Inpatient Management of Opioid Use Disorder: **Methadone**

Authors:
Diana Coffa, MD, Kristin Harter, PharmD, Hannah Snyder, MD

Advisors:
Jadine Cehand NP, CNS, Curtis Geier, PharmD, Michelle Geier, PharmD, Corinna Gamez, MD, Tamara Lenhoff, PharmD, Kelly Pfeiffer, MD, Brad Shapiro, MD, Scott Steiger, MD, Becky Tsui, MD, Sarah Windels, Barry Zevin, MD

UCSF University of California San Francisco

California Health Care Foundation

SHOUT SUPPORT FOR HOSPITAL OPIOID USE TREATMENT

This guideline applies to patients in inpatient medical settings. If any of the following points are different for pregnant patients, it is noted in each segment of the following document.

Goal of Treatment:

- COWS (Clinical Opioid Withdrawal Score – See Appendix A) of 5 or less for a period of 24 to 36 hours
- Elimination of drug hunger or cravings
- No sedation or respiratory depression from medication
- If patient uses illicit opioids while on methadone, patient should not feel substantially intoxicated

Monitoring:

- COWS score is used to monitor a patient's response to buprenorphine, it can be done by a provider or RN
- As treatment is initiated, COWS assessments and sedation assessments should be checked at 30 minutes and 4 hours after each dose for all induction patients or for those patients who are being re-titrated to a maintenance dose, and should be documented in a daily COWS sheet
- Each COWS must be reported to a supervising provider if performed by an RN
- Based on the COWS, the provider may decide if there will be a change in monitoring frequency
- ***Pregnancy Only:*** Fetal monitoring beyond what is necessary for initial fetal evaluation is not necessary solely for methadone administration unless ordered by the provider.

Patients on outpatient methadone:

- Provider MUST contact patient's outpatient opioid treatment program (methadone clinic) to confirm dosing and last administration
- Continue the patient's current dose, after checking that inpatient medications do not change metabolism or prolong QTC, that the patient is not sedated, and that they are not intoxicated
- Methadone should typically be continued during acutely painful events, but methadone alone will not control severe acute pain—see separate acute pain guidelines
- If the methadone clinic cannot be reached for any reason, follow steps 4-6 below to control symptoms in the interim, starting with 20 mg of methadone for the first dose
- If a patient has missed outpatient dosing and unable to speak to a provider at their methadone clinic, one approach is to give full dose if 1-2 days are missed, half dose if 3-4 days are missed, and treat as new start if 5 or more days are missed. However, we strongly recommend discussing any missed dose adjustments with the methadone clinic as these are high risk situations.
- Naloxone must also be ordered by the provider as a PRN for signs of overdose (0.1 mg IV q 1 to 2 minutes PRN RR < 8/min or Ramsey sedation scale $\geq$ 4)

Patients who are considering starting methadone

1. Determine clinical indication for methadone therapy:

Indication	Contraindications	Caution
❑ Opioid use disorder, severe, with or without comorbid chronic pain ***and*** ❑ Desire for methadone treatment to assist with cessation or reduction in use	❑ Allergy to methadone ❑ Respiratory depression	❑ QTc>500 ❑ Recent use of benzodiazepines, alcohol, or other sedatives ❑ Liver disease ❑ ***Pregnancy only:*** induction may occur at outpatient clinic or inpatient under obstetric team guidance **If the patient falls under the "caution" category, call the UCSF Substance Use Warmline (855.300.3595 or https://tinyurl.com/yd4ymyx6) or your local addiction specialists.**

2. Discuss options with patient and obtain patient preference for methadone vs. buprenorphine (see Appendix B – Non-pregnancy Decision Guide; ***Pregnancy Only:*** See Appendix C – Pregnancy Only Decision Guide). In the inpatient setting clinicians can legally order buprenorphine or methadone if the patient is admitted primarily for another medical reason.[1,2] Prior to starting methadone, ensure that there is a local methadone clinic that will be able to enroll your patient in their program.

3. Prior to induction:

- Verify DSM 5 criteria for opioid use disorder
- Check baseline EKG for QTc, CURES report (https://cures.doj.ca.gov), urine tox screen, urine pregnancy test.

[1] https://www.deadiversion.usdoj.gov/21cfr/cfr/1306/1306_07.htm
[2] Noska A, Mohan A, Wakeman S, Rich J, Boutwell A. Managing Opioid Use Disorder During and After Acute Hospitalization: A Case-Based Review Clarifying Methadone Regulation for Acute Care Settings. *Journal of addictive behaviors, therapy & rehabilitation*. 2015;4(2):1000138.

Pregnancy Only: also check baseline maternal vital signs, NST as indicated, and a urine tox (utox can only be performed after patient verbal consent)

- If a patient is experienced mixed alcohol and opioid withdrawal, be very cautious and consult with experts to determine which pathology predominate as the combination of benzodiazepines and opioids can be high risk
- Naloxone must also be ordered by the provider as a PRN for signs of overdose (0.1 mg IV q 1 to 2 minutes PRN RR < 8/min or Ramsey sedation scale ≥ 4).
- Adjunctive Medications for Opioid Withdrawal can be very helpful to safely control symptoms and should be used routinely unless there is a contraindication:
    - Diphenhydramine 25-50 mg, PO three times daily prn insomnia/anxiety
    - Ondansetron 4 mg PO every 6 hours PRN nausea
    - Ibuprofen 400-800 mg, PO four times daily prn pain ***(Pregnancy Only****: Ibuprofen is contraindicated)*
    - Acetaminophen 650 mg PO 6 four times daily PRN pain
    - Loperamide 4mg PO x 1 initially, then 2mf prn each additional loose stool (NTE 16 mg/24 hours)
    - Clonidine 0.1 mg PO q4 hours prn w/d symptoms (NTE 2 doses/24 hours and include BP parameter)
    - DO NOT ORDER benzodiazepines as standard PRN adjunctive therapy.

4. Methadone dosing considerations:

- Peak concentration of methadone is ~3.5 hours after dose received and onset of action is 30 minutes to 1 hour after dose is received, so provider or RN per provider order must evaluate for sedation and withdrawal symptoms via COWS assessment 30 minutes and 4 hours after each dose
- Steady state is reached after ~4.5 days at same dose (levels continue to rise for several days after dose increase)
- The initial dose depends on patient (standard is 10 to 30 mg), as the severity of withdrawal does not reliably indicate the level of tolerance. Dosing is at provider's discretion, but provider may contact an expert, such as at the Substance Use Warmline or local opioid treatment program
- If a patient is uninterested in methadone maintenance therapy and only wants withdrawal treatment while hospitalized, do not exceed 40 mg and taper such that patient receives 20 mg or less on day of discharge. Of note, this is not recommended and increases risk of relapse.
- In patients who are NPO, methadone can be administered via NG tube, as a sublingual liquid, or IV. Discuss dosing intervals and IV vs PO bioavailability with pharmacy prior to use.

DAY 1

- Give 10-20 mg methadone
- Provider or RN per provider order must evaluate 30 minutes and 4 hours later for sedation via Ramsey AND withdrawal via COWS
- If withdrawal is present with COWS >8 (see COWS scoring below), may give additional 10-20 mg dose
- Provider or RN per provider order must evaluate 30 minutes and 4 hours later for sedation via Ramsey sedation score or withdrawal via COWS
- Continue dosing as above as needed, but do not exceed 40 mg methadone in first 24 hours; for most patients lower doses will be sufficient
- If at any point patient experiences sedation, additional methadone doses are not to be ordered and subsequent doses should be held or decreased
- Do not write PRN methadone orders
- Order adjunctive medications as needed to treat withdrawal symptoms (see below)
- Have Social Work provide list of Opiate Treatment Programs (OTP) and send referral to program of patient's choice after confirming programs capacity for new patients
- ***Pregnancy Only:*** Not all programs take pregnant patients, please check before sending referral

DAY 2

- Evaluate the patient for sedation and withdrawal symptoms before am dose
- If no complaints of withdrawal or sedation, order methadone daily dose equal to total dose of methadone administered on day 1
- If withdrawal symptoms are present and there is no sedation, then order total daily dose from day 1 + 10 mg as single daily dose
- Provider or RN per provider order must evaluate 30 minutes and 4 hours later for sedation via Ramsey AND withdrawal via COWS
- If withdrawal is present and no sedation after 4 hours, provider may order another one-time 5 - 10 mg dose as long as the daily limit of 50 mg for day to has not been reached
- If somnolence or respiratory depression is present at any point, hold additional methadone doses and decrease next day's dose
- Do not exceed 50 mg on day 2; in most cases lower doses should be sufficient to control withdrawal and prevent sedation

DAY 3

- Evaluate the patient for sedation and withdrawal symptoms before am dose
- If no complaints of withdrawal or sedation, order methadone daily dose equal to total dose of methadone administered on day 2
- If withdrawal symptoms are present and there is no sedation, then order total daily dose from day 2 + 10 mg as single daily dose (not to exceed 60 mg)
- Provider or RN per provider order must evaluate 30 minutes and 4 hours later for sedation via Ramsey AND withdrawal via COWS
- If withdrawal is present and no sedation after 4 hours, provider may order another one-time 5 - 10 mg dose as long as the daily limit of 60 mg for day to has not been reached
- If somnolence or respiratory depression is present at any point, hold additional methadone doses and decrease next day's dose
- Do not exceed 60 mg on day 3; in most cases lower doses should be sufficient to control withdrawal and prevent sedation

For questions or concerns, please consider consulting the UCSF Clinician Consultation Center Substance Use Warmline at (855) 300-3595 Monday through Friday, between 10 a.m. and 6 p.m EST. or https://tinyurl.com/yd4ymyx6

Subsequent hospital days

- Generally best to hold dose steady for 5 days before further increase, due to long half-life serum levels will continue to increase
- After 5 days at steady dose, titration at approximately 10 mg every 5 days can continue based on ongoing cravings or withdrawal
- Actively reinforce plans for maintenance therapy and work on discharge plans
- Provider or RN per provider order should monitor COWS protocol until cessation of withdrawal symptoms for 24 to 36 hours has occurred (COWS < 5)
- If any evidence of somnolence or respiratory depression, consult with pharmacy or Substance Use Warmline to determine appropriate dose decrease—hold additional dosing until this is done

Discharge planning

- Social work or provider should confirm OTP's intake availability and details with their intake coordinator
- Some OTPs require that if patient is to discharge on a weekend or holiday, they will need to be transported to the clinic on a non-holiday weekday to complete the intake process prior to hospital discharge
- Skilled nursing facilities (SNFs) that are not classified as hospitals can only keep patients on methadone if patients are already enrolled in an outpatient methadone program—discuss these details with the SNF early in the process
- You cannot prescribe methadone on discharge. The patient will need to go to the designated OTP, usually early the day after discharge. The OTP will often request that you fax a discharge summary prior to the patient's arrival.
- Prescribe naloxone on discharge as a prn medication for signs/symptoms of overdose and also consider PREP/PEP if indicated for HIV prevention

Other Dosing Considerations

- Replacing Vomited Doses:
  - If tablets are used and full dose is visible in emesis, can consider replacing 75% of dose
  - If emesis occurs < 15 minutes after administration, consider replacing 50% of dose
  - If emesis occurs > 15 minutes after administration, do NOT replace the dose. Check a COWS 4 hours after emesis and re-titrate the dose. Provider may order a 5-10 mg one time dose. Provider or RN per providers orders should check for sedation and a COWS assessment 30 minutes and 4 hours after additional dose
- Addressing Overdose:
  - Overdose is marked by obtundation, apnea, respiratory failure, and hypoxia
  - RN to call provider and start oxygen for RR < 12, O2 saturation < 95%, and/or change in mental status
  - Administer naloxone per provider order for RR < 8 or sedation scale $\geq$ 4
  - if any of these symptoms occur, hold subsequent doses and contact the warmline or your local addiciton experts
- Split Dosing:
  - Split dosing may be necessary for patient with acute or chronic severe pain.
  - ***Pregnancy Only:*** As gestational age increases, plasma levels of methadone change secondary to a decrease in half-life and an increase in clearance and volume of distribution. This generally occurs during the second and third trimester. As such, provider may strongly consider splitting the daily methadone dose to an AM and PM dose if the patient experiences withdrawal symptoms or cravings at night.

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Drug Interactions

Some common drugs may have pharmacokinetic or synergistic interactions with methadone. The methadone dose may require adjustment. Please consult with clinical pharmacist for more complete list of interactions.

- Drugs that may INCREASE methadone concentration or effect (okay to use, but monitor the patient): azole antifungals, some SSRI's, tricyclic antidepressants, eryrthromycin, ciprofloxacin, quetiapine
- Drugs that may DECREASE methadone concentration/effect: rifampin, many antiretrovirals, phenytoin, carbamezapine
- ****CAUTION**** co-administration of CNS depressants such as benzodiazepines may lead to increased sedation and respiratory depression, while co-administration of naltrexone or buprenorphine may lead to precipitated withdrawal

Breastfeeding Guidelines:

Methadone maintenance for opioid use disorder is not a contraindication for breastfeeding. Patients taking methadone for opioid use disorder who are not currently abusing other substances and who wish to breastfeed should be encouraged to regardless of the methadone dose. Current evidence shows that breastfeeding while on methadone maintenance is beneficial to neonates with neonatal abstinence syndrome (NAS). Neonates receiving breast milk from these patients experience lower NAS scores, require less pharmacologic treatment such as morphine, and have shorter lengths of hospital stay.

Consult Contacts:

UCSF Substance Use Warm-line: 855.300.3595 or https://tinyurl.com/yd4ymyx6 (available M-F, between 10 a.m. and 6 p.m EST)

PATIENT NAME:	DATE OF ASSESSMENT:
PATIENT DATE OF BIRTH:	MEDICAL RECORD NUMBER:

Clinical Opioid Withdrawal Score (COWS)

For each item, write in the number that best describes the patient's signs or symptom. Rate only the apparent relationship to opiate withdrawal. *For example: If heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.*

Enter scores at time zero, 30 minutes after first dose, 2 hours after first dose, etc.	*Time:*	*Time:*	*Time:*	*Time:*
Resting Pulse Rate: Record beats per minute *after patient is sitting or lying down for one minute* • 0 - pulse rate 80 or below • 1 - pulse rate 81–100 • 2 - pulse rate 101–120 • 4 - pulse rate greater than 120				
Sweating: *Over past ½ hour not accounted for by room temperature or activity* • 0 - no chills or flushing • 1 - subjective chills or flushing • 2 - flushed or observable moistness on face • 3 - beads of sweat on brow or face • 4 - sweat streaming off face				
Restlessness: *Observation during assessment* • 0 - able to sit still • 1 - reports difficulty sitting still, but is able to do so • 3 - frequent shifting or extraneous movement of legs/arms • 5 - unable to sit still for more than a few seconds				
Pupil size • 0 - pupils pinned or normal size for light • 1 - pupils possibly larger than normal for light • 2 - pupils moderately dilated • 5 - pupils dilated that only rim of the iris is visible				
Bone or joint aches: *If patient was having pain previously, only the additional component attributed to opiate withdrawal is scored* • 0 - not present • 1 - mild/diffuse discomfort • 2 - patient reports severe diffuse aching of joints/muscles • 4 - patient is rubbing joints or muscles and is unable to sit still because of discomfort				
Runny nose or tearing: *Not accounted for by cold symptoms or allergy* • 0 - none present • 1 - nasal stuffiness or unusually moist eyes • 2 - nose running or tearing • 4 - nose constantly running or tears streaming down cheeks				
GI upset: *Over last ½ hour* • 0 - no GI symptoms • 1 - stomach cramps • 2 - nausea or loose stool • 3 - vomiting or diarrhea • 5 - multiple episodes of diarrhea or vomiting				
Tremor: *Observation of outstretched hands* • 0 - no tremor • 1 - tremor can be felt, but not observed • 2 - slight tremor observable • 4 - gross tremor or muscle twitching				
Yawning: *Observation during assessment* • 0 - no yawning • 1 - yawning once or twice during assessment • 2 - yawning three or more times during assessment • 4 - yawning several times/minute				
Anxiety or irritability • 0 - none • 1 - patient reports increasing irritability or anxiousness • 2 - patient obviously irritable or anxious • 4 - patient so irritable or anxious that participation in the assessment is difficult				
Gooseflesh skin • 0 - skin is smooth • 3 - piloerrection of skin can be felt or hairs standing up on arms • 5 - prominent piloerrection				
5—12 = mild; *13—24 = moderate;* *25—36 = moderately severe;* *> 36 = severe withdrawal* **TOTAL** OBSERVER INITIALS				

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Appendix B – Non-Pregnancy Decision Guide

	Methadone	Buprenorphine
Mechanism	Full opioid agonist	Partial opioid agonist, usually paired with naloxone (opioid antagonist)
Patients for whom should use caution or avoid	Allergy, severe liver disease, QTc prolongation, drug-drug interactions, high risk job	Allergy, severe liver disease, heavy EtOH or benzo, need for acute opioids, recent methadone
Risk of withdrawal when starting medication	None	Some, if not in withdrawal prior to starting may have precipitated withdrawal
Side effects/risks	Hypogonadism, Torsades, constipation, sweating	GI upset, constipation, headache, insomnia
Sedation/respiratory depression	At high doses in non-tolerant patients or slow metabolizers has potential for sedation, worse in combination with some medications	Ceiling effect for respiratory depression therefore less risky (unless concurrent use of sedating drugs, e.g., alcohol/benzodiazepines)
Overdose risk from opioid replacement	Low-moderate, higher when initiating treatment or in combo with other medications	Low, increased by concurrent sedating medications
Retention in treatment	Higher in methadone[1], with possible contribution from increased structure of programs	May be slightly lower than methadone, retention improves at doses over 16mg
Visit frequency	Daily visits to maintenance treatment program, take-homes may be allowed if stable for long term. This structure helps some patients, some dislike it.	Can range from daily to monthly depending on patient treatment needs, may be provided in primary care setting. Also available in some methadone clinics, increasing structure and decreasing diversion risk.
Diversion potential	Low for directly observed therapy (DOT), high for take home	Low for DOT, moderate for take-homes, reduced by co-formulation with naloxone
Who can prescribe after discharge?	Opioid treatment program only	Any physician, NP, or PA who has been trained and possesses DATA2000 waivers (aka X-number)
Mortality	Both options substantially decrease all-cause mortality over no treatment, methadone may have higher mortality but may be confounded[2]	Both options substantially decrease all-cause mortality over no treatment, buprenorphine may have lower mortality but may be confounded

Some patients may decline buprenorphine or methadone, but still be interested in medication assisted treatment. In these cases, one option is naltrexone, however it has been shown to have very high drop-out rates so is not considered first line[3]. Naltrexone can only be started after a patient has completely withdrawn from opioids—roughly 5-7 day for short acting and 7-10 days for long acting. One option is to give naloxone as a trial before administering naltrexone, to make sure the patient doesn't experience precipitated withdrawal. Dosing usually begins with 25mg on the first day, and is then increased to 50 mg daily. For IM formulation, the dose is usually 380 mg q4 weeks. The most common side effects are nausea, vomiting, and headache

[1] McLellan A, Arndt I, Metzger D, Woody G, O'Brien C. Treatment Retention among Patients Randomized to Buprenorphine/Naloxone Compared to Methadone in a Multi-Site Trial. Addiction . 2014; 109(1): 79–87.

[2] Sordo L, Barrio G, Bravo M, Indave B, Degenhardt L, Wiessig L, Ferri M, Pastor-Barriuso R. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ. 2017:357:j1550

[3] Minozzi S, Amato Le Vecchi S, Davoli M, Kirchmayer, U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database of Systematic Reviews: Reviews. 2011.

Appendix C – Pregnancy Decision Guide

	Methadone	Buprenorphine
Mechanism	Full opioid agonist	Partial opioid agonist, usually paired with naloxone (opioid antagonist)
Patients for whom should use caution or avoid	Allergy, severe liver disease, QTc prolongation, drug-drug interactions, high risk job	Allergy, severe liver disease, heavy EtOH or benzo, need for acute opioids, recent methadone
Risk of withdrawal when starting medication	None	Some, if not in withdrawal prior to starting may have precipitated withdrawal
Side effects/risks	Hypogonadism, Torsades, constipation, sweating	GI upset, constipation, headache, insomnia
Sedation/respiratory depression	At high doses in non-tolerant patients or slow metabolizers has potential for sedation, worse in combination with some medications	Ceiling effect for respiratory depression therefore less risky (unless concurrent use of sedating drugs, e.g., alcohol/benzodiazepines)
Overdose risk from opioid replacement	Low-moderate, higher when initiating treatment or in combo with other medications	Low, increased by concurrent sedating medications
Retention in treatment[4]	Higher in methadone (88% in the MOTHER study), with possible contribution from increased structure of programs	Slightly lower than methadone (67% in the MOTHER study, with most drop outs during induction)
Visit frequency	Daily visits to maintenance treatment program, take-homes may be allowed if stable for long term. This structure helps some patients, some dislike it.	Can range from daily to monthly depending on patient treatment needs, may be provided in primary care setting. Also available in some methadone clinics, increasing structure and decreasing diversion risk.
Diversion potential	Low for directly observed therapy (DOT), high for take home	Low for DOT, moderate for take-homes, reduced by co-formulation with naloxone
Who can prescribe after discharge?	Opioid treatment program only	Any physician, NP, or PA who has been trained and possesses DATA2000 waivers (aka X-number)
Mortality	Both options substantially decrease all-cause mortality over no treatment, methadone may have higher mortality but may be confounded[5]	Both options substantially decrease all-cause mortality over no treatment, buprenorphine may have lower mortality but may be confounded
Neonatal Outcomes[6]	Reduced preterm birth and low birth weight rates Higher doses do NOT correlate with more NAS NAS is 75% - in MOTHER study: 17.5 day average length of hospitalization 10.4 mg morphine required during hospitalization	Reduced preterm birth and low birth weight rates Later average gestational age and higher average birth weight than methadone Higher doses do NOT correlate with more NAS NAS less severe than for methadone – in MOTHER study: 10 day average length of hospitalization 1.1 mg morphine required during hospitalization

Naltrexone is not a good option in pregnancy due to safety concerns

[4] Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med. 2010;363(24):2320-31.
[5] Sordo L, Barrio G, Bravo M, Indave B, Degenhardt L, Wiessig L, Ferri M, Pastor-Barriuso R. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ. 2017:357:j1550
[6] Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med. 2010;363(24):2320-31.