Buprenorphine/Naloxone (Suboxone®) Reference Guide for ED Providers

Buprenorphine is the first-line treatment for opioid use disorder. **Starting buprenorphine in the ED nearly doubles the likelihood that patients will follow up with addiction treatment compared to offering referral alone (1).** Treatment strategies that are based on withdrawal management alone without plans for transition to opioid agonist treatment (OAT) are associated with high rates of relapse and high mortality rates. In contrast, OAT is associated with improved health outcomes and reduced overdose rates, including for people who are not abstinent from other opioid use. Buprenorphine is first line treatment for opioid use disorder because of its safety profile, but people who are not stabilizing with buprenorphine or prefer another type of OAT should be referred to appropriate settings where methadone or slow-release oral morphine can be prescribed.

MECHANISM OF ACTION

Specific features combine to create the distinct profile that makes buprenorphine both safe and effective in the treatment of opioid use disorder:

1. **High affinity and slow dissociation:** Buprenorphine binds strongly to mu-opioid receptors and dissociates slowly, preventing withdrawal symptoms for 24 hours and beyond. The high affinity for opioid receptors means that it is not displaced by other opioids. It blocks the activity of other opioids used concurrently, making the use of other opioids less rewarding and reinforcing.
2. **Partial opioid agonist:** Buprenorphine provides enough opioid agonist activity to prevent withdrawal symptoms and cravings, with less euphoria and sedation than full agonist opioids.
3. **Ceiling effect:** Doses beyond 24–32mg do not have additional opioid effects. As a result, the risk of respiratory depression and overdose is substantially reduced relative to other opioids.

Relative to methadone and other full-opioid agonists, buprenorphine has a much more favorable safety profile including lower risk of overdose, especially when combined with alcohol and benzodiazepines. It also carries a lower risk of QTc prolongation. It does not require special authorization to prescribe.

Naloxone is included in buprenorphine tablets (e.g., Suboxone®) to reduce the risk of diversion through injection; it is not absorbed when tablets are taken sublingually and does not impact the action of buprenorphine.

DOSAGE FORMS

- Buprenorphine/naloxone 2/0.5mg SL and 8/2mg SL tablets (ODB covered)
    - Tablets MUST be taken sublingually; they are not effective when swallowed due to first-pass effect
- Buprenorphine 12mg SL and 16mg SL tablets (not ODB covered)
- Buprenorphine/naloxone 2/0.5mg SL, 4/1mg SL, 8/2mg SL, and 12/3mg SL soluble film (Suboxone®, not ODB covered)
- Extended-release monthly injection (Sublocade®, ODB covered)
- Six-month subcutaneous implants (Probuphine®, ODB covered)

CONTRAINDICATIONS

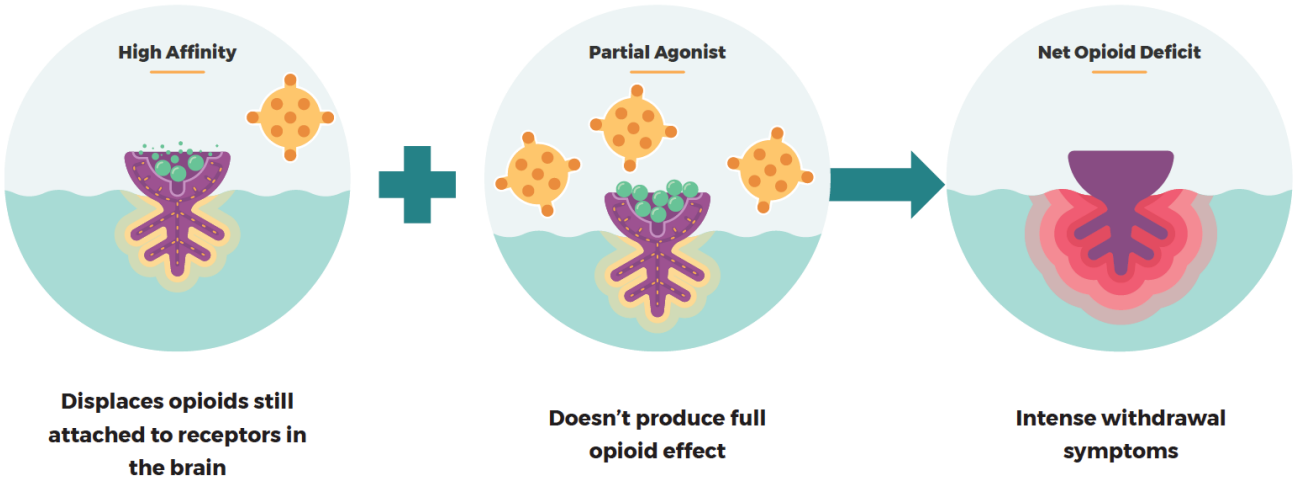
- **Allergy or sensitivity to buprenorphine or naloxone**
- Acute severe hepatitis, or severe liver dysfunction or failure
- Acute intoxication/impaired level of consciousness
- Severe respiratory compromise
- Unable to give informed consent due to psychosis or other causes

Note: Opioid withdrawal can exacerbate unstable cardiac, respiratory, and psychiatric conditions. In these cases, administration of buprenorphine may still be appropriate. Alternatively, carefully titrated doses of short-acting opioids might also be considered.

PRECIPITATED WITHDRAWAL

Precipitated withdrawal is a state of acute and severe withdrawal that occurs if the initial dose of buprenorphine is given when the patient still has other opioids active on the receptors.

Precipitated Withdrawal – a state of acute and severe withdrawal symptoms brought on by initiating buprenorphine when a patient has other opioids in their system.



Because buprenorphine is a partial opioid agonist with high affinity, it displaces other opioids from opioid receptors. The partial mu agonist effect of buprenorphine may not fully compensate for the loss of the current opioid. This results in severe withdrawal symptoms due to a net opioid deficit.

To prevent precipitated withdrawal, ensure that the patient is in moderate withdrawal (**COWS**≥13) and confirm timing of last opioid use OR offer buprenorphine with microdosing (see below).

ED INITIATION AND DOSING FOR BUPRENORPHINE/NALOXONE

There are three options for starting buprenorphine:

- **Traditional start:** First dose is given in the ED (or pharmacy) when the patient is in withdrawal
- **Home start:** Patient is given a prescription to start at home when they are in withdrawal
- **Microdosing:** For patients who cannot stop opioids long enough to avoid precipitated withdrawal, e.g., those using fentanyl

TRADITIONAL ED START

Ensure COWS≥13 and sufficient time from last opioid use:

- Short-acting prescription opioids (e.g., IR oxycodone, hydromorphone, morphine): At least **12 hours**.
- Intermediate-acting prescription opioids (e.g., CR oxycodone, hydromorphone): At least **18 hours**.
- We do not recommend starting buprenorphine through the ED for patients on methadone or fentanyl patches.
- Given the contamination of street drugs with fentanyl and fentanyl analogues, we recommend waiting at least **48 hours** before starting buprenorphine OR **offering microdosing** (see below).

Give first dose:

- Buprenorphine 4mg (2x2mg tablets SL); 2mg if the patient is elderly, on benzodiazepines, or at other risk of sedation.
- Instruct the patient to keep the tablet under their tongue until it fully dissolves and to avoid eating, drinking, or swallowing during this time.

Reassess in 1 hour:

- If withdrawal symptoms are **improving but not resolved**, repeat the same dose (2–4mg) and discharge the patient with tablets or a prescription to complete their Day 1 dosing (usual Day 1 maximum 16mg, 8mg for elderly).
- If withdrawal symptoms are **markedly worse**, do not give another dose of buprenorphine; the patient may be experiencing precipitated withdrawal. Observe and treat with non-agonist therapies for mild-moderate symptoms. Offer the opportunity to start buprenorphine at home when withdrawal symptoms are appropriate (see below).

Write a **prescription** for 16mg:

- Prescription should last until planned follow-up at RAAM/community clinic.
- Doses are typically dispensed daily at a pharmacy of choice until follow-up.
- Higher initial doses and longer prescriptions are associated with more effective control of withdrawal symptoms and cravings and with better treatment follow-up.
- Caution should be used with patients with heavy alcohol or benzodiazepine use, and with medically complex or older patients.

Home start follows the same dosing as usual treatment initiation (i.e., first dose 2–4mg followed by subsequent doses q1–4h), but the patient is given an **outpatient prescription** or supply of buprenorphine to start at home when they are in sufficient withdrawal. Withdrawal symptoms can be assessed using the SOWS (Self-assessment of Opioid Withdrawal Symptoms) or a **patient instruction sheet**. Patients should be advised that if they are unsure whether they are in sufficient withdrawal, they should wait another 1–2 hours before taking their first dose.

Microdosing does not require the patient to be in withdrawal or abstinent from opioids to start buprenorphine. By starting buprenorphine at a very low dose (0.25–0.5mg) and increasing incrementally with repeated doses, buprenorphine does not displace full mu-opioid agonists but accumulates gradually at the opioid receptor. Over time, an increasing number of opioid receptors become occupied by buprenorphine. Once the dose of buprenorphine is at 4mg it can be increased more rapidly and other opioids tapered rapidly or stopped abruptly (3, 4).

There are no approved guidelines for microdosing, but a growing body of case reports and community of practice demonstrating successful use in in-patient and community settings (5).

A **prescription** for buprenorphine using microdosing can be written for up to 7 days and dispensed as a blister pack. It is important to remind patients that they must follow the order of the pack and not skip doses or take additional doses if they miss a day.

	HOME START	MICRODOSING
Indications	• Can abstain from opioid use for an appropriate period of time. • Can follow instruction sheet. • Support at home. • No concurrent alcohol or benzodiazepine use.	• On methadone or street fentanyl (very long half-life of these medications makes home start difficult). • Cannot tolerate withdrawal symptoms. • Continued opioid use. • Should not undergo withdrawal for medical reasons (e.g., pregnancy, coronary artery disease).
Advantages	• Achieves therapeutic dose more rapidly than microdosing.	• Almost certainly avoids precipitating withdrawal. • Can be taken while opioid use continues.
Disadvantages	• Risk of precipitated withdrawal if instructions are not followed and buprenorphine is taken too early.	• Longer time to achieve therapeutic dose. • Instructions can be confusing (better with blister packing).

Steps	• Review **Home Start Patient Information sheet**.
	• Remind patients that buprenorphine must be taken SL.
	• Offer Rx withdrawal medications.
	• Write **Rx** until planned follow-up **(max 3 days)**:
	  ◦ Day 1 max 16mg
	  ◦ Day 2–3 max 16mg
	• Give **handout on buprenorphine treatment**.
	• Offer **naloxone kit**.
	• Offer **harm reduction resources**.
	• Plan RAAM/clinic follow-up.
		• Review **Microdosing Patient Information sheet**.
		• Remind patients that buprenorphine must be taken SL.
		• Write **Rx** until planned follow-up (**max 7 days**).
		• Give **handout on buprenorphine treatment**.
		• Offer **naloxone kit**.
		• Offer **harm reduction resources**.
		• Plan clinic follow-up.

TREATING PRECIPITATED WITHDRAWAL

There are no formal guidelines for the treatment of buprenorphine-precipitated withdrawal. Recommendations are based on consensus:

- For mild cases, observation is sufficient, with instructions for restarting treatment with a test dose when the patient is in sufficient withdrawal.
- For moderate to severe symptoms, treatment options include non-agonist and short acting opioid therapies.
- Non-agonist therapies are preferred, such as clonidine, ondansetron, and loperamide.
- Benzodiazepines should not be used to treat opioid withdrawal because of the risks of sedation when combined with opioids.
- Case reports have demonstrated the utility of offering high doses of buprenorphine (e.g., 16–32mg) for treating precipitated withdrawal symptoms (6, 7). This is not recommended therapy due to a lack of published evidence (2).

BUPRENORPHINE PRESCRIPTIONS

- Include start and stop dates (inclusive) until the day of planned follow-up (maximum 7 days, ideal 3–5).
- Write amounts in mg and number of tablets.
- Generally written for daily observed dosing at the pharmacy.
- Should include a request that the pharmacy dispense a naloxone kit if not done through the ED.
- Does not need to specify a pharmacy location if the patient is unsure where they will be.
- If a patient does not have ID, consider contacting the pharmacy to explain and writing a description of the person on the Rx.

DISCHARGING A PATIENT ON BUPRENORPHINE

In addition to the prescription, all patients should receive the following on discharge:

- Contact details and hours of follow-up appointment
- Patient handout on buprenorphine
- Naloxone kit or a request that naloxone be dispensed added to the prescription
- Information for harm reduction resources

SUPPORTS TO FACILITATE BUPRENORPHINE INITIATION AND CONTINUATION

- Buprenorphine on formulary and stocked in the ED
- Cards with RAAM clinic/local clinic telephone numbers and hours
- Community pharmacy lists with hours, phone and fax numbers
- Contact details for hospital or community addictions specialists
- Lists/contact information for local harm reduction resources

SPECIAL SITUATIONS

Pregnancy: Pregnant patients with OUD should be started on OAT as soon as possible in order to avoid withdrawal, which is associated with spontaneous abortion and pre-term labour.. Buprenorphine and methadone are both first-line treatments for OUD in pregnancy. Buprenorphine can be initiated if the patient is already in withdrawal, or using microdosing; patients should not be advised to stop their opioids to go into withdrawal in order to initiate treatment with buprenorphine. When caring for a pregnant patient using opioids, contact a colleague with experience for guidance and involve the obstetrical team early whenever possible.

Acute pain: Patients on buprenorphine with acute pain should be treated as per usual protocols, using non-opioids first when appropriate and opioids when necessary. **Patients on buprenorphine may require higher doses of opioids to achieve pain relief** because of the high affinity of buprenorphine on the opioid receptor. Patients may be discharged with a prescription for up to 3 days of opioid for pain management when appropriate.

Combined substance use/withdrawal presentations: Patients who are intoxicated should not be started on buprenorphine. Patients in withdrawal from alcohol and opioids should have alcohol withdrawal treated as a priority because of the risk of seizures, and be started on buprenorphine at lower doses while receiving benzodiazepines. Since many street drugs are contaminated with benzodiazepines or benzodiazepine-like drugs, some patients experience combined benzodiazepine and opioid withdrawal. In general, this syndrome should be treated as opioid withdrawal with buprenorphine or other opioid agonist treatment, and not with benzodiazepines.

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