ACLP How To Guide: Opioid Withdrawal

How to Manage Opioid Withdrawal

Learning Objectives:

1. Differentiate opioid intoxication from withdrawal
2. Review how to assess a patient for opioid use disorder treatment, including medication assisted treatment (MAT)
3. Review supportive measures to treat opioid withdrawal
4. Recognize precipitated withdrawal and strategies to treat it

Step 1: Determine if Patient is in Acute Opioid Intoxication or Withdrawal (Table 1)

Table 1: Diagnoses of Opioid Intoxication and Opioid Withdrawal (Integrating DSM-V Criteria)

Opioid Intoxication	Opioid Withdrawal
A. Recent use of opioids (Urine toxicology is positive for most opioids such as morphine, heroin, codeine, oxycodone, fentanyl, for 12 to 36 hours after use. *Methadone, buprenorphine, and fentanyl will not be detected on standard urine drug screen tests, and they must be ordered separately if GCMS is not readily available* B. Significant behavioral and psychological alterations become apparent during or shortly after use of an opioid. C. Pupils will become constricted and will be accompanied by one of the following during or shortly after use of an opioid (indicative of decreased responsiveness): a. Somnolence or loss of consciousness b. Slurred speech or unsteady gait c. There will be deficits in attention or memory D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance	A. Sudden cessation or reduction of normal opioid dose, OR opioid antagonist given after opioid use B. Three (or more) of the following, developing within minutes to several days after Criterion A: ● dysphoric moods ● nausea or vomiting ● muscle aches ● lacrimation or rhinorrhea ● pupillary dilation, ● piloerection or sweating ● diarrhea ● yawning ● insomnia ● autonomic hyperactivity (tachypnea, hyperreflexia, tachycardia, sweating, hypertension, hyperthermia) C. The symptoms in Criterion B cause clinically significant distress in social, occupational or other important areas of functioning D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance
Administer intranasal or initiate IV naloxone at 0.4 mg to 0.8 mg IV if patient has signs of overdose, including diminished consciousness with difficult arousing, hypopnea or apnea, choking/gurgling, cold/clammy/discolored skin, poor muscle tone. Do not administer opioids if there is concern for intoxication	Use the Clinical Opioid Withdrawal Scale (COWS) score to determine level of withdrawal severity ● Mild withdrawal: Score 5 to 12 ● Moderate withdrawal: Score 13 to 24 ● Moderately severe withdrawal: Score 25 to 36 ● Severe withdrawal: Score greater than 37

Step 2: Assess the Patient for OUD Treatment

- Distinguish whether a patient has OUD using diagnostic criteria OR whether the patient is appropriately using prescribed opioid prescriptions OR if the patient is mis-using opioids but does not meet full criteria for OUD.

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- "Misuse" = to use a prescribed substance in a manner other than how it is prescribed, such as taking it more frequently or a higher dose than prescribed OR for a reason other than why it is prescribed (such as taking an opioid to treat anxiety)
    - Patients can misuse due to having UNDER-treated pain ("pseudo-addiction") or if other mental health symptoms are under-treated
- If opioid "misuse" is discovered, it should be explored and a treatment plan should be initiated to decrease the risk of misuse. In these cases, the patient usually does not require MAT
- Be aware of any implicit biases you may be experiencing in assuming a patient has opioid use disorder and be open to understanding their experience of opioid use.

An assessment for OUD Treatment should include:

- A medical history & physical exam (especially skin, cardiac, respiratory & neuro, due to higher risk of associated injuries and infections)
- A brief psychiatric history (given high risk of comorbid psychiatric disorders)
- Social history focused on evaluation of family and psychosocial supports & planned discharge location (to help with connection with outpatient services)
- Comprehensive substance use history including:
    - Opioid of choice, frequency of use, route of administration (e.g., oral, intravenous, intranasal--helps gauge likelihood of severe withdrawal or infections)
    - Prescription opioid use history checked through the state's Prescription Drug Monitoring Program (PDMP), where available, to detect unreported use of other controlled medications that may interact adversely with MAT
    - Previous attempts to stop using opioids, type of medication and non-medication strategies used and response to treatments
- Request & Review labs:
    - Urine drug screen, urine buprenorphine, urine fentanyl, urine methadone (for patients who report being prescribed methadone by OTP). Consider also ordering GCMS
    - CBC (especially if any signs of bacterial infection such as endocarditis)
    - Hepatitis B/C and HIV (especially for those who inject)
        - Offer vaccination for patients who inject drugs and have negative hepatitis B serology
    - Consider testing for syphilis and tuberculosis if indicated
    - Assess liver and kidney function with liver enzyme, serum bilirubin, and serum creatinine blood tests to adjust MAT dosing or defer from initiation (in case of liver failure/significant cirrhosis)
    - Pregnancy testing for women of reproductive age
    - EKG (especially if methadone is to be re-initiated in the inpatient setting—recommend baseline, repeat EKG after 5-7 days of dose change and when doses exceed 100 mg

Step 3: Determine Best MAT Option for Patient and Initiate Treatment (Table 2)

General Considerations for MAT:

- Buprenorphine and naltrexone can block the effects of other opioids taken concurrently and thus can induce precipitated opioid withdrawal
    - Naltrexone should not be given until withdrawal is complete
    - Buprenorphine initiation and dose will depend on the patient's last use of full opioid agonist and the protocol used (standard, micro-induction, macro-induction)

- Methadone and buprenorphine can be used for medically supervised withdrawal and continued for maintenance treatment.
- Methadone, buprenorphine, and naltrexone all have evidence for reducing cravings
- Naltrexone should not be prescribed in pregnancy
- Engage patient with open, nonjudgmental questions around their beliefs & experiences around MAT. Offer interpreters for conversations if needed for evaluation and MAT discussion
- Patients may have their own biases around MAT and OUD; if discovered, offer nonjudgmental psychoeducation while validating their concerns.
- Assess structural vulnerabilities that may impact a patient's access to ongoing MAT and incorporate those obstacles when pursuing resources for a patient after discharge.
    - Studies demonstrate that medical providers have stigma towards patients with OUDs and towards MAT. Be aware of your own implicit biases and colleagues' biases. Initiate conversations with colleagues if you notice unwarranted obstacles in place for initiating MAT for a patient.
    - Be aware of existing structural disparities that impact access to MAT for structurally vulnerable populations, including people of color, LGBTQ+ populations, and different age groups**.** Use knowledge of these disparities and practice cultural humility when assessing a patient and when offering specific MAT.
        - Despite similar rates of OUD, Black American patients are less likely to be offered MAT, and even when offered, are much less likely to receive buprenorphine prescription than their White American counterparts (even in a study controlling for age, sex, and type of payment).
        - LBGTQ patients have special medical considerations in MAT initiation including whether they are taking Prep for exposure prophylaxis, whether they may be living with HIV and taking antiretroviral therapy (ART), and whether they are on hormone therapy. Interactions with these medications should be assessed and conversations around appropriate clinical follow up are important.
    - When initiating MAT, coordinate with case management to ensure patient's connection with appropriate level of continued OUD treatment services on discharge that incorporates patient cultural, language, and social preferences.
- Be aware of limitations in different MAT choices.
    - Methadone is only prescribed in structured opioid treatment programs (OTPs)
        - In OTPs, patients initially must be seen frequently; over time they may be able to get more take-home doses. OTPs can be useful for patients requiring structure and easy access to substance use counseling; however, they can be harder to access for patients living in rural areas and for those with limited transportation options due to socioeconomic factors.
        - Depending on the state, methadone is likely only to show up on PDMP records if prescribed for PAIN, not OUD
        - DEA update 8/2023: Any provider may **dispense (not prescribe)** a one-time 3-day methadone supply. Theoretically, this may be done via inpatient unit upon discharge, ED, or even specialty; however, despite this rule, there may be differences between state which may complicate institutions to be in compliance with Federal guidelines. **Refer to your institution/hospital policy regarding dispensing rules of methadone**
    - Buprenorphine can be induced faster than methadone and can be more accessible if there are certified providers in the patient's area. It is available in OTPs and office settings, and no longer requires a waiver for prescribing.

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    - When buprenorphine is initiated, there is a risk of precipitated withdrawal which occurs within minutes to hours after initial buprenorphine dose (see next page)
- Whether or not MAT is initiated, offer supportive measures to ameliorate symptoms of opioid withdrawal, including anxiety, insomnia, nausea/vomiting, diarrhea, pain, and autonomic symptoms (**Table 3**)

If a patient is appropriate for MAT but declines:

- Provide treatment to avoid acute opioid withdrawal while hospitalized for medical issues. Acute withdrawal increases the risk of AMA discharge, impaired engagement with medical team & patient suffering.
- Discuss with primary team that buprenorphine or methadone should not be prescribed at discharge if the patient has no interest/intent to follow-up with outpatient prescriber
- Provide symptomatic treatments for opioid withdrawal as needed (Table 3)

Precipitated withdrawal

- Intense and rapid onset (within minutes-hours) of worsening withdrawal symptoms (increase in COWS score by $\geq$5) which occurs when a patient who is physically dependent on full agonist opioids receives an opioid antagonist (naloxone or naltrexone) or partial agonist (buprenorphine)
    - Buprenorphine has a high binding affinity but low intrinsic activity at the mu receptor. This allows it to displace full agonist opioids from the mu receptor; but because of its lower intrinsic activity, it results in a net decrease in the agonist effect, resulting in precipitated withdrawal
        - It can be avoided using the traditional standard induction, in which the person is required to be in at least moderate withdrawal (COWS>12) and at least 12-24 hours have elapsed since last use of short-acting opioids, 36 hours since last use of long-acting opioids, and 48 hours since last use of methadone
        - Micro-induction and macro-induction protocols also mitigate the risk for precipitated withdrawal and avoid the need for the patient to undergo withdrawal Some prescribers may prefer to use patches or buccal films during the initial few days, however as outlined in the Buprenorphine Micro-induction How-to guide, other protocols exist using the intravenous formulation. Macro-induction protocols vary based on institution and prescriber preference. For one example of macro-induction, refer to the 2021 JAMA paper describing high-dose induction protocol used in the emergency department (Herring et al 2021).
- Treatment
    - Utilization of a full-opioid agonist (methadone or hydromorphone)
    - Higher doses of buprenorphine: Case reports suggest use of as high as 80 mg in a 24 hour period, which will eventually be tapered down to a safer level ($\leq$32 mg at discharge)
    - Symptomatic treatment: clonidine, gabapentin, loperamide, ondansetron, etc as detailed in Table 3. Avoid benzodiazepines.

Table 2: MAT Options for Opioid Use Disorder

Medication	Methadone	Buprenorphine	Naltrexone
Mechanism of Action	Mu opioid receptor agonist, Weak NMDA agonist	Partial mu opioid receptor agonist, antagonist at kappa and delta receptors	Mu opioid receptor antagonist
Uses	Medically supervised withdrawal, maintenance MAT, pain (TID dosing preferred for this indication, though not always possible)	Medically supervised withdrawal, maintenance MAT, pain (TID or QID dosing preferred for this indication)	Prevention of relapse to opioid misuse, following medically supervised withdrawal
Formulations and Typical Dose range	Available in oral formulation only, with doses ranging from 20-200 mg daily. Patients with OUD generally require 80-120 mg to suppress opioid cravings	• Sublingual tablet: 2-32 mg daily • Sublingual film, tablet (in combination with naloxone): 2/0.5-32/8 mg daily • Intravenous, transdermal patch, and buccal film (used in microinduction) • Injection (not typically initiated in the hospital setting)	• Oral: 50 mg daily • Intramuscular injection: 380 mg every 28 days
Possible Adverse Effects	• Most common: constipation, sedation, hyperhidrosis, dizziness, N/V • Concerns: respiratory depression, QTc prolongation, sexual dysfunction, orthostatic hypotension, misuse, neonatal abstinence syndrome, hypoglycemia • Risk of overdose if titrated too quickly • Check drug-drug interactions given CYP3A4 metabolism	• Most common: constipation, N/V, hyperhidrosis, insomnia, blurred vision • Concerns: precipitated withdrawal, peripheral edema, respiratory depression (especially if combined with other CNS depressants), misuse (though less likely compared to full mu opioid agonists), neonatal abstinence syndrome. Injection site itching or pain with subcutaneous formulation. Nerve damage, accidental overdose, misuse if extruded, local migration or protrusion with implant formulation. • Check for drug-drug interactions given CYP3A4 metabolism	• Most common: N/V, anxiety, insomnia, HA, elevated LFTs, muscle and joint cramps • Concerns: precipitated opioid withdrawal, hepatotoxicity, depression, suicidality, decreased appetite • Intramuscular: pain, swelling, induration, insomnia
Patient already on MAT admitted to hospital	Verify outpatient dose with OTP program, continue if verified unless medically contraindicated.	Verify outpatient dose, consider transition to full opioid agonist if patient requires acute pain management, otherwise continue unless medically contraindicated	Discontinue if patient will require opioid medication for pain/sedation, monitor for withdrawal precipitation
Initiation	Day 1: Start 10–30 mg with reassessment in 3–4 hours. Second dose not to exceed 10 mg on the first day if withdrawal symptoms are persisting (*Maximum total daily dose 40 mg*). Dose is typically titrated 5-10 mg every 7 days depending on tolerability and response In the era of potent synthetic opioids such as fentanyl and nitazenes, Canadian guidelines have been updated to promote higher starting doses (40-60 mg) and faster titration (increasing by 10-15 mg every 3-5 days)	Standard induction with oral buprenorphine: starts when the patient is in moderate withdrawal (COWS>12) after at least 12 hours (may need to wait longer for fentanyl and other long-acting, potent opioids). On day 1, 2-4 mg buprenorphine is typically initiated; withdrawal symptoms are continually reassessed, and dose may be titrated to maximum of 8 mg in the first day. On day 2, reassess withdrawal symptoms and buprenorphine tolerability—may increase dose up to maximum of 16 mg. Dose may be further adjusted on subsequent evaluations over the following days, maximum dose (which is typically covered by insurance) is 24 mg, but some patients may require up to 32 mg per day. Various micro- and macro-induction protocols also exist as mentioned previously.	Patients need to have completed withdrawal and be opioid free for 7 days (short acting) and up to 14 days (long acting). Better evidence for monthly injection versus daily oral formulation.

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Table 3: Common Supportive Measures for Symptoms of Opioid Withdrawal

Symptoms	Medication	Dosing	Notes
Autonomic symptoms	Clonidine	Day 1: 0.1–0.2 mg every 4–6 h with a maximum dose of 1.2 mg Day 2 onward: taper by 0.1–0.2 mg per day Dose as needed if patient on MAT	• May also treat anxiety, restlessness, pain (may be scheduled in these cases) • IV administration and 7-day patch are also available • Monitor for hypotension, sedation • Avoid abrupt discontinuation, especially if the patient has uncontrolled blood pressure and heart rate
Autonomic symptoms	Lofexidine	Day 1**:** 0.54–0.72 mg every 6 h (total daily dose 2.16–2.88 mg) Day 2 onward: decrease each dose by 0.18 mg every 1–2 days Dose as needed if patient on MAT	• No generic in US so can limit accessibility • Monitor for hypotension, sedation • Dose-dependent QT interval prolongation; use with caution (eg, monitor baseline and post-dose electrocardiogram)
Anxiety, Irritability Restlessness	Diphenhydramine	50 to 100 mg orally every 4 to 6 hours as needed (maximum 300 mg daily)	• May also treat nausea, insomnia • Use reduced dose in hepatic impairment • IV and IM administration available
Anxiety, Irritability Restlessness	Hydroxyzine	25 to 100 mg orally every 6 to 8 hours as needed (maximum 400 mg daily)	• May also treat lacrimation, rhinorrhea, insomnia • Use reduced dose (50%) in renal or hepatic impairment • IM and solution administration available
Abdominal cramping	Dicyclomine	10 to 20mg orally q6-8 hours as needed (Max 160mg daily)	• IM administration available (lower doses are used) • Use with caution and reduce dose in renal or hepatic impairment
Diarrhea	Bismuth	524 mg orally q30 to 60min as needed (up to 4200mg daily)	Monitor for dehydration and maintain fluid levels with oral or IV hydration
Diarrhea	Loperamide	4mg orally followed by 2mg after each loose stool (Max 16mg daily)	Monitor for dehydration and maintain fluid levels with oral or IV hydration
Nausea/ Vomiting	Ondansetron	4 to 8mg orally or IV every12 hours as needed (maximum 16 mg/day)	• Monitor for dehydration and maintain fluid levels with oral or IV hydration • Dose dept QT interval prolongation, use with caution (monitor baseline EKG and post-dose EKG) • Use caution & reduced dose (50%) in severe hepatic impairment
Nausea/ Vomiting	Prochlorperazine	5 to 10 mg orally three times daily before meals or every six hours as needed (maximum 40 mg/day)	• Monitor for dehydration and maintain fluid levels with oral and/or IV hydration • Use with caution in mild to moderate hepatic impairment; avoid in severe hepatic impairment • IV and rectal administration available
Nausea/ Vomiting	Promethazine	12.5 to 25 mg orally every 4 to 6 hours as needed (maximum 50 mg/day)	• Monitor for dehydration and maintain fluid levels with oral and/or IV hydration • Use with caution in mild to moderate hepatic impairment; avoid in severe hepatic impairment • IM and rectal administration available

Insomnia	Trazodone	25 to 100 mg orally at bedtime	• May titrate nightly up to 200 mg at bedtime if needed • Use with caution in severe hepatic or renal impairment
Insomnia	Doxepin	3-10 mg orally at bedtime	• Use with caution and reduce dose in severe hepatic impairment • Use with caution in PR interval prolongation and in widened QRS complex
Myalgias, joint pain, headache	Ibuprofen	400 mg orally every 4 to 6 hours as needed (maximum 2400 mg daily)	• Patient should be well-hydrated and without significant kidney disease • Use with caution in mild to moderate hepatic or renal impairment • Avoid all NSAIDs in severe renal impairment or cirrhosis; avoid in patients on lithium
Myalgias, joint pain, headache	Acetaminophen	650 to 1000 mg orally every 4 to 6 hours as needed (maximum 4000 mg daily for age <65 without liver derangements; maximum 3000 mg for age >65)	• Appropriate analgesic for most patients • Use reduced dose (i.e. 2000 mg daily) or avoid in severe hepatic impairment or if malnourished

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