorphine only formulation - Subutex).
    - See package inserts for all adverse effects and precautions.
- Obtain a controlled medication agreement, as per usual clinical practice for DEA scheduled medications.
- Writing the prescription: Buprenorphine is Schedule III and must be electronically prescribed.
    - Suboxone comes in a film or tablet sublingual formulation. Both can be cut in half.
    - Typical starting prescription is 7-10 days. For example:
        - Suboxone 8mg/2mg strips SL bid #14 R-0 for 7 days
        - Suboxone 2mg/0.5mg tablets SL, 1-2 tablets qid prn withdrawals, #22 R-0 for 7 days
- Consider prescribing PRN medications to help with withdrawal symptoms:
    - Ondansetron 4-8mg (OR Prochlorperazine 10mg) three times daily for nausea/vomiting.
    - Clonidine 0.1mg two to three times daily for agitation (caution hypotension).
    - Hydroxyzine (or Trazodone) 25-50mg at bedtime for insomnia.
    - NSAIDS
    - Loperamide 2 mg prn after each additional loose stool. NTE 16 MG/24 Hours
- Formulations: pharmacies often carry the **Buprenorphine-Naloxone combination product (Suboxone)**. Buprenorphine is FDA-approved for OUD in the following commonly used forms:
    - Buprenorphine-Naloxone SL tablets or films (brand names: Suboxone)
    - Buprenorphine tablets, also known as the mono product (brand name: Subutex)
    - Buprenorphine extended-release weekly or monthly SQ injection (brand name: Brixadi)
    - Buprenorphine extended-release monthly SQ injection (brand name: Sublocade)

BUPRENORPHINE START/INDUCTION:

Ideally, Day 1 should be a Monday, Tuesday, or Wednesday so that patient can reach provider during business hours during the first 3 days in case issues arise.

- **Day 1:** Max first day dose is typically 16mg. Fentanyl may require up to 24-32 mg. (FDA recommends 8mg as first day max, but clinical practice frequently supports higher doses.)

- **Wait for moderate-severe withdrawal**. Withdrawal should be nearly intolerable before taking the first dose. Give the patient the Subjective Opioid Withdrawal Scale (SOWS). Patients should ideally have a SOWS score > 17 before starting. General guidelines on timing after last opioid use:
  - Short-acting opioids (such as heroin, oxycontin, percocet, vicodin): the last dose should be at least 12 hours prior to first dose of buprenorphine.
  - Long-acting opioids (such as methadone, fentanyl): the last dose should be at least 36-72 hours prior to first dose of buprenorphine and clients should be in severe withdrawal prior to first dose of buprenorphine. Precipitated withdrawal is more common in these cases (regardless of COWS/SOWS scores).

Subjective Opiate Withdrawal Scale (SOWS)

Instructions: We want to know how you're feeling. In the column below today's date and time, use the scale to write in a number from 0-4 about how you feel about each symptom right now.

Scale: 0 = not at all 1 = a little 2 = moderately 3 = quite a bit 4 = extremely

	DATE					
	TIME					
	SYMPTOM	SCORE	SCORE	SCORE	SCORE	SCORE
1	I feel anxious					
2	I feel like yawning					
3	I am perspiring					
4	My eyes are tearing					
5	My nose is running					
6	I have goosebumps					
7	I am shaking					
8	I have hot flushes					
9	I have cold flushes					
10	My bones and muscles ache					
11	I feel restless					
12	I feel nauseous					
13	I feel like vomiting					
14	My muscles twitch					
15	I have stomach cramps					
16	I feel like using now					
	TOTAL					

Fig. 1: Subjective Opiate Withdrawal Scale (SOWS). Give the patient a copy and instruct them to take first dose when SOWS score >17. Source: ASAM, adapted from Handelsman 1987.

- **When moderate-severe withdrawal is reached, what dose to take:**
  - Low to moderate dependence: start with 2 mg. Reassess symptoms. May repeat 2-4mg after 30 min to 2 hours if withdrawal/cravings not yet controlled.
  - High dependence: start with 4mg. Reassess symptoms. May repeat 2-4mg every 30 minutes to 2 hrs if withdrawal/cravings not yet controlled.
  - High dependence with long-acting opioid like fentanyl: consider starting with a high dose, such as 8-16mg. Seek consultation.
  - If not currently physically dependent, start with 2 mg and repeat x1 if needed.
- **If precipitated withdrawal (PW) occurs**: PW typically presents with abrupt and dramatic worsening of withdrawal symptoms soon after taking initial doses of buprenorphine (30 min to 1 hour later).
  - If PW occurs, give additional doses of buprenorphine 2 mg every 30min-2 hours until resolved. Clinical practice also increasingly supports treating PW with additional high doses of buprenorphine (e.g. 8mg doses), not to exceed 24mg in the first day. Seek consultation.
- **Consider prn medications to help with withdrawal symptoms:**
  - Ondansetron 4-8mg (OR Prochlorperazine 10mg) three times daily for nausea/vomiting.
  - Clonidine 0.1mg two to three times daily for agitation (caution hypotension).
  - Hydroxyzine (or Trazodone) 25-50mg at bedtime for insomnia.
  - NSAIDS
  - Loperamide 2 mg prn after each additional loose stool. NTE 16 MG/24 Hours

- **Day 2:** Max Day 2 dose is 24mg (16mg per FDA, 32mg may be needed with fentanyl).
  - If patient wakes up with no or some withdrawal, start with total dose taken on Day 1
  - If patient wakes up with excess sedation or nausea, reduce dose by 2-4 mg
  - Reassess every 30min to 2 hours, if withdrawal symptoms, add additional 2-4 mg.
- **Day 3:** Max Day 3 dose is 24mg (16mg per FDA, 32mg may be needed with fentanyl).
  - Same instructions as on Day 2.

LOW-DOSE BUPRENORPHINE START:

An alternative method for starting buprenorphine which is increasingly used in clinical settings. Large scale studies of this approach are still forthcoming.

- Low-dose induction (also called micro-induction) involves clients cross-tapering from full agonists, starting with very low doses of buprenorphine. This method can especially be considered for clients:
  - With severe OUD, using high doses of fentanyl or other long-acting opioids.
  - With prior difficulty succeeding with traditional buprenorphine inductions.
  - With higher health literacy (able to adhere to detailed directions involving cutting pills/strips).

    - Who prefer to continue full agonists during induction process.
- Many protocols exist. Seek consultation. Sample protocols:
    - From Valley Homeless Health Program: Day 1: 0.5 mg daily. Day 2: 0.5 mg twice daily. Day 3: 1 mg twice daily. Day 4: 2 mg twice daily. Day 5: 4 mg twice daily. Day 6: 6 mg twice daily. Day 7: 8 mg twice daily and STOP opioid use.
    - Further protocols also available from CA Bridge.

EXTENDED-RELEASE BUPRENORPHINE:

Consider for patients who have difficulty adhering to daily sublingual buprenorphine dosing. Long-acting formulations may also have the advantage of producing more stable serum buprenorphine levels. Patients must be able to present in person for at least monthly subcutaneous long-acting injections.

- **Sublocade**:
    - Initiation:
        - First stabilize the patient on a daily dose of 8mg to 24mg of sublingual buprenorphine for a minimum of 7 days.
        - Administer 300mg SQ monthly in the abdominal subcutaneous tissue (see figure 1) for the first 2 months. Give doses at least 26 days apart
    - Maintenance:
        - Administer 100mg SQ monthly in the abdominal subcutaneous tissue, rotating injection sites each month (figure 1). Give doses at least 26 days apart.
        - Patients who are not stabilized on 100mg monthly can be increased to 300mg monthly dosing.

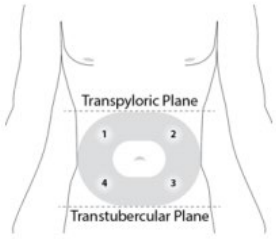

Fig 2: Injection sites for Sublocade. Rotate sites each month. Source: prescribing info.

- **Brixadi** (weekly dosing):
    - Initiation:
        - Patients who are not already stabilized on SL buprenorphine treatment can be started on Brixadi (weekly), but should be given a single test dose of 4mg SL buprenorphine to ensure that the medication is tolerated without precipitating withdrawal symptoms.
            - If the test dose is tolerated, administer Brixadi (weekly) 16mg SQ dose.
            - Within 3 days of the first dose, administer Brixadi (weekly) 8mg SQ dose to reach a target dose of Brixadi (weekly) 24mg.
        - Patients who are already being treated with SL buprenorphine can be switched directly to Brixadi (weekly) or Brixadi (monthly) at the appropriate equivalent maintenance dose (see below under "Maintenance").
        - Regarding injection sites (figure 2): for Brixadi (weekly), for patients not already receiving buprenorphine treatment, the upper arm site should only be used after steady-state has been achieved after 4 consecutive doses.
    - Maintenance:
        - Administer subsequent Brixadi (weekly) 24mg SQ doses on a weekly basis. Dose adjustments can be made weekly with the maximum dose being Brixadi (weekly) 32mg.
        - See figure 3 for equivalent doses of sublingual buprenorphine and Brixadi weekly and monthly.

Daily dose of sublingual buprenorphine	BRIXADI (weekly)	BRIXADI (monthly)
≤ 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

Figure 3: Equivalent doses of daily sublingual buprenorphine, Brixadi (weekly) and Brixadi (monthly). Source: prescribing info.

- **Brixadi** (monthly dosing):
  - Initiation:
    - Patients can be transitioned from SL buprenorphine or weekly Brixadi dosing to monthly dosing.
    - Brixadi (weekly) doses of 16mg, 24mg, and 32mg are approximately equivalent to Brixadi (monthly) doses of 64mg, 96mg, and 128mg (see figure 3)
  - Maintenance:
    - Administer subsequent Brixadi (monthly) SQ doses on a monthly basis. Dose adjustments can be made monthly, up to a maximum dose of Brixadi (monthly) 128mg.
    - Additional doses of Brixadi (weekly) 8mg can be administered at dosing intervals to target clinical effect.

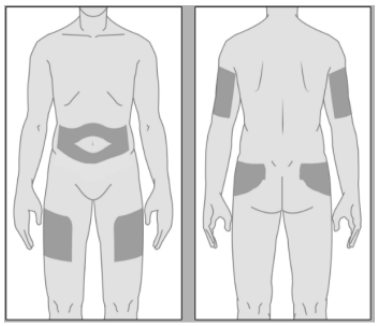

Fig 4: Brixadi injection sites. Do not administer at same site for at least 8 weeks for weekly injection. No rotation required for monthly injection. Source: prescribing info.

MAINTENANCE: It is recommended that patients are seen approximately weekly until stabilized and then monthly for ongoing care. Stable patients can be seen every 2-3 months.

- Dosing:
  - Continue dose on which patient has stabilized. Buprenorphine withdrawal protocols (without maintenance) are not recommended, with very few exceptions. Please consult if considering this.
  - Typical maintenance range: Buprenorphine/naloxone 4mg/1mg to 24mg/6mg SL once daily. Some patients, especially fentanyl users, may require up to 32mg/8mg SL.
  - 16mg daily has shown better patient retention in treatment than lower doses.
  - Higher doses often needed at beginning and can be gently reduced over time.
  - Once daily dosing is appropriate for most patients with OUD. If the patient has concurrent pain consider splitting dose into BID, or TID. There is no ceiling effect for analgesia.
  - Consider injectable buprenorphine (Sublocade) or observed daily dosing at an opioid treatment program if concerns of diversion or adherence. Consult for additional information or to coordinate.
- Check LFTs semi-annually to annually. Consider consultation in moderate to severe hepatic impairment. Please see exclusions section above. Learn More.
- Check Urine Tox Screen, including fentanyl and buprenorphine screens: as needed (every 1-2 visit during initiation phase, every 1-2 months or as needed when stable).
  - Do not stop buprenorphine, if UDS positive for methamphetamine, opioids, or other substances. Adapt treatment plan. Consider consultation with any questions.
  - Consider dose reduction if on concurrent sedative hypnotics.
  - Clients who misuse high-dose benzodiazepines or other CNS depressants* may need additional monitoring.
- Buprenorphine and Norbuprenorphine urine levels: test periodically to assess adherence.
  - Norbuprenorphine (metabolite) should be present, usually higher than buprenorphine.
  - Buprenorphine with little or no metabolite indicates tampered urine sample by adding buprenorphine.
    - No guidelines about correlation with dosing, how much consistency to expect (multifactorial: timing of UDS, whether taking in divided doses, individual metabolism, pregnancy etc.)

DURATION/TERMINATION:

- Long term maintenance is standard of care. OUD is in remission when successfully treated with MAT.
- Continue treatment indefinitely if client is benefitting.
- Discontinuation:
  - When discontinued, regardless of cause, relapse rates are consistently over 50% (Bentzley 2015)

- Consider using the recovery capital checklist to gage how prepared the patient may be to maintain remission of OUD once medication is discontinued (Zweben 2021).
- If patient strongly prefers to discontinue, discuss risks associated with relapse including heightened overdose risk. Taper very slowly with close monitoring. (Ling 2009) There are rapid taper protocols. Seek consultation.
- Continue psychosocial services and frequently assess opioid and other drug use throughout the taper and afterwards.
- Establish a plan to immediately resume buprenorphine if client experiences cravings or relapses.
- Buprenorphine should be continued at the maintenance dose through the perioperative period. (Lembke 2019). Consult for additional guidance.

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