

# Buprenorphine/Naloxone (Suboxone®)

## Reference Guide for ED Providers

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Opioid agonist therapy (OAT) with buprenorphine, methadone, or slow-release oral morphine is the standard of care for treating opioid use disorder (OUD). **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 OAT are associated with high rates of relapse and high mortality rates and are not recommended. In contrast, OAT is associated with improved health outcomes and reduced overdose rates, including for people who continue to use other opioids. Buprenorphine is often offered first for OUD because of its safety profile, but people who are not stabilizing with buprenorphine or prefer another type of OAT should be supported to access methadone or slow-release oral morphine.

### 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 for at least 24 hours at an appropriate dose. The high affinity for opioid receptors means that it is not displaced by other opioids. Buprenorphine blocks the activity of other opioids used concurrently, which makes the use of other opioids less rewarding and reinforcing and is also protective against opioid overdose.
- 2. Partial opioid agonist:** Buprenorphine provides enough opioid agonist activity to prevent withdrawal symptoms and cravings, with less sedation and other side effects than full-agonist opioids.
- 3. Ceiling effect:** Doses beyond 24–32 mg do not have additional effects with regard to respiratory depression. 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 favourable safety profile, including a lower risk of QT prolongation and lower risk of overdose, especially when combined with alcohol and benzodiazepines. No special authorization is required to prescribe buprenorphine.

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 or a person's response to other opioid use.

### DOSAGE FORMS

- Tablets (must be taken sublingually; not effective when swallowed due to first-pass effect):
  - Buprenorphine/naloxone 2/0.5 mg SL and 8/2 mg SL tablets (covered on ODB formulary)
  - Buprenorphine/naloxone 12/3 mg SL and 16/4 mg SL tablets (not covered on ODB formulary)
- Film (not covered on ODB formulary):
  - Buprenorphine/naloxone 2/0.5 mg SL, 4/1 mg SL, 8/2 mg SL, and 12/3 mg SL soluble film
- Extended-release monthly injection (covered on ODB formulary):
  - Buprenorphine 100 mg/0.5 mL and 300 mg/1.5 mL injectable solution

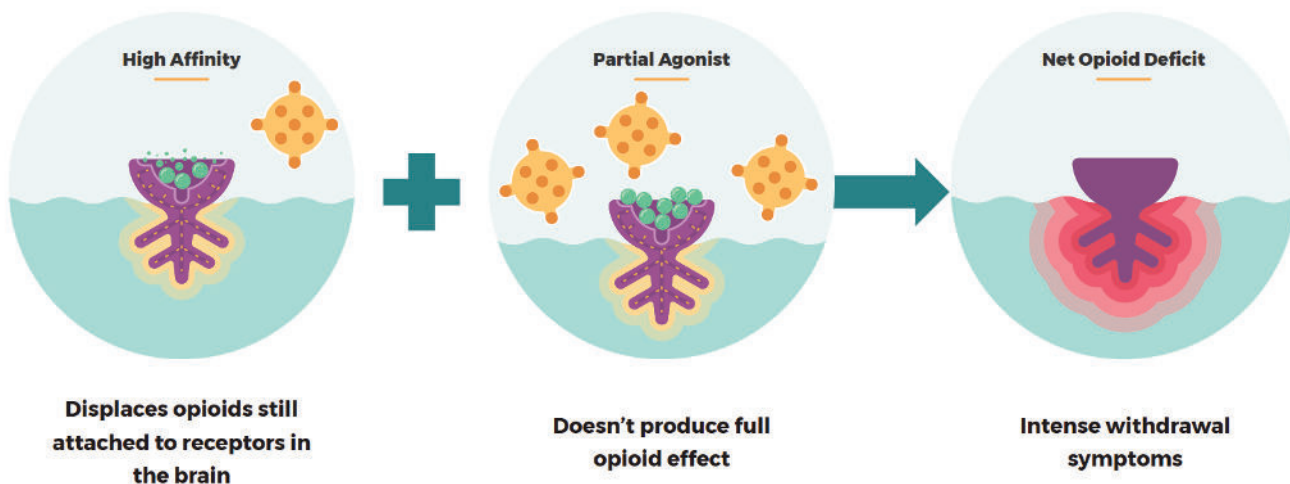
## CONTRAINDICATIONS

- **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 person still has other opioids active on the receptors.



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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 acute and severe withdrawal symptoms due to a net opioid deficit.

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

An alternative approach to initiating buprenorphine for people who do not meet the usual criteria and would benefit from achieving a full therapeutic dose of buprenorphine rapidly (e.g., people who use fentanyl who present in withdrawal) is called *macro dosing*.

## ED INITIATION AND DOSING FOR BUPRENORPHINE/NALOXONE

There are several options for starting buprenorphine:

- **Traditional start:** First dose is given in the ED (or pharmacy) when the person is in withdrawal.
- **Home start:** Person is given a prescription to start at home when they are in withdrawal.
- **Microdosing:** For people who should not undergo withdrawal for medical reasons or who are using opioids with a very long half-life (e.g., methadone or unregulated drugs containing fentanyl) such that waiting for the onset of withdrawal would pose a significant barrier.
- **Macro dosing:** For people who do not meet criteria for other methods and for whom delays in treatment pose significant risk (should be reserved for people with very high opioid tolerance and at high risk of not engaging in treatment with standard approaches).

### TRADITIONAL START

Ensure **COWS**  $\geq$  13 and appropriate time from last opioid use:

- 12–16 hours for short-acting prescription opioids (e.g., IR oxycodone, hydromorphone, morphine)
- 18–24 hours for intermediate-acting prescription opioids (e.g., CR oxycodone, hydromorphone)
- 48+ hours for fentanyl or any opioids from the unregulated supply
- **We do not recommend starting buprenorphine through the ED for people who take methadone.**

Give first dose:

- Buprenorphine 4 mg (2x2 mg tablets SL); 2 mg 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 talking during this time.

Reassess in one hour:

- If withdrawal symptoms are **improving but not resolved**, repeat the same dose (2–4 mg) and discharge the patient with tablets or a prescription to complete their Day 1 dosing (usual Day 1 maximum 16 mg, 8 mg for elderly).
- If withdrawal symptoms are **markedly worse**, the patient may be experiencing precipitated withdrawal. Precipitated withdrawal can be treated with additional buprenorphine doses (see below).

Write a **prescription** for 16 mg:

- Prescription should last until planned follow-up.
- 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 2–4 mg 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. People can assess their own withdrawal using the Subjective Opioid Withdrawal Scale (**SOWS**) or a **patient instruction sheet**. Patients should be advised that if they are unsure whether they are in sufficient withdrawal, they should wait another one to two hours before taking their first dose.

**Microdosing (or low-dose induction)** does not require the patient to be in withdrawal or abstinent from opioids to start buprenorphine. By starting buprenorphine at a very low dose (0.25–0.5 mg) 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 4 mg, it can be increased more rapidly and other opioids tapered rapidly or stopped abruptly (3–5). There are various microdosing protocols, which take from a few days to a week to achieve a therapeutic dose of buprenorphine and are being successfully used in community and inpatient settings.

A [prescription](#) for buprenorphine using microdosing can be written for up to seven 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.

**Macro dosing (or high-dose induction)** is an alternative approach to initiating buprenorphine for people with high opioid tolerance (i.e., people who use fentanyl) who are in withdrawal but do not meet criteria for a traditional start and for whom delays in treatment pose a significant risk of ongoing fentanyl use and overdose. Higher initial and total Day 1 doses are off-label but have been shown to be effective in achieving therapeutic levels of buprenorphine efficiently. This approach should be reserved for people who use fentanyl who have had an overdose reversed with naloxone or are in withdrawal and last used fentanyl at least 18 hours ago.

	HOME START	MICRODOSING	MACRODOSING
<b>Indications</b>	<ul style="list-style-type: none"> <li>• Can abstain from opioid use for an appropriate period of time.</li> <li>• Can follow instruction sheet.</li> <li>• Support at home.</li> <li>• No concurrent alcohol or benzodiazepine use.</li> </ul>	<ul style="list-style-type: none"> <li>• Taking methadone or unregulated fentanyl (very long half-life of these medications makes home start difficult).</li> <li>• Cannot tolerate withdrawal symptoms.</li> <li>• Continued opioid use.</li> <li>• Should not undergo withdrawal for medical reasons (e.g., pregnancy, coronary artery disease).</li> </ul>	<ul style="list-style-type: none"> <li>• Unregulated fentanyl use.</li> <li>• Currently in withdrawal but does not meet criteria for traditional start and at least 18 hours since last use, OR in withdrawal from full naloxone reversal of an opioid overdose.</li> <li>• Treatment delay poses significant risk of adverse outcomes.</li> </ul>
<b>Advantages</b>	<ul style="list-style-type: none"> <li>• Achieves therapeutic dose more rapidly than microdosing.</li> </ul>	<ul style="list-style-type: none"> <li>• Almost certainly avoids precipitating withdrawal.</li> <li>• Can be taken while opioid use continues.</li> </ul>	<ul style="list-style-type: none"> <li>• Achieves therapeutic dose in one visit.</li> <li>• Starting treatment in the ED is associated with higher rates of treatment retention than delay/referral.</li> </ul>
<b>Disadvantages</b>	<ul style="list-style-type: none"> <li>• Risk of precipitated withdrawal if instructions are not followed and buprenorphine is taken too early.</li> </ul>	<ul style="list-style-type: none"> <li>• Longer time to achieve therapeutic dose.</li> <li>• Instructions can be confusing (better with blister packing).</li> </ul>	<ul style="list-style-type: none"> <li>• Off-label practice.</li> <li>• Withdrawal symptoms may get worse before resolving.</li> </ul>
<b>Steps</b>	<ul style="list-style-type: none"> <li>• Review <a href="#">Home Start Patient Information sheet</a>.</li> <li>• Remind patients that buprenorphine must be taken SL.</li> <li>• Offer Rx withdrawal medications.</li> <li>• Write <b>Rx</b> until planned follow-up (<b>max 3 days</b>): <ul style="list-style-type: none"> <li>• Day 1 max 16 mg</li> <li>• Day 2–3 max 16 mg</li> </ul> </li> <li>• Give <a href="#">handout on buprenorphine treatment</a>.</li> <li>• Offer <a href="#">naloxone kit</a>.</li> <li>• Offer <a href="#">harm reduction resources</a>.</li> <li>• Plan clinic follow-up.</li> </ul>	<ul style="list-style-type: none"> <li>• Review <a href="#">Microdosing Patient Information sheet</a>.</li> <li>• Remind patients that buprenorphine must be taken SL.</li> <li>• Write <b>Rx</b> until planned follow-up (<b>max 7 days</b>).</li> <li>• Give <a href="#">handout on buprenorphine treatment</a>.</li> <li>• Offer <a href="#">naloxone kit</a>.</li> <li>• Offer <a href="#">harm reduction resources</a>.</li> <li>• Plan clinic follow-up.</li> </ul>	<ul style="list-style-type: none"> <li>• Confirm COWS <math>\geq</math> 13 and at least 18 hours since last fentanyl use</li> <li>• Explain process and document consent.</li> <li>• Provide 16 mg (2 x 8 mg tablets) buprenorphine SL.</li> <li>• Wait 1 hour.</li> <li>• Provide an additional 8–16 mg every 1–2 hours until withdrawal is resolved or sedation (maximum 32 mg).</li> <li>• Write <b>Rx</b> for total amount given until planned follow-up (<b>max 7 days</b>).</li> <li>• Give handout on <a href="#">buprenorphine treatment</a>.</li> <li>• Offer <a href="#">naloxone kit</a>.</li> <li>• Offer <a href="#">harm reduction resources</a>.</li> <li>• Plan clinic follow-up.</li> </ul>

## TREATING PRECIPITATED WITHDRAWAL

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

- For very mild cases, observation is sufficient, with instructions for restarting treatment with a test dose when the patient is in sufficient withdrawal. Non-agonist therapies can be used, such as clonidine, ondansetron, and loperamide.
- For moderate to severe symptoms, treatment options include opioid therapies. Emerging evidence supports the utility of offering high doses of buprenorphine (e.g., 8–16 mg q1h, usual maximum 32 mg) (6, 7). This choice is preferred over offering other short-acting opioids, which will have reduced opioid agonist effect due to the presence of buprenorphine on the opioid receptor and will simply delay withdrawal. For further explanation, see [High-Dose Buprenorphine Initiation \(“Macro dosing”\) for ED Providers](#).
- Benzodiazepines should not be used to treat opioid withdrawal because of the risks of sedation when combined with opioids.

## BUPRENORPHINE PRESCRIPTIONS

- Include start and stop dates (inclusive) until the day of planned follow-up (ideally three to five days, maximum seven days).
- 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 indicated 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 and should not be started with macrodosing. 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 acutely 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 should be started on buprenorphine at lower doses while receiving benzodiazepines. Since many unregulated 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 in the ED setting, not with benzodiazepines.

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1. D'Onofrio G, O'Connor PG, Pantaloni MV, Chawarski MC, Busch SH, Owens PH, et al. Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial. *JAMA*. 2015;313(16):1636-44.
  2. Strayer RJ, Hawk K, Hayes BD, Herring AA, Ketcham E, LaPietra AM, et al. Management of Opioid Use Disorder in the Emergency Department: A White Paper Prepared for the American Academy of Emergency Medicine. *J Emerg Med*. 2020;58(3):522-46.
  3. Hämmig R, Kemter A, Strasser J, von Bardeleben U, Gugger B, Walter M, et al. Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. *Subst Abuse Rehabil*. 2016;7:99-105.
  4. Patel P, Dunham K, Lee K. Buprenorphine/Naloxone Microdosing: The Bernese Method – A Brief Summary for Primary Care Clinicians. Toronto, ON: META:PHI; 2019.
  5. Randhawa PA, Brar R, Nolan S. Buprenorphine-naloxone “microdosing”: an alternative induction approach for the treatment of opioid use disorder in the wake of North America’s increasingly potent illicit drug market. *CMAJ*. 2020;192(3):E73.
  6. Szczesniak LM, Calleo VJ, Sullivan RW. Buprenorphine therapy in the setting of induced opioid withdrawal from oral naltrexone: a case report. *Harm Reduct J*. 2020;17(1):71.
  7. Herring AA, Schultz CW, Yang E, Greenwald MK. Rapid induction onto sublingual buprenorphine after opioid overdose and successful linkage to treatment for opioid use disorder. *Am J Emerg Med*. 2019;37(12):2259-62.