Agents Used to Treat Opioid Use Disorder

A. FDA Approved Indications in Substance Use Treatment (Documentation Required)

1. Buprenorphine
    i. Buprenorphine sublingual tablets (Subutex)
    ii. Generic buprenorphine/naloxone sublingual tablets
    iii. Buprenorphine/naloxone sublingual films (Suboxone)
    iv. Buprenorphine/naloxone sublingual tablets (Zubsolv)
    v. Buprenorphine extended-release injection (Sublocade)

2. Lofexidine oral tablets (Lucemyra)

3. Methadone
    i. Oral Concentrate (10mg/ml)
    ii. Oral Solution (5mg/5ml)
    iii. Oral Solution (10mg/5ml)

4. Naltrexone
    i. Generic naltrexone oral tablets
    ii. Naltrexone for depot injection (Vivitrol)

B. Commonly Prescribed Non-FDA approved Medications to Manage Opioid Withdrawal:

1. Clonidine
    i. Generic Clonidine oral tablets
    ii. Clonidine oral tablets (Catapres)
    iii. Clonidine patches (Catapres)

2. Ondansetron
    i. Generic ondansetron oral tablets
    ii. Generic ondansetron orally disintegrating tablets
    iii. Ondansetron oral tablets (Zofran)
    iv. Ondansetron orally disintegrating tablets (Zofran)

3. Hydroxyzine (Vistaril) oral capsules

4. Gabapentin oral tablets or capsules (Neurontin)

5. Naloxone
    i. Injectable and intranasal generic
    ii. Naloxone HCL (Narcan Nasal Spray)
    iii. Naloxone autoinjector (Evzio)

C. Emergency treatment of known or suspected opioid overdose:

Naloxone

iv. Injectable and intranasal generic
v. Naloxone HCL (Narcan Nasal Spray)
vi. Naloxone autoinjector (Evzio)

C. Minimal Documentation/Monitoring (Documentation Required)

1. All standard outpatient requirements (see section R for details).

2. Document rationale when making any medication changes.

3. CURES:

- Review of cures report is required prior to initiation of any controlled medication, and again at intervals no longer than 6 months throughout treatment or whenever misuse of the medication is suspected, including when it's used more frequently or at higher dose than prescribed without provider consultation or being prescribed by more than one provider at the same time. **DOCUMENT YOUR OBSERVATION IN THE PROGRESS NOTE.**

- In cases where there are discrepancies between CURES report and the urine toxicology report, diversion should be considered, and the following steps are recommended: (Note: There may be a delay of 1-2 weeks before recent dispensing data appears on the CURES report).

    1. Perform a thorough review of medication adherence by confirming the directions, the timing of the medications and compare them to appointments, pharmacy dispensing data, and the timing of the toxicology screen.

    2. Prescribe smaller quantities of the medications, order more frequent random toxicology screens, and schedule more frequent follow up appointments prior to refills.

4. NALOXONE: (Assembly Bill No. 2760)

A. When prescribing opioids, the prescriber shall offer a prescription for naloxone to a patient if:

    i. The prescription daily dose is >90 morphine mg equivalents
    ii. An opioid is prescribed with a benzodiazepine
    iii. The patient has an increased risk of overdose

B. When prescribing opioids, the prescriber shall provide education on overdose prevention and the use of naloxone to the following individuals:

    i. Patient
    ii. One or more persons designated by the patient (If available/applicable)

For more information, please use the following Link:
https://leginfo.legislature.ca.gov/faces/billTextClient.xhtml?bill_id=201720180AB2760

5. Sedation checks before dosing, BAL testing, observation 3 to 4 hours after dosing (at the time of the peak methadone level), etc. should be considered depending on the clinical situation and whenever there is a change in the patient's status.

6. Document coordination of care with other providers involved in the care of the patient, as clinically indicated.

7. When managing patients with OUD or AUD, document a plan to minimize the risk of overdose:

A. Educate patients about the risks of drinking alcohol while on medication assisted treatment with methadone or buprenorphine including sedation, overdose, and death.

B. Educate patients about the effect of alcohol use on methadone. Combining Alcohol with Methadone can lead to profound CNS depression and lead to increased risk of side effects and overdose which can increase the risk of death.

C. Based on the level of sedation and the clinical situation, following strategies should be considered:

- Serial breathalyzer testing
- Sedation checks before dosing
- Urine drug screening for alcohol or metabolites of alcohol (ethyl glucuronide & ethyl sulfate) and/or repeating labs i.e., LFTs and hemogram and alerting the patient's PCP.

D. Patients should be discouraged from illicit use of Suboxone, Methadone, Methamphetamine And Benzodiazepines (i.e., Illicit Methadone Supplementation).

9. When treating patients with concurrent use of BZDs, other CNS depressants and opioids document:

A. A plan to minimize the risk of overdose or other adverse events. Educate patients about the risks (including risk of death) inherent when BZDs, CNS depressants and opioid agonists are combined.

B. Diligently assess for BZD and other CNS depressant use, including asking about substances used, source, amount, and frequency of use. Add screening for specific substances to urine toxicology as indicated.

C. Educate patients about illicit pills that may be fentanyl or a potent designer benzodiazepine increasing the risk of sedation/overdose/death.

D. Advise the patient that BZDs should not be the treatment of choice for anxiety. Discuss with patient the increased risk of benzodiazepine use disorder in patients with OUD and request that the patient talks to the prescriber and transition to a non-BZD medication like an SSRI or SNRI in combination with CBT if available.

E. If the prescribing MD is unwilling to transition from BZDs to another medication, a "letter to

prescribing physician should be sent requesting that, quantity be limited and documentation regarding treatment failure provided. (See attached).

F. If there is evidence that the patient is not taking medication as prescribed, i.e., diverting or is unsafe to continue MAT; obtain a ROI to coordinate care with the prescribing physician and express the concerns. If the patient declines to allow coordination of care, advise that it may not be possible to continue medication assisted treatment for safety reasons.

11. If a patient has a history of long-term BZD use:

A. Evaluate to determine the safest treatment plan.

B. As clinically indicated: taper/detox, monitoring at a higher level of care may be indicated prior to initiating OAT.

C. In others, gradually decreasing to the lowest effective dose is indicated. Clearly document risk vs. benefit of selected treatment course.

12. **If a patient on MAT is reported or directly observed by the provider to be altered or sedated, following steps need to be considered to ensure patient safety:**

A. Hold the daily dose of methadone/buprenorphine.
B. Assess, ensure patient has a safe ride home, and transport to ER for observation/intervention if clinically indicated.
C. Alert police if patient drives while appearing sedated/altered.
D. Meet with the patient (when not altered) to assess need for more intensive treatment or medical detoxification.
E. Alert any physicians prescribing sedatives.
F. Consider decreasing the methadone or buprenorphine dose.
G. Discontinue all take out doses.

D. Maximum Dosing:

1. Methadone:

A. Maximum dose varies for each patient and based on clinical efficacy and safety. Factors to be considered include observed response pre- and/or post- dosing, peak and trough methadone levels, signs/symptoms of over-medication, reported or observed side effects, urine toxicology results, EKG findings, co-occurring medical conditions and medications.

B. Consider ordering peak and trough methadone level when dose reaches 90mg to screen for rapid metabolism, high serum methadone level and as clinically indicated thereafter.

2. Buprenorphine

A**. Maximum Daily Dose (MDD)** for most patients is 24mg daily.

B. MDD up to 32mg for patients with co-occurring pain (generally divided BID to QID) or

for whom a lower dose has been determined to be insufficient (by observation of signs of persistent opioid withdrawal on a lower dose).

C. Confirmation that the patient is adhering to SL dosing is recommended.

3. Naltrexone:

A. Extended release (injectable): 380mg IM monthly

B. Oral: **Up to** 100mg **per day**.

4. Clonidine: Clonidine is an alpha-2 adrenergic agonist. It can provide relief to many of the physical symptoms of opioid withdrawal including sweating, diarrhea, vomiting, abdominal cramps, chills, anxiety, insomnia, and tremor. It can also cause drowsiness, dizziness, and low blood pressure. Blood pressure needs to be monitored at baseline and throughout the withdrawal management with Clonidine. Sudden cessation of clonidine treatment has, in some cases, resulted in symptoms such as nervousness, agitation, headache, and tremor accompanied or followed by a rapid rise in blood pressure. Such responses are dose depended.

Please see Table: 4 in the following reference for dosage information and more details.

❖ For more information on management of opioid withdrawal visit the following websites:
(Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence)

https://www.ncbi.nlm.nih.gov/books/NBK143167/
https://www.ncbi.nlm.nih.gov/books/NBK310652/

E. Duration of Treatment:

A. Varies depending on the treatment goal; for methadone, duration is defined in federal and state regulations and eligibility criteria are more stringent for maintenance treatment.

A. Long-term or extended detoxification (>30 days but not >180 days)

B. Maintenance treatment

B. Medication assisted treatment for OUD is considered long-term treatment for a chronic condition.

F. Standard laboratory, ECG monitoring and other screening as clinically indicated (Documentation Required)

1. Pre-admission screening:

A. Onsite urine drug screen with temperature testing
B. Breathalyzer testing
C. Clinical Opioid Withdrawal Score (COWS)
D. EKG if clinically indicated
E. Other medical clearance as indicated (i.e. if patient left the ER or hospital AMA or appears

unstable, infectious or in need of acute medical or mental health care)

2. Labs on Admission:

A. Blood work: Panel 7, LFTs, Hepatitis serology (B&C), RPR, HIV (with patient consent).
B. Urine: At Valley Medical Center the urine toxicology Panel includes Amphetamine, Barbiturates, BZDs, Cocaine, Fentanyl, opiates, PCP, and Oxycodone. THC, and other suspect drugs need to be added depending on history, medical U.A.
C. Provide HIV education and offer testing

3. Routine Labs: Per the practice of SCC OTPs; screen for medical concerns in a population that often does not receive regular medical care.

A. Annually: repeat the admission labs, except include hepatitis serologies only if clinically indicated.

B. Trough methadone level should be done when dose reaches 90-100mg. Repeat peak and/or trough levels as clinically indicated. Steady State Concentration is reached after 5-7 consecutive days at the same dose. The trough is drawn about 24 hours after the last dose and the peak can be drawn 3-4 hours after ingestion of the daily dose. The optical peak to trough is less than two and greater than two suggests a rapid rate of metabolism. A peak and trough level should be done if rapid metabolism is suspected and prior to initialing a split dosing.

4. Screening for Tuberculosis:

A. At admission and annually
B. PPD skin testing (if no history of prior positive), may be waived if documented test in the preceding 90 days.

C. Screening questionnaire + CXR if history of positive

5. ECG monitoring:

A. As clinically indicated before admission
B. During/after titration to a therapeutic dose
C. Follow up ECG as clinically indicated and specially under the following circumstances: (Table 2)

1. Pre-existing cardiovascular disease and/or family history of cardiovascular disease.

2. Drug-drug and drug-disease interaction with potential to increase risk of toxicity i.e., other drugs with the potential to increase the QTc interval.

*** Prolonged QTc interval has been defined as >450msec for men and >460-470msec for women.**

G. **Patient Education:**

A. Patient education prior to admission and routinely as needed. (Documentation Required)

1. Educate patients about the risks of drinking alcohol while on medication assisted treatment with methadone or buprenorphine including sedation, overdose and death.

2. Educate patients about the effect of alcohol use on methadone metabolism

B. Medical Counsel for women who are pregnant or post-partum (tailored to individual need and trimester of pregnancy).

1. Impact of specific substance use on patient, pregnancy, and baby
2. Importance of participation in prenatal, postpartum, and pediatric care
3. Impact of opioid withdrawal on patient, pregnancy, and baby
4. Neonatal abstinence syndrome – symptoms, factors affecting severity, treatment, impact of subtherapeutic methadone dose and use of cigarettes, alcohol, etc.
5. Post-partum depression – symptoms, treatment
6. Risk of relapse after delivery
7. Impact of pregnancy and delivery on methadone metabolism
8. Breastfeeding – factors to consider

H. Black Box Warning

A. The BBW for Methadone includes the following topics: appropriate use, addiction, abuse and misuse, respiratory depression, accidental ingestion, QT prolongation, neonatal opioid withdrawal syndrome, CYP450 interactions, risks from concomitant use with BZDs, CNS depressants, and opioid addiction treatment.

B. See PI for Methadone for a complete discussion.

I. Warnings and Precautions (Documentation Required)

- For patients with substance use refer to Section P: medication guidelines for prescribing controlled psychotropic medications to patients with substance use.
- Respiratory Depression
- Cardiac Conduction Effects
- Incomplete Cross-tolerance between Methadone and other Opioids
- Misuse, Abuse, and Diversion of Opioids
- Physical Dependence
- Interactions with other CNS Depressants
- Interactions with Alcohol and Drugs of Abuse
- Head Injury and Increased Intracranial Pressure
- Acute Abdominal Conditions
- Hypotensive Effects
- Use with caution in elderly and debilitated patients
- Drug Interactions
- Potentially Arrhythmogenic Agents
- Withdrawal symptoms

- Anti-retroviral Agents
- Pregnancy, labor and Delivery and Breastfeeding
- Pediatric Use
- Caution if renal or hepatic impairment present
- Caution if sleep apnea present
- Caution if CNS depression present
- Caution if seizure hx present
- Caution if depression present

J. Drug-Drug Interactions – For more details refer to Table 3, PIs, and www.epocrates.com

For Patients being considered for MAT:

If the patient is taking/using a stimulant, benzodiazepine, or other CNS depressant(s) such as a muscle relaxant, sleeping pill, anti-convulsant, antihistamine, psychotropic, opioid, and/or alcohol:

A. document coordination of care with other providers who are or have been involved in the care of the patient.

B. Delay induction if patient appears is sedated or under the influence of a licit or illicit substance.

C. Extreme caution is warranted when patients are using sedatives, particularly if they have a history of overdose(s) accidental or intentional.

D. Methadone may interact with drugs that are metabolized by the CYP450 3A4 and potentially CYP2D6 and CYP2B6. (See Tables 1, 2 & 3)

E. Document drug-drug interactions particularly if the patient is on a medication that may prolong QTC interval.

K. Adverse Effects: (for a complete list of Adverse Effects please see PI for each drug i.e., METHADOSE Label (fda.gov)

Serious Adverse Effects:

- Dental problems associated with buprenorphine-containing drugs dissolved in the mouth
- Respiratory depression & failure
- Systemic hypotension
- Cardiac arrest
- Death
- Cardiac Arrhythmias (Torsade's de pointes)
- Hyperalgesia
- Overdose
- Withdrawal sxs if abrupt D/C
- Apnea
- Drug abuse & Dependence
- Cardiac Conduction Effects: Arrhythmias, Bigeminal rhythms, bradycardia, cardiomyopathy,

ECG abnormalities, extrasystoles, flushing, heart failure, Seizures
- Suicidality
- Hypotension
- Syncope

Common Adverse Effects:
- Constipation
- Mild Sedation
- Excess Sweating
- Dizziness/lightheadedness
- Asthenia
- Ataxia
- Headache
- Abdominal pain, anorexia, dry mouth, glossitis
- Agitation, confusion, disorientation, dysphoria, euphoria, insomnia, seizure
- Amenorrhea
- Disinhibition
- Irritability
- Libido changes
- Menstrual irregularities
- Diplopia
- Dysarthria
- Incontinence
- Urinary retention
- Dystonia
- ALT, AST elevation

L. Impacts of Pregnancy related to MAT: Refer to CSAM Chapter 4: Pregnancy and Neonatal Withdrawal

Comments related to Kratom:

Patients should be discouraged from using Kratom due to its safety concerns. The U.S. Food and Drug Administration (FDA) continues to warn people to avoid using products containing kratom or its ingredients. https://www.webmd.com/vitamins/ai/ingredientmono-1513/kratom

References:

1. CSAM
2. ASAM
3. SAMSHA
4. Epocrates
5. Micromedex
6. Physician's Package Inserts for various medications
7. UpToDate: Pharmacotherapy for opioid use disorder
8. Withdrawal Management, https://www.ncbi.nlm.nih.gov/books/NBK310652/
9. Keratom herbal supplement; https://www.nbcnews.com/health/health-news/what-kratom-popular-herbal-supplement-has-caught-flak-fda-n1066526
10. https://www.webmd.com/vitamins/ai/ingredientmono-1513/kratom
11. Benzodiazepines: How they work and how to withdraw. http://benzo.org.uk/manual/bzha01.htm
12. Opioid Therapies and Cytochrome P450 https://www.jpsmjournal.com/action/showPdf?pii=S0885-3924%2812%2900492-7
12. Clinical Factors Associated with Prolonged QTc and/or TdP https://www.crediblemeds.org/ndfa_list

Attachments:

Table 1: Common Cytochrome P450 3A/3A4 Inhibitors and Inducers
Table 2: Some reported causes and potentiators of the long QT Syndrome
Table 3: Pharmacokinetics & Drug-Drug Interactions