

DSH PSYCHOTROPIC MEDICATION

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Appendix – Medications for Substance Use Disorders

NOTE: Directive statements and procedures described in this chapter are informational and advisory in nature.

These procedures do not cover management of pregnant women with severe mental illness treated with buprenorphine or methadone. These pregnancies are likely to be considered high risk and will require careful collaboration with a Maternal-Fetal Medicine Specialist, an Addiction Specialist, and the PRN Group.

AB2760 requires that patients suffering from an opioid use disorder be offered naloxone at discharge (does not apply if discharge is to a detention facility or to the California Department of Corrections and Rehabilitation).

ACAMPROSATE PROTOCOL:

- I. Indications:
 - A. Acamprosate should be prescribed for patients suffering from:
 - 1. DSM diagnosis of alcohol use disorder
 - a. As an aid to maintain abstinence from alcohol and as part of a comprehensive psychosocial substance use treatment program.
 - 2. Patients admitted on acamprosate and who are stable should be continued.
 - B. Contraindications:
 - 1. Hypersensitivity to acamprosate or any component of its formulation.
 - 2. Severe renal insufficiency (eGFR <30 mL/min)
- II. Precautions (risk/benefit analysis supports use):
 - A. Moderate renal insufficiency (eGFR 30-50 mL/min)
 - B. Depression, suicidal ideation or attempts.
 - C. Pregnancy (no evidence of teratogenicity but human data are lacking) or breast feeding.
 - D. Elderly patients due to risk of decreased renal function
 - E. History of hypersensitivity to sulfites
- III. The following initial workup should be completed:
 - A. There is informed consent or alternate legal authorization.

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B. Initial work-up includes:

1. Comprehensive metabolic panel.
2. Random urine toxicology test.
3. Pregnancy test in women of child-bearing age.

IV. Monitoring:

A. Annual monitoring of eGFR.

B. Quarterly monitoring of eGFR in patients with eGFR of 30-50 mL/min.

V. Dose initiation and titration:

A. In patients with eGFR > 50 mL/min, the starting dose is 666 mg orally three times daily. This is also the maintenance dose.

B. In patients with eGFR of 30-50 mL/min, the starting dose is 333 mg orally three times daily. This is also the maintenance dose.

C. Initiate acamprosate as soon as possible after alcohol withdrawal. Acamprosate should be continued if the patient relapses on alcohol.

VI. Possible Adverse Reactions:

- A. Diarrhea.
- B. Nausea.
- C. Flatulence.
- D. Depression.
- E. Anxiety.
- F. Weakness.
- G. Dizziness.
- H. Insomnia.
- I. Dry mouth.
- J. Paresthesia.
- K. Pruritis.
- L. Sweating.

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References:

Mylan Pharmaceuticals Inc (2019). Acamprosate package insert.
US Department of Health and Human Services Substance Abuse and Mental Health Services Administration (2009). Incorporating alcohol pharmacotherapies into medical practice. Treatment Improvement Protocol (TIP) Series 49.

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BUPRENORPHINE PROTOCOL:

Note: Transmucosal (sublingual/SL) buprenorphine is available as a single drug (buprenorphine) and as a combination drug (buprenorphine/naloxone) in a 4:1 ratio. Both products are prescribed similarly and will be referred to in the protocol below as “buprenorphine”.

Buprenorphine extended release (ER) is administered subcutaneously and is available in 3 formulations: 1) **Sublocade®**—monthly (no longer abdominal only); 2) **Brixadi™ weekly**, and 3) **Brixadi™ monthly**. These buprenorphine ER brand names are used throughout to facilitate differentiation.

I. Indications:

A. Buprenorphine is indicated for:

1. Documented DSM diagnosis of opioid use disorder (OUD) or opioid withdrawal. Also indicated for pain treatment; however, that is not the focus of this protocol (Please see the U.S. Centers for Disease Control guidelines).
 - i. As an aid to maintain abstinence from opioids and as part of a comprehensive psychosocial substance use treatment program.
2. Patients admitted on buprenorphine and who are stable should be continued on the medication.

B. **Sublocade®** should only be prescribed to patients who have been treated with a minimum of 8 mg qd of SL buprenorphine for at least 7 days.

C. **Brixadi™ weekly/monthly** for buprenorphine naïve patients, and currently intolerant to another opioid, recommend titrating the patient to stabilizing dose of SL buprenorphine ≥ 8 mg/day for at least 7 days, prior to injection, to confirm tolerability. For patients not currently taking buprenorphine and currently tolerant to another opioid, provide 4 mg SL test dose to confirm tolerability and to rule out precipitated withdrawal.

II. Contraindications:

A. Hypersensitivity to buprenorphine, naloxone, or any component of their formulations.

B. Routine treatment with opioid analgesics, e.g. hydrocodone, morphine; or an opioid agonist used to treat OUD, e.g. methadone or opioid antagonists, e.g. naltrexone. Does not apply to acute treatment, e.g. post-operative pain treatment if buprenorphine dose is ≤ 16 mg per day

C. Buprenorphine SL/ER is not recommended in patients with severe hepatic impairment, e.g. Child Pugh Class C.

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- D. During ongoing treatment with a monoamine oxidase inhibitor (MAOI) or within 14 days of MAOI discontinuation due to increased risk of serotonin syndrome or opioid toxicity.
- E. The following contraindications are specific to Sublocade® and Brixadi™ formulations and are in addition to those listed above:
 - 1. Hypersensitivity to the ATRIGEL® delivery system used to deliver the Sublocade® formulation which is composed of a biodegradable 50:50 poly(DL-lactide-co-glycolide) polymer and a biocompatible solvent, N-methyl-2-pyrrolidone.
 - 2. For Brixadi™, hypersensitivity to the constituents of the injection.

Injection constituents include:
 - i. Brixadi™ weekly: buprenorphine, 50 mg/mL, 10% w/w anhydrous ethanol and soybean phosphatidylcholine/glycerol dioleate.
 - ii. Brixadi™ monthly: buprenorphine, 356 mg/mL buprenorphine based, 30% w/w N-methyl pyrrolidine and soybean phosphatidylcholine/glycerol dioleate.
 - 3. In an opioid naïve patient.
 - i. For Sublocade®, patient must have undergone initiation and stabilization with a minimum of 8 mg QD of transmucosal buprenorphine for at least 7 days.
 - ii. For Brixadi™, the patient must demonstrate tolerability to a 4 mg SL buprenorphine dose prior to starting Brixadi™ **weekly**.
 - 4. Patients with preexisting moderate to severe hepatic impairment, (Child Pugh Class B/C <0.1% DSH population) are not candidates for treatment with Sublocade® or Brixadi™.

III. Precautions/risks (risk/benefit analysis supports use):

- A. Serious risk of harm or death could result if buprenorphine ER injection is administered intravenously. When the medication comes into contact with bodily fluids, it forms a solid mass which can cause occlusion, local tissue damage, and thromboembolic events.
- B. Treatment of emergent acute pain occurring during treatment with buprenorphine should proceed with non-opioid analgesics whenever possible. If opioid therapy is required, the patient will require higher doses and careful monitoring. Pain treatment with buprenorphine may require b.i.d. to t.i.d. dosing.

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- C. Misuse or abuse, as buprenorphine can be abused similarly to other opioids. Monitor patients for medication diversion.
 - 1. Some Buprenorphine ER patients may attempt to remove the drug-containing subcutaneous solid mass.
- D. Risk of opioid withdrawal in the following situations:
 - 1. Administration of buprenorphine to a patient treated with a full agonist opioid may precipitate opioid withdrawal.
 - i. In acute pain situations for patients already stabilized on buprenorphine, lowering the buprenorphine dose temporarily may make full agonists more effective for pain control.
 - ii. When initiating buprenorphine de novo, verify that the patient demonstrates objective signs of mild to moderate opioid withdrawal before administering buprenorphine.
 - iii. A Clinical Opiate Withdrawal Score (COWS) of at least 10 to 12, can serve as a guide for identifying mild to moderate withdrawal.
 - 2. Rapid taper or abrupt discontinuation of buprenorphine in a patient who is treated with a stable dose of buprenorphine will result in opioid withdrawal. For patients treated with Sublocade® or Brixadi™, the risk of opioid withdrawal after discontinuation may last several months.
- E. Respiratory depression and death has occurred in association with buprenorphine.
- F. While buprenorphine should not be withheld from patients who are prescribed benzodiazepines or CNS depressants, these patients require careful observation.
 - i. When possible, avoid prescribing benzodiazepines, muscle relaxants, or other CNS depressants to patients treated with buprenorphine.
 - ii. Clinicians should avoid or delay administering buprenorphine in patients who are sedated.
- G. Patients should abstain from drinking alcohol while treated with buprenorphine.
- H. Buprenorphine should be used with caution in patients with compromised respiratory function, e.g., COPD, decreased respiratory reserve, hypoxia, hypercapnia, obesity hypoventilation syndrome, central sleep apnea and sleep-related hypoxia.
- I. Hepatic disease

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1. A range of hepatic abnormalities have been observed with buprenorphine, including transient transaminitis, cytolytic hepatitis, hepatitis with jaundice, hepatic failure, and hepatic encephalopathy.
 - i. The incidence of hepatic toxicity is low. It is most often associated with abuse of the SL formulation.
 2. In patients with pre-existing moderate hepatic impairment (Child-Pugh score of 7-9), the buprenorphine-naloxone combination product is not recommended, as drug exposure is increased for buprenorphine and increased more than tenfold for naloxone. Therefore, naloxone may interfere with buprenorphine's efficacy.
- J. Adrenal insufficiency can occur with chronic opioid treatment. If diagnosed, treat with physiologic replacement of corticosteroids. Buprenorphine should be tapered and discontinued to allow adrenal function to recover.
- K. Pregnancy if potential benefit justifies risk to the fetus. Buprenorphine/naloxone can be continued during pregnancy.
1. Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged treatment with buprenorphine during pregnancy. NOWS may be life-threatening and requires careful observation and management.
 2. Buprenorphine passes into breast milk. Breast feeding decreases duration of NOWS and should be encouraged. Infants should be monitored for sedation or respiratory depression with breastfeeding.
- L. Use with caution in elderly patients due to age-related changes including decreased hepatic function that may impact buprenorphine metabolism. Monitor for signs and symptoms of toxicity or overdose.
- M. Use with caution in patients with head injury, intracranial lesions, or other potential causes of elevated intracranial pressure as buprenorphine can elevate cerebrospinal fluid pressure.
- N. Use with caution in patients with dysfunction of the biliary tract, as buprenorphine can cause elevation of intracholedochal pressure.
- O. Use with caution in patients taking anticholinergic agents due to the increased risk of constipation and other anticholinergic side effects.
- P. Buprenorphine can cause physical and cognitive impairment. Use with caution in patients operating motor vehicles or heavy machinery until tolerance and lack of impairment have been established.
- Q. Buprenorphine can obscure acute abdominal conditions. Use with caution in the presence of abdominal pathology.

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- R. Use with caution in patients with orthostatic hypotension, as buprenorphine may exacerbate this condition.
 - S. There is a risk that patients receiving subcutaneous preparations may tamper with the injection site.
 - T. With Sublocade® or Brixadi™, there is a risk of injection site mass, abscess, ulceration, and necrosis.
 - U. There is a risk of ongoing opioid withdrawal with insufficient dosing.
 - V. While buprenorphine may prolong the QTc interval, QTc prolongation is not mediated by hERG potassium channels; thus the risk of arrhythmia is low.
- IV. The following initial workup should be completed:
- A. There is informed consent or alternate legal authorization, as well as chart documentation of opioid use disorder or alternative indication.
 - B. Initial workup includes:
 - 1. Urine toxicology.
 - 2. Pregnancy test in women of child-bearing age.
 - 3. Complete metabolic panel.
 - 4. Prothrombin time and INR.
 - 5. Hepatitis B and C panels and HIV testing in patients whose serostatus is unknown.
 - 6. ECG within one year.
 - 7. Assessment of bowel function
 - i. Establish baseline bowel function.
 - ii. If the patient is constipated, optimize laxatives to normalize bowel function prior to starting buprenorphine. Avoid psyllium and polycarbophil. (Refer to Chapter 36: Appendix – Management of Medication-induced Constipation Revision: 01/01/2022.)
 - iii. Review the patient's medication list identifying constipating medications and those with anticholinergic activity that may contribute to constipation. Taper, switch and/or discontinue any of these medications that are not essential to the patient's care. For example, rather than use diphenhydramine for insomnia,

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consider hydroxyzine, which has no anticholinergic activity. Hold iron during the first 4-6 weeks of buprenorphine treatment.

V. Monitoring:

- A. Random saliva or urine toxicology performed at least monthly and which includes testing for buprenorphine and norbuprenorphine when patient is on transmucosal buprenorphine. Buprenorphine and norbuprenorphine are not detected via standard UDS, as they are not metabolized to morphine.
- B. Hepatic functions, pregnancy, and bowel function monthly or as clinically indicated
 1. Semi-annual monitoring of hepatic panel in patients without risk factors.
 2. More frequent monitoring in patients with clinical and/or laboratory evidence of hepatic disease, e.g., transaminases >5 times the upper limit of normal, abnormal bilirubin or abnormal prothrombin time.
 - i. In cases of liver injury, the patient should be followed with serial clinical and laboratory monitoring until evidence of hepatic injury resolves.
- C. Annual monitoring includes ECG

VI. Dose initiation (induction) and titration:

- A. The following are the available buprenorphine products for OUD:

Product	Formulation	Available Strengths
Buprenorphine	Sublingual tablet	2 mg; 8 mg
Buprenorphine HCl/ naloxone HCl*	Sublingual film	2 mg/0.5 mg; 4 mg /1 mg; 8 mg /2 mg; 12 mg /3 mg
	Sublingual tablet	2 mg /0.5 mg; 8 mg/2 mg
Zubsolv Buprenorphine HCl/naloxone HCl	Sublingual tablet	0.7 mg/ 0.18 mg; 1.4 mg /0.36 mg 2.9 mg /0.71 mg; 5.7 mg /1.4 mg 8.6 mg /2.1 mg; 11.4 mg/ 2.9 mg
Buprenorphine ER injection Sublocade®	Subcutaneous injection (into abdomen, thigh, buttock, or back of the upper arm)	100 mg every 28 days 300 mg every 28 days
Buprenorphine ER Injection Brixadi™	Subcutaneous injection (into buttock, thigh, abdomen, or upper arm)	Brixadi™ weekly: 8 mg, 16 mg, 24 mg, 32 mg. Brixadi™ monthly: 64 mg, 96 mg, and 128 mg.

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*Buprenorphine/naloxone transmucosal products are abuse-deterrent formulations, but they can still be misused. Naloxone is minimally absorbed orally; however, if the product is insufflated or injected, naloxone is absorbed and antagonizes the opioid agonist effect of buprenorphine and other opioid agonists.

B. Oral buprenorphine induction proceeds as follows:

1. For patients who are actively using opioids, the patient should experience clear signs of opioid withdrawal before taking the first buprenorphine dose. This usually occurs at least 12-16 hours after the last dose of a short-acting opioid, e.g. heroin, 18-24 hours after an intermediate-acting opioid, e.g. sustained-release oxycodone, and 36-48 hours (or longer) after a long-acting opioid, e.g. methadone.
2. For patients dependent upon fentanyl, a low-dose high-dose protocol can be used, starting with microinduction with 1 mg SL buprenorphine doses on day one prior to the onset of fentanyl withdrawal, followed by titration to high dose buprenorphine, up to 32 mg qd, on day two.
3. To assess withdrawal, score signs of withdrawal using the COWS, which can be located here: [Clinical Opiate Withdrawal Scale \(drugabuse.gov\)](http://ClinicalOpiateWithdrawalScale(drugabuse.gov)). Verify that the patient demonstrates objective signs of mild to moderate opioid withdrawal before administering buprenorphine. A COWS score of at least 12 will allow the induction to proceed more safely. If there is no or very little clinical evidence of withdrawal, reassess the day/time of last opioid use. Progression of withdrawal can either be reassessed later in the day or on the following day.
4. Once opioid withdrawal is established, the patient is given 2-4 mg of buprenorphine. The tablet/film is placed under the tongue and allowed to dissolve which takes anywhere from 3-10 minutes. Relief of opioid withdrawal should begin in 30-45 minutes. After approximately 2 hours, an additional 2-4 mg dose of buprenorphine can be given if there is continued withdrawal and lack of sedation. The FDA label recommends a maximum dose of 8 mg on Day 1.
5. On Day 2 of initiation/induction, review the patient's experience on Day 1, score current withdrawal symptoms using the COWS, and determine the need for a dose adjustment. If the patient continues to demonstrate opioid withdrawal, they can receive the total dose used on Day 1 plus an additional 2-4 mg (conservative dosing due to potential for other sedating medications). If the patient felt sedated after Day 1, decrease the dose by 2-4 mg. If neither withdrawal nor sedation were experienced, use the total dose given on Day 1. If the patient reports having a good night's sleep, this is an indication of adequate coverage of opioid tolerance.

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6. Sometimes initiation/induction takes longer than two days and the patient will require additional dose adjustments. The same principles and doses cited above may be used for these adjustments.
7. For patients who are not actively using opioids, the patient can be started on a dose of 1 mg buprenorphine daily. The low starting dose is required due to the absence of tolerance and the high likelihood that a DSH patient may be treated with a sedating medication such as olanzapine. Increase the dose by 1 mg weekly, or more slowly, to 4 mg. If the patient continues to experience opioid cravings, dose increases can proceed by 2 mg weekly until the dose reaches 8 mg. Continue to reassess the patient to determine the need for further titration.
8. For patients who are taking methadone and wish to switch to buprenorphine, methadone should be slowly tapered to 30-40 mg per day or less. The patient should remain on this dose for one week. Methadone should be stopped for at least 36-48 hours prior to the first dose of buprenorphine. Evidence of objective opioid withdrawal with a COWS score of 11-12 or more suggests sufficient withdrawal. Begin with an initial dose of 2 mg buprenorphine can be given with repeat doses of 2 mg every 2 hours as needed for withdrawal to a maximum of 8 mg (hold for sedation), up to a maximum dose on Day 1 of 8 mg.

On Day 2 of initiation/induction, review the patient's experience on Day 1, score current withdrawal symptoms using the COWS, and determine the need for a dose adjustment. Initiation/induction should be conducted slowly. Unrelieved withdrawal can be treated with non-opioid therapies for the first few days.

9. Typical buprenorphine oral maintenance dose ranges from 4 mg to 24 mg daily. Doses above 24 mg per day have generally shown no clinical advantage and are not recommended. The first exception to this is fentanyl, with doses up to 32 mg of buprenorphine being sometimes required. The second exception is treatment during the second and third trimesters of pregnancy, where doses up to 32 mg of buprenorphine may also be needed due to increased metabolism.

C. Buprenorphine ER formulations: **Sublocade®** and **Brixadi™**

1. Buprenorphine ER should be considered and recommended over sublingual buprenorphine for:
 - a. Patients who are deemed to be at risk of diverting sublingual buprenorphine (e.g., in a forensic population or in patients with a significant history of criminality).
 - b. Patients who are being discharged to the community, in order to increase the rate of maintenance of buprenorphine in the patient's system while making a transition to continuing care.

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D. **Sublocade®** Subcutaneous (no longer abdominal only) Injection Initiation:

1. Verify that the patient has been stabilized on SL buprenorphine ≥ 8 mg/day for at least 7 days.
2. The recommended dose of **Sublocade®** is two monthly initial doses of 300 mg followed by 100 mg monthly maintenance doses.
 - i. For some groups of patients, continuing the maintenance dose at 300mg is recommended without any trial of 100mg maintenance dose (per physician's discretion): patients with 15 years or more of opioid use history, patients with history of injection opioid use, patients with history of high-potency opioid use like fentanyl, or patients on 16 mg or more daily oral buprenorphine.
 - ii. For patients who do not demonstrate a satisfactory clinical response to the 100 mg maintenance dose, the dose can be increased to 300 mg monthly.
 - iii. Adjunctive sublingual buprenorphine can be provided to address cravings until the next **Sublocade®** dose.
3. If a **Sublocade®** dose is missed, it should be given as soon as possible with the following dose given no less than 26 days later. Occasional delays in dosing of up to 2 weeks are not expected to have a clinically significant impact. It is also acceptable to dose up to 2 days early.
4. The **Sublocade®** injection is delivered subcutaneously in the abdomen, thigh, buttock, or back of the upper arm per the package insert instructions.
 - i. The injection forms a solid mass on contact with body fluids. Instruct the patient that they may have a lump for several weeks that will decrease in size over time.
 - ii. Instruct the patient not to rub or massage the injection site and to be aware of restricting belts or clothing waistbands.
5. If the **Sublocade®** depot must be removed, it can be surgically excised under local anesthesia within 14 days of injection.
 - i. The excised depot must be handled and disposed of per facility procedure for a Schedule III drug.

E. **Brixadi™** Subcutaneous Injection Initiation

1. Instructions for administration (details in the package insert):

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- i. **Brixadi™** weekly and monthly are for subcutaneous injection only into the upper outer quadrant of the buttock, thigh (anterolateral or posterolateral) or periumbilical region of the abdomen.
 - ii. Do not inject **Brixadi™** into upper arm until pt. has received at least 4 consecutive doses.
2. For buprenorphine naïve patients, and currently intolerant to another opioid, recommend titrating the patient to stabilizing dose of SL buprenorphine ≥ 8 mg/day for at least 7 days, prior to **Brixadi™** monthly or **Brixadi™** weekly injection, to confirm tolerability.
3. Clinicians can administer either **Brixadi™** weekly or **Brixadi™** monthly for patients who are stabilized on other buprenorphine preparations.
4. To avoid missed doses, clinicians can administer **Brixadi™** weekly up to 2 days before or after scheduled dose and administer **Brixadi™** monthly up to 1 week before or after scheduled dose.
 - i. If a dose is missed, clinicians should administer the next dose as soon as practically possible.
5. For patients not currently taking buprenorphine and currently tolerant to another opioid:
 - i. Provide 4 mg SL test dose to confirm tolerability and to rule out precipitated withdrawal.
 - ii. If tolerated, administer **Brixadi™** weekly, 16 mg.
 - iii. Administer an additional dose of **Brixadi™** weekly, 8 mg, within 3 days of the first dose to achieve the recommended 24 mg **Brixadi™** weekly dose.
 - iv. If needed, during the first week of treatment, administer an additional 8 mg dose of **Brixadi™** weekly, waiting at least 24 hours after the previous injection, for a total weekly dose of 32 mg.
 - v. Clinicians should not administer **Brixadi™** monthly to patients not currently on buprenorphine treatment.

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6. Switching to **Brixadi™** from transmucosal (SL) products:

- i. Patients on sublingual buprenorphine may be switched directly to either **Brixadi™** weekly or **Brixadi™** monthly.

Daily dose SL 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

Note: Suboxone 8/2 mg = Zubsolv 5.7/1.4 mg tab.

7. Switching to **Brixadi™** from **Sublocade®**

- ❖ As of 10/27/23, no published data exist that provides guidance for transitioning to **Brixadi™** from **Sublocade®**. The following guidelines are offered:
 - i. If a patient is on **Sublocade®** 100 mg q4 weeks, provide **Brixadi™** monthly 64 mg q4 weeks.
 - a. If cravings or withdrawal symptoms occur, provide 8 mg of **Brixadi™** weekly, and increase the next dose of **Brixadi™** monthly to 96 mg q4 weeks.
 - ii. If a patient is on **Sublocade®** 300 mg q4 weeks, provide **Brixadi™** monthly 96 mg q4 weeks.
 - a. If cravings or withdrawal symptoms occur, provide 8 mg of **Brixadi™** weekly, and increase the next dose of **Brixadi™** monthly to 128 mg q4 weeks.

8. Transitioning between **Brixadi™** weekly and **Brixadi™** monthly.

- i. Patients may be transitioned from weekly to monthly or vice versa based on clinical judgment.
- ii. Recommended dose when transitioning between Brixadi™ weekly and **Brixadi™** monthly formulations:

Brixadi™ weekly	Brixadi™ Monthly
16 mg	64 mg
24 mg	96 mg
32 mg	128 mg

- iii. It is recommended to wait until a **Brixadi™** weekly steady-state plasma level has been achieved (4 weeks) before switching to **Brixadi™** monthly.

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9. Brixadi™ Dose Adjustments:

- i. An additional **Brixadi™** weekly 8 mg injection may be administered, based on clinical judgment, during a dosing interval, up to a maximum dose of 32 mg per week of **Brixadi™** weekly or 128 mg per month of **Brixadi™** monthly.

10. Drug monitoring:

- i. After achieving steady state drug levels (4 weeks for **Brixadi™** weekly and 4 months for **Brixadi™** monthly), buprenorphine may be detected in the plasma for up to 4 weeks for **Brixadi™** weekly and 4 months for **Brixadi™** monthly.

F. Dosing accounts for drug-drug interactions:

1. Benzodiazepines and other Central Nervous System Depressants

- i. Concomitant use increases the risk of respiratory depression, sedation, coma and death.
- ii. Stopping benzodiazepines or muscle relaxants prior to and during treatment with buprenorphine is preferred. If treatment cannot be stopped, decreasing to the lowest possible dose with increased monitoring may be appropriate.
- iii. Certain antipsychotics such as clozapine, chlorpromazine and olanzapine can be sedating. Adjust the antipsychotic dose to maximize efficacy and minimize sedation before starting buprenorphine. Consider using Brixadi over Sublocade if choosing an injectable formulation due to more flexible dosing schedule and shorter half-life.

2. Cytochrome P450 3A4 Inhibitors and Inducers

- i. Buprenorphine is a CYP 3A4 substrate
- ii. Concomitant use of CYP 3A4 inhibitors, e.g. erythromycin, ketoconazole, and ritonavir, can increase the plasma concentration of buprenorphine. This, in turn, can increase or prolong opioid effects, particularly when an inhibitor is added to a stable dose of buprenorphine.
- iii. After stopping a CYP 3A4 inhibitor, the buprenorphine plasma concentration will decline. This may result in signs of opioid withdrawal or decreased efficacy of the medication to suppress opioid cravings. Consider titrating the buprenorphine dose until stable drug effects are achieved.

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- iv. Concomitant use of CYP 3A4 inducers, e.g. rifampin, carbamazepine, phenytoin, and some antiretrovirals, can decrease the plasma concentration of buprenorphine. This may lead to decreased efficacy or the onset of opioid withdrawal. If concomitant therapy is necessary, consider increasing the buprenorphine dose until stable drug effects are achieved.
- v. If a CYP 3A4 inducer is stopped, the effects of the inducer slowly wane, and the buprenorphine plasma concentration will increase. Consider a buprenorphine dose reduction and monitor for signs of sedation or respiratory depression.

3. Serotonergic Drugs

- i. Rarely, serotonin syndrome can occur when buprenorphine is combined with serotonergic drugs including antidepressants of all classes, tramadol, linezolid, and intravenous methylene blue.

4. Diuretics

- i. Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

5. Anticholinergic Drugs

- i. Concomitant use of anticholinergic drugs may increase risk of severe constipation/paralytic ileus/bowel obstruction and/or urinary retention/hydronephrosis.
- ii. Monitor patients carefully. Consider prophylactic laxatives. If constipation does not respond to laxative polypharmacy, consider treating with a peripherally acting mu opioid receptor antagonist, e.g. naloxegol, naldemedine (Refer to Chapter 36: Appendix – Management of Medication-induced Constipation)

VII. Treatment of Overdose

- A. Due to buprenorphine's partial agonism at the mu opioid receptor, there is a ceiling effect or flattening of the effect curve for respiratory depression, sedation, and euphoria. Overdose usually occurs when buprenorphine is combined with other opioids, CNS depressant drugs like benzodiazepines and/or alcohol.
- B. Monitor respiratory and cardiac status carefully. If respiratory rate is depressed, provide an airway and assisted ventilation. In addition to oxygen, IV fluids, vasopressors and other supportive measures should be considered. Transfer the patient to a higher level of care.
- C. Administer naloxone with the understanding that higher than normal doses and repeated administration may be required. See CHAPTER 48 NALOXONE

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HYDROCHLORIDE NASAL SPRAY (NARCAN) PROTOCOL for further information on administration.

D. Tapering and Discontinuing Buprenorphine:

1. If transmucosal (SL) buprenorphine is stopped abruptly or the dose is decreased significantly, the patient will experience opioid withdrawal.
2. There is no ideal tapering protocol for SL buprenorphine. Tapers should be flexible and tailored to the individual.
3. Generally, a taper occurs slowly over several months or longer to give the patient time to acclimate to the lower dose and reduce discomfort from opioid withdrawal and cravings.
4. The final several milligrams of the taper are typically the most difficult and may require a longer time to taper. At lower doses, the film preparation may be preferred to allow for micro-tapering.
5. Consideration can be given to providing comfort medications for opioid withdrawal symptoms as clinically indicated.

E. Steady-state buprenorphine concentrations remain at therapeutic levels for an average of 2-5 months with Sublocade® and Brixadi™ monthly and will self-taper over time. While withdrawal signs are not common, if they do occur, they will be delayed. Withdrawal can be treated with transmucosal buprenorphine or non-opioid therapies.

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VIII. Possible Adverse Reactions:

- A. Constipation.
- B. Pain.
- C. Nausea.
- D. Vomiting.
- E. Headache.
- F. Diarrhea
- G. Insomnia
- H. Orthostatic hypotension.
- I. Sweating
- J. Rhinitis.
- K. Opioid withdrawal
- L. The most common injection site reactions with the ER formulation are pain, pruritis, and erythema.
- M. Opioid-induced androgen deficiency resulting in decreases in testosterone and bone loss, e.g. osteopenia, osteoporosis. Androgen deficiency may also result in reduced fertility.

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DISULFIRAM PROTOCOL:

I. Indications:

A. Disulfiram can be prescribed for patients suffering from:

1. DSM diagnosis of Alcohol Use Disorder who have a strong desire to remain in a state of enforced abstinence. These patients may have had episodes of inpatient intoxication, have access to alcohol, or may be preparing for discharge to the community.
 - a. As part of a comprehensive psychosocial substance use treatment program.
2. Patients admitted on disulfiram and who are stable should be continued on disulfiram.

B. Contraindications:

1. Concurrent or recent treatment with alcohol, paraldehyde, or alcohol-containing preparations, e.g. cough syrups, mouthwash, hand sanitizers, etc., or alcohol-containing foods, e.g. vinegar.
2. Concurrent treatment with metronidazole, which due to additive increase in CNS dopamine when combined with disulfiram, increases risk of psychosis.
3. Severe myocardial disease or coronary artery occlusion.
4. Decompensated psychosis or schizophrenia-spectrum disorder with ongoing positive symptoms, which could be worsened due to disulfiram's inhibition of dopamine- β -hydroxylase resulting in increased dopamine accumulation.
5. Hypersensitivity to disulfiram, any component of its formulation, or thiurams.

C. Precautions (risk/benefit analysis supports use):

1. Chronic medical conditions including diabetes mellitus, hypothyroidism, epilepsy, cerebral damage, chronic or acute nephritis, moderate or severe hepatic impairment.
2. History of rubber contact dermatitis.
3. Pregnancy (human data are lacking). Do not give disulfiram to nursing mothers.
4. Concurrent treatment with phenytoin can result in phenytoin toxicity due to disulfiram's inhibition of CYP P450 2C9.

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5. Elderly patients, due to greater frequency of decreased hepatic, renal, or cardiac function.

II. The following initial workup should be completed:

- A. There is informed consent or alternative legal authorization.
- B. With discussion of the disulfiram-alcohol reaction that results from disulfiram's inhibition of alcohol metabolism and the accumulation of high levels of the metabolite acetaldehyde. This reaction begins 10-30 minutes after ingestion of alcohol and includes the following toxic effects with varying intensities (severe reactions may be fatal):
 1. Sweating, warmth and flushing.
 2. Tachypnea, difficulty breathing or dyspnea.
 3. Blurred vision, head and neck throbbing, thirst.
 4. Nausea and vomiting.
 5. Chest pain/palpitations, hypotension, bradycardia with certain patients experiencing severe cardiovascular effects including cardiovascular collapse, arrhythmia, myocardial infarction in patients with preexisting coronary artery disease, and congestive heart failure in patients with preexisting myocardial dysfunction.

III. Initial workup includes:

- A. Complete physical examination.
- B. Breath, blood, or urine alcohol tests, if clinically indicated to confirm abstinence.
- C. Complete hepatic panel, prothrombin time, and renal function tests.
- D. Pregnancy test in women of child-bearing age.
- E. ECG.

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IV. Monitoring:

- A. Two weeks after starting therapy, obtain hepatic functions.
 - 1. Repeat hepatic panel monthly for the first 6 months of treatment, then every 3 months thereafter.
 - 2. Hepatic panel should be obtained immediately in any patient with signs of hepatic impairment, e.g. fatigue, anorexia, nausea, jaundice, dark urine, light-colored stool. Disulfiram-induced liver injury typically shows an equivalent ALT:AST with very high elevations.
- B. Regular pregnancy testing in women of childbearing age.
- C. Semi-annual ECG in patients with history of cardiovascular disease or diabetes mellitus.
- D. Regular and random urine toxicology testing

V. Dose initiation and titration:

- A. Typical starting and maintenance dose is 250 mg orally daily or at bedtime. Consider a lower starting and maintenance dose in patients 55-60 years or older.
- B. For patients who can drink alcohol without any symptomatology when adherent to this dose, the dose can be increased up to 500 mg/day, which is the maximum dose.

VI. Possible Adverse Reactions:

- A. Dermatological side effects including acneiform eruption or allergic dermatitis
- B. Mild drowsiness
- C. Fatigue
- D. Headache
- E. Impotence
- F. Metallic or garlic-like aftertaste
- G. Neuritis and/or neuropathy including optic neuritis, peripheral neuritis, or peripheral neuropathy
- H. Hepatic toxicity including hepatic failure has been reported and may develop in patients without a history of liver disease or even after months of treatment.
- I. New psychosis or exacerbation of chronic psychotic illness

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J. Disulfiram-alcohol reaction:

1. The duration of this reaction varies from 30-60 minutes in mild cases to several hours or more in severe cases. Severe cases require transfer to a higher level of care for supportive measures to manage hypotension and shock. These measures include administration of oxygen, IV fluids, vasopressors and antihistamines.
2. The reaction can occur for up to two weeks after the discontinuation of disulfiram. Disulfiram inhibits acetaldehyde dehydrogenase.

K. Drug interactions with disulfiram and management:

Drug	Effect with Disulfiram	Recommended Action
Certain benzodiazepines, e.g., chlordiazepoxide, diazepam	Decreased clearance	Switch to lorazepam or oxazepam
Isoniazid	Unsteady gait, mental status changes	Discontinue disulfiram
Metronidazole	Increased likelihood of psychosis	Do not prescribe disulfiram with metronidazole
Warfarin	Inhibits warfarin metabolism	Adjust warfarin dose
Sulfonylureas	May produce disulfiram-like reactions with alcohol	Monitor if prescribing disulfiram and sulfonylureas concomitantly
Phenytoin	Increases phenytoin plasma level via CYP 2C9 inhibition	Obtain baseline phenytoin level, monitor regularly, adjust dose as necessary
Theophylline	Increases plasma levels via CYP 1A2 inhibition	Obtain baseline theophylline level, monitor regularly, adjust dose as necessary
Tricyclic antidepressants	May cause delirium when administered with amitriptyline Increases plasma levels of desipramine and imipramine	Adjust dose, discontinue disulfiram, switch to another class of antidepressant

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METHADONE PROTOCOL:

I. Indications:

B. Methadone should be prescribed for patients suffering from DSM diagnosis of opioid use disorder and who are:

1. Treated with methadone and stable on it at the time of admission to DSH.
2. Treated with buprenorphine at a maximal dose of at least 24 mg daily and still experiencing urges to use opioids or using illicit opioids.
3. Unable to be treated with buprenorphine or naltrexone.
4. As an aid to maintain abstinence from opioids and as part of a comprehensive psychosocial substance use treatment program.

C. Contraindications:

1. Hypersensitivity to methadone or any component of its formulation.
2. Acute asthma or severe respiratory conditions that result in abnormally high carbon dioxide levels.
3. Current paralytic ileus.
4. Corrected QT interval of >500 ms.
5. Current treatment or treatment within the last one day for oral and 28 days for long-acting injectable naltrexone.
6. Current treatment or treatment within the last 8 hours with a mid-dose opioid partial agonist, e.g. buprenorphine.

II. Precautions (risk/benefit analysis supports use):

A. Respiratory depression as methadone can cause respiratory depression, particularly during initial dosing and dose titration.

1. Patients who are older, cachectic, or who have COPD are more susceptible to respiratory depression. Treat cautiously with lower doses.

B. Concurrent, active substance use disorders involving benzodiazepines and/or alcohol as use of these substances increases the risk of respiratory depression.

C. Rapid taper or abrupt discontinuation of methadone in a patient who is treated with a stable dose of methadone will result in opioid withdrawal.

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- D. Misuse or abuse as methadone can be abused similarly to other opioids. Monitor patients for medication diversion. Use of the liquid formulation is recommended if risk of diversion is suspected.
- E. QT interval prolongation and cardiac arrhythmia. Methadone has an FDA black box warning for QTc prolongation and torsade de pointes.
 - 1. The prevalence of QTc prolongation has been estimated at 2%. Risk factors include: high methadone doses, concomitant treatment with certain medications, congenital prolonged QTc, hypokalemia, and bradycardia.
- F. Pregnancy if potential benefit justifies risk. Chronic use may decrease fertility in both men and women.
- G. Neonatal abstinence syndrome occurs in newborns of mothers treated with methadone. Not all infants need treatment. Methadone passes into breast milk. Breast feeding should be encouraged.
- H. Physiological dependence. Patients treated with methadone will experience opioid withdrawal if they stop taking it.
- I. Cognition and psychomotor performance may be affected as methadone can have sedating effects in certain patients.
- J. Moderate to severe hepatic impairment (Child Pugh B or C). Patients with hepatic impairment require a lower methadone starting dose and a more cautious titration.
- K. Adrenal insufficiency has been reported in patients treated with chronic opioids.

III. The following initial workup should be completed:

- A. There is informed consent or alternate legal authorization.
- B. There is chart documentation of (If methadone treatment is present at admission, it should be continued pending completion of initial workup and chart documentation.):
 - 1. Complete medical, psychiatric and substance use history with careful attention to: medical comorbidities involving the pulmonary and cardiovascular systems, medications that may interact with methadone, use of opioids, benzodiazepines, and alcohol, and prior history of treatment with methadone or buprenorphine.
 - 2. Physical examination including vital signs with oxygen saturation and body weight.
- C. Initial workup includes:

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1. Urine toxicology
2. Complete metabolic panel
3. PT and INR.
4. Hepatitis B and C panels and HIV testing in patients whose serostatus is unknown.
5. Pregnancy test in women of child-bearing age.
6. ECG within 30 days.
7. Intake assessment of cardiac risk factors which can include:
 - i. Family history of sudden cardiac death, arrhythmia, myocardial infarction, heart failure, prolonged QTc, or unexplained syncope.
 - ii. Patient history of arrhythmia, myocardial infarction, heart failure, prolonged QTc, unexplained syncope, palpitations, or seizures.
 - iii. Current use of medications that may increase the QTc.
 - iv. Patient history of use of cocaine or methamphetamine which can prolong the QTc.
 - v. Electrolyte assessment for hypokalemia or hypomagnesemia.
8. Development of a cardiovascular risk stratification plan, which can include the following:
 - i. ECG on admission and repeat within 30 days
 - ii. Annual ECG monitoring for patients treated more than 120 mg of methadone per day
 - iii. Discuss risks and benefits of methadone with patients with corrected QT intervals between 450 and 500 ms. Adjust modifiable risk factors to reduce risk.
 - iv. If during treatment a patient's QTc exceeds 500 ms, engage in a risk/benefit discussion. After addressing risk factors, consider reducing the methadone dose or switching the patient to buprenorphine. Perform follow-up ECG monitoring.
9. Assessment of bowel function:
 - i. Establish baseline bowel function.

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- ii. If the patient is constipated, optimize laxatives to normalize bowel function prior to starting methadone. Avoid psyllium and polycarbophil. (Refer to Chapter 36: Appendix – Management of Medication-induced Constipation Revision: 01/01/2022.)
- iii. Review the patient's medication list identifying constipating medications and those with anticholinergic activity that may contribute to constipation. Taper, switch and/or discontinue any of these medications that are not essential to the patient's care. For example, rather than use diphenhydramine for insomnia, consider hydroxyzine, which has no anticholinergic activity. Hold iron during the first 4-6 weeks of methadone treatment.

IV. Monitoring:

- A. Observed random urine or saliva toxicology performed at least monthly. Methadone is not detected on a standard UDS, as it is not metabolized to morphine.
- B. Regular assessment of bowel functioning.
- C. Monthly weight and BMI.
- D. Methadone peak and trough plasma levels as clinically indicated.
- E. ECG annually or as clinically indicated.
- F. Regular pregnancy testing in women of child-bearing age, if there is clinical suspicion that the patient has been sexually active.

V. Dose initiation (induction) and titration:

- A. The first few days of methadone treatment are critical.
 - 1. Due to increasing blood levels as methadone accumulates in combination with patients' tendency to use illicit opioids to treat withdrawal, during induction the risk of overdose is high.
 - 2. At every point during the methadone dose determination, from induction onward, collaborate with staff to observe for and be mindful of concomitant use of illicit drugs, alcohol, medical conditions that may compromise respiratory function, prescribed medications that are sedating, or prescribed medications that may increase methadone's effective plasma level.
- B. The determination of the initial methadone dose is based on:
 - 1. Pharmacology of methadone

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2. Characteristics of the patient including medical conditions, current medications, and use of other substances.
3. Current level of opioid tolerance
 - i. Tolerance cannot be measured.
 - ii. Tolerance is assessed indirectly by considering the quantity, potency and route of opioid(s) used, and the time elapsed since last use of opioids.
- C. Induction for a healthy young patient who has at least moderate opioid tolerance, e.g. has been using potent opioids daily, and who demonstrates at least early signs of opioid withdrawal, can begin with an initial dose of 10-30 mg. The maximum first dose is limited to 30 mg. Use lower doses for patients who are age 55 or older, are treated with sedating medications, take medications that can increase methadone serum levels, or have medical conditions that can cause hypoxia, hypercapnia, or cardiac arrhythmias, e.g. asthma, COPD, obesity, sleep apnea, hypokalemia or hypomagnesemia. For patients returning from an outside medical facility and for whom the methadone history while away is not known, start as if the dosing is initial induction and increase if objective signs and symptoms of withdrawal observed.
 1. The patient should remain for observation for 2-4 hours to see whether the dose is sedating or relieves withdrawal signs
 2. On Day 1, the goal is to reduce withdrawal for 3-4 hours after the dose (while methadone is at peak plasma level). The first dose of methadone should not be expected to completely suppress opioid withdrawal and the dose is too high if it does.
 3. On Day 2, screen the patient for signs of overmedication including sedation, unusual energy with or without euphoria, or feeling completely well for 24 hours after the first dose. If any of these signs are present, reduce the dose by 20-30%.
 - i. If complete suppression of withdrawal was achieved 2-4 hours after dosing on Day 1, delay any dose increase for another day or two.
 - ii. If the patient did not experience complete suppression of withdrawal within 2-4 hours of dosing on Day 1, it is safe to increase the dose by 5 mg
- D. On Day 3, the patient's response to the previous day's dose serves as a guide to the determination of subsequent doses. The most helpful question is to ask the patient whether the dose completely controlled symptoms of withdrawal for 2-4 hours after dosing. Continue in this way until steady state is reached at Day 5.

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- E. Induction for a patient whose level of tolerance is unclear or for a patient who has a low level of tolerance begins with an initial dose of 5 mg methadone. The patient should remain for observation for 2-4 hours to see whether the dose is sedating.
 - 1. On Day 2, screen the patient for sedation, euphoria, and the duration of suppression of urges to use opioids or opioid withdrawal as described above. Adjust or continue the dose as described above and using increments of 2.5 mg to 5 mg.
 - 2. On Day 3, the patient's response to the previous day's dose serves as a guide to the determination of subsequent doses. The rate of titration and the doses used will be slower and lower, respectively for patients with lower tolerance.
- F. Induction for a patient who has no tolerance should begin with an initial dose of 2.5 mg of methadone. The patient should remain for observation for 2-4 hours to see whether the dose is sedating.
 - 1. If there is no evidence of sedation on Day 1, continue 2.5 mg daily for 5 days until steady state is achieved. Alternately, if sedation is observed, the dose can be lowered to 2 mg and continued for 5 days, until steady state is achieved.
- G. Methadone's long half-life and accumulation in the tissue means that even when holding the dose constant over several days, the patient's methadone serum level will rise each day until it reaches steady state. For example, if the patient is treated with 10 mg for the first few days of induction, the serum level on Day 2 will reflect the 10 mg from Day 2 dosing plus 5 mg that remained in the body from Day 1 dosing. On Day 3, the serum level will reflect 10 mg from Day 3 plus 5 mg remaining in the body from Day 2 plus 2.5 mg remaining in the body from Day 1 (for an equivalent total dose of 17.5 mg).

VI. Stabilization on a Therapeutic Methadone Dose:

- A. After the initial induction phase which establishes tissue stores, dose adjustments can be made using the "start low and go slow" approach.
 - 1. Patients typically reach 24-hour coverage of physical symptoms within the first few weeks of treatment. Complete suppression of craving and complete abstinence from illicit opioids may take longer.
 - 2. For patients with at least moderate opioid tolerance, dose adjustments of 5 mg can be made every 3-5 days as needed.
 - 3. For patients with no or low tolerance, make dose adjustments of 2.5 to 5 mg weekly as needed.
 - 4. The goal is to achieve a therapeutic dose which should:

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- i. Suppress physical signs and symptoms of opioid withdrawal between doses.
 - ii. Minimize intrusive thoughts/dreams about opioids and urges to use or cravings.
 - iii. Not be sedating.
 - iv. Have minimal side effects such as sedation, sweating, constipation and decreased libido.
 - v. Block the euphoria produced by opioids.
 - vi. Note that a therapeutic dose will not treat acute pain. If a patient experiences pain, they will need to be treated.
5. Methadone can induce its own metabolism via CYP 3A4, which increases clearance over time. The eventual dose will be higher than the initial dose.
6. Methadone doses above 100 mg daily need to be clearly justified in the patient's chart and should prompt a request for Medication Review Committee (MRC) or Therapeutic Review Committee (TRC) consultation which should include review by an Addiction Specialist.
- B. While most patients can be stabilized on a single daily dose, some patients are rapid metabolizers, e.g. pregnant women, and require split dosing to alleviate withdrawal between doses. As the methadone peak to trough ratio increases from 2:1 to 4:1, the rapid decline in methadone serum level is increasingly likely to be perceived as withdrawal (see below for discussion of methadone serum levels). Concurrent pain management also will likely require split dosing.

Splitting the dose can be accomplished in one of two ways:

 1. 5-10 mg of the morning dose can be transferred to the evening. Continue to make transfers in increments of 5-10 mg every 5-7 days until the patient feels comfortable and without symptoms of withdrawal between doses.
 2. Divide the daily dose in half, given one half in the morning and the other in the evening. This may cause the patient to experience some amount of withdrawal after the morning dose.
 3. If split dosing cannot be continued, the evening dose will need to be slowly added back to the morning dose in 5-10 mg increments every 3-5 days. If sedation is observed after the morning dose, return the morning dose to the last tolerated dose and taper the evening dose to discontinuation. Discontinuing the split dose in a patient who is a rapid metabolizer will make it impossible to achieve a therapeutic dose.

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VII. Interpreting Methadone Blood Levels:

- A. Serum peak and trough levels of methadone may be utilized as an adjunct to clinical evaluation, allowing evaluation of the safety and adequacy of the dose and to identify patients who are rapid metabolizers. Typical peak plasma concentrations are 800 to 1000 ng/ml and typical trough levels are 400 to 500 ng/ml.
- B. Obtain serum methadone levels after a patient has reached steady state, which occurs after 5-7 consecutive days at the same dose.
 - 1. The trough level is drawn before the daily dose and about 24 hours after the previous dose. If taken in divided doses (such as in the treatment of chronic pain), the blood level should be measured before the morning dose. However, methadone should generally be administered in a single daily dose for opioid maintenance treatment.
 - 2. The peak level is drawn 3-4 hours after ingestion of the daily dose.

VIII. Dosing accounts for drug-drug interactions:

- A. Benzodiazepines or other Central Nervous System Depressants
 - 1. Concomitant use increases the risk of respiratory depression, sedation, coma, and death.
 - 2. Stopping benzodiazepines, muscle relaxants and other sedating medications prior to treatment with methadone is preferred. If treatment cannot be stopped, decreasing to the lowest possible dose with increased monitoring may be appropriate.
 - 3. Certain antipsychotics such as clozapine, chlorpromazine, and olanzapine can be sedating. Adjust the dose to maximize efficacy and minimize sedation before starting methadone.
- B. Methadone is primarily metabolized by CYP P450 3A4 with contributions from other CYP P450 enzymes including 2B6, 2C19, 2C9 and 2D6.
 - 1. Concomitant use of CYP 3A4 inhibitors, e.g. erythromycin, clarithromycin, azole antifungals, and certain antiretrovirals, can increase the plasma concentration of methadone resulting in sedation and prolonged opioid effects. This is especially evident when an inhibitor is added to a stable dose of methadone.
 - i. After stopping a CYP 3A4 inhibitor, the methadone plasma concentration will decline. This may result in signs of opioid withdrawal or decreased efficacy of the medication to suppress opioid cravings. Consider titrating the methadone dose until stable drug effects are achieved.

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2. Concomitant use of CYP 3A4 inducers, e.g. rifampin, carbamazepine, phenytoin, and some antiretrovirals, can decrease the plasma concentration of methadone. This may lead to decreased efficacy or the onset of opioid withdrawal. If concomitant therapy is necessary, consider increasing the methadone dose until stable drug effects are achieved.
 - i. If a CYP 3A4 inducer is stopped, as the effects of the inducer slowly wane, and the methadone plasma concentration increases over four to six weeks. Monitor for signs of sedation or respiratory depression. If the patient appears sedated, reduce the methadone dose by 2.5 mg to 10 mg per day. Doses of 20 mg per day or less should be decreased by 2.5 to 5 mg per day, while doses > 20 mg per day can be decreased by 5 mg to 10 mg per day.
3. There are many interactions between different antiretroviral medications and methadone. Before starting methadone in a patient with HIV or before starting or switching a patient's HIV medication, review possible drug-drug interactions using a comprehensive database located here:
<http://hivinsite.ucsf.edu/interactions>

C. Anticholinergic Drugs:

1. Concomitant use of anticholinergic drugs may increase risk of severe constipation which may lead to bowel obstruction and perforation.
2. Common examples include psychiatric medications, e.g. clozapine, olanzapine, chlorpromazine; anti-parkinsonism medications, e.g. benztropine; anti-spasmodics, e.g. hyoscyamine and dicyclomine; medications for overactive bladder, e.g. oxybutynin.
3. Monitor patients carefully. Consider prophylactic laxatives. If constipation does not respond to laxative polypharmacy, treat with a peripherally acting mu opioid receptor antagonist, e.g. naloxegol or naldemedine. (Refer to Chapter 36: Appendix – Management of Medication-induced Constipation Revision: 01/01/2022)

D. Antiarrhythmics:

1. Concomitant use of certain antiarrhythmics contributes to the blockage of the potassium channel involved in cardiac repolarization. Blockade of this channel prolongs the corrected QT interval.
2. Specific drugs of concern are procainamide, quinidine and amiodarone.
3. Monitor cardiovascular status carefully.

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E. Drugs acting on the mu opioid receptor:

1. Treatment of a patient who is stable on methadone with an opioid receptor antagonist such as naltrexone or naloxone will precipitate severe opioid withdrawal.
2. Treatment of a patient who is stable on methadone with the opioid receptor partial agonist buprenorphine will precipitate severe opioid withdrawal.

IX. Treatment of Overdose:

- A. The first two weeks of treatment are the highest risk period for methadone-related deaths due to increasing tissue stores. Specifically, methadone is deposited in the tissue over 3-7 days to reach steady state. This means that during induction, a given dose will have a stronger effect and last longer with each day of ingestion.
- B. Overdose is more common when methadone is combined with other opioids, CNS depressant drugs such as benzodiazepines, and/or alcohol.
- C. Monitor respiratory and cardiac status carefully. If respiratory rate is depressed, provide an airway and controlled ventilation. In addition to oxygen, IV fluids, vasopressors and other supportive measures should be considered. Transfer the patient to a higher level of care.
- D. Administer naloxone with the understanding that higher than normal doses and repeated administration may be required. See CHAPTER 48 NALOXONE HYDROCHLORIDE NASAL SPRAY (NARCAN) PROTOCOL for further information on administration.

X. Tapering and Discontinuing Methadone:

- A. Longer lengths of stay in methadone treatment are associated with superior outcomes. Patients should stay in treatment for as long as they continue to benefit and develop no contraindications.
- B. If methadone is stopped abruptly or the dose is decreased significantly, the patient will experience opioid withdrawal.
- C. There is no ideal tapering protocol for methadone. Tapers should be flexible and tailored to the individual.
 1. Generally, a taper occurs slowly over several months or longer to give the patient time to acclimate to the lower dose and reduce discomfort from opioid withdrawal and cravings.
 2. One approach is to decrease the methadone dose by 5 to 10 percent every 1-2 weeks. Once the dose reaches 20 – 40 mg, the patient may

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begin to experience more urges to use opioids. Either the patient can continue to taper methadone at a slower rate.

XI. Possible Adverse Reactions:

- A. Constipation.
- B. Sedation.
- C. Sweating.
- D. Sexual dysfunction or decreased libido.
- E. Drowsiness.
- F. Amenorrhea.
- G. Weight gain.
- H. Edema of the extremities.
- I. Opioid-induced androgen deficiency resulting in decreased testosterone and bone loss, e.g. osteopenia, osteoporosis.

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Naltrexone Protocol:

I. Indications:

A. As part of a comprehensive psychosocial treatment program for either or both of the following clinical indications:

1. DSM diagnosis of Alcohol Use Disorder (AUD)
2. DSM diagnosis of Opioid Use Disorder (OUD)

B. Contraindications:

1. Active treatment with opioid analgesics, e.g. hydrocodone, morphine; or opioid medications used to treat OUD, e.g. methadone, buprenorphine.
2. Acute opioid withdrawal.
3. Any individual who has a demonstrated adverse response to a naloxone challenge test or who has a urine toxicology test positive for opioids.
4. Fulminant hepatitis or severe hepatic impairment (Child-Pugh Class C). Milder, chronic hepatitis is not a contraindication.
5. Anticipated need for opioid analgesics in the next seven days, e.g. pending surgery, recent acute injury, etc.
6. Hypersensitivity to naltrexone or any component of its formulation. Note that the delivery system for XR-NTX is the same polyactide coglycolide polymer delivery system employed by risperidone Consta®. Patients with allergies to risperidone Consta® should not be treated with XR-NTX.

II. Precautions:

A. Risk of severe opioid intoxication and fatal overdose:

1. After naltrexone is discontinued in OUD patients, due to reduced physiological tolerance.
2. When patients attempt to surmount naltrexone's opioid receptor antagonist effect by using extreme quantities of opioids.

B. Precipitated opioid withdrawal in patients who have not completely withdrawn from opioids prior to treatment with naltrexone.

1. An opioid-free interval of 7-10 days is required for patients treated with or using short-acting opioids. An opioid-free interval of 10-14 days or longer may be required for patients treated with methadone.

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- C. Pregnancy (no evidence of teratogenicity but human data are lacking) or breast feeding in patients with AUD. Naltrexone is not recommended for treating OUD in pregnant women.
- D. Hepatitis, more common in patients with existing liver disease and more common with higher doses of oral naltrexone (≥ 300 mg/day)
- E. Acute pain management in emergency situations will require non-opioid analgesia or high dose opioid anesthesia in monitored settings
- F. Moderate to severe renal function (eGFR <50 ml/min) due to reduced elimination
- G. Depression and suicidal ideation
- H. Injection site reactions with injectable extended-release naltrexone (XR-NTX), including some severe cases that require surgical intervention.
- I. Patients who develop dyspnea and hypoxemia should be evaluated immediately for consideration of eosinophilic pneumonia (XR-NTX)

III. The following initial workup should be completed:

- A. There is informed consent or alternate legal authorization.
- B. Initial workup includes:
 - 1. Physical examination with particular attention to signs of active opioid use such as fresh injection sites, signs of intoxication with opioids or any other substance, and/or signs of opioid withdrawal, e.g. diaphoresis, lacrimation, yawning, restlessness, and rhinorrhea.
 - 2. Laboratory analysis: Hepatic panel, hepatitis panel, HIV test, renal function test, and urine toxicology test.
 - 3. Pregnancy test in women of childbearing age.

IV. Monitoring:

- A. Assess the patient within a week of administering the first XR-NTX dose for injection site or adverse reactions.
- B. In healthy patients without liver disease, monitor hepatic panel at 1, 3, and 6 months and yearly after that. Perform hepatic panel more frequently if there are abnormalities, a history of liver disease, or other hepatotoxic medications are prescribed.
- C. Regular and random urine toxicology tests
- D. Regular pregnancy testing in women of child-bearing age

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V. Dose initiation and titration:

- A. The typical oral starting and maintenance dose in a healthy adult is 25 to 50 mg daily. If an initial dose of 12.5 mg is well-tolerated, then in to 50 mg per day. The most common dose-limiting factor is post-dose nausea. In patients at risk for adverse events, (e.g. Women, younger patients, those with shorter abstinence) oral naltrexone can be started at 12.5 mg or 25 mg daily with food and gradually titrated to 50 mg/day over several weeks. In patients with AUD, at least 3-7 days of abstinence are recommended prior to starting naltrexone to reduce the risk of medication side effects. It is safe to continue naltrexone in patients who are actively drinking alcohol.

In patients with OUD, oral naltrexone is not superior to placebo or no medication treatment in terms of reducing illicit opioid use or treatment retention. Nevertheless, in certain circumstances oral naltrexone can be considered for treatment of OUD. These include treatment in environments with a high level of monitoring and in patients who cannot or will not take XR-NTX. A 50 mg dose of oral naltrexone provides a plasma level that exceeds what is required to saturate the mu-opioid receptor. In patients with OUD, oral naltrexone should only be initiated after the patient has completely withdrawn from opioids.

- B. XR-NTX is initiated as a 380 mg deep intramuscular gluteal injection every 28 days. Injection is into the upper outer quadrant of the gluteal muscle, with alternating sides every injection. Pretreatment with oral naltrexone is not required. Using the correct needle length based on the patient's body habitus will ensure the medication is delivered into the muscle rather than the subcutaneous adipose tissue as injection into the subcutaneous tissue increases the risk of injection site reactions. XR-NTX must not be administered into the deltoid muscle or intravenously. Given the risk of severe injection site reactions, the FDA requires a risk evaluation and mitigation strategy (www.vivitrolrems.com) that includes aids to reinforce proper XR-NTX injection technique. If a patient misses a dose, they should receive the next dose as soon as possible.

VI. Possible Adverse Reactions:

- A. Nausea
- B. Vomiting.
- C. Anorexia.
- D. Dizziness.
- E. Fatigue.
- F. Somnolence or sedation
- G. Insomnia.
- H. Headache.
- I. Anxiety.

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- J. Hepatic enzyme abnormalities.
- K. Nasopharyngitis (XR-NTX)
- L. Injection site reactions including induration, pruritis, nodules, and swelling (XR-NTX)
- M. Precipitated opioid withdrawal
- N. Hypersensitivity reactions

VII. Drug Interactions with naltrexone:

- A. Opioid-containing cough and cold medications may have decreased benefit.
- B. Opioid-containing antidiarrheal medications such as loperamide will not be effective.

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