High-Dose Buprenorphine Initiation ("Macrodosing") for ED Providers

RATIONALE FOR MACRODOSING BUPRENORPHINE

High-dose buprenorphine (also referred to as *macrodosing*) is an alternative approach to initiating buprenorphine for patients who would benefit from achieving a full therapeutic dose rapidly. Many patients seen in the ED post-overdose would benefit from buprenorphine for treatment of opioid use disorder and prevention of overdose; however, use of fentanyl within 48 hours of presentation is an exclusion for standard buprenorphine initiation. Moreover, standard initiation suggests a maximum Day 1 dose of 16mg of buprenorphine; this dose is generally inadequate to provide relief of withdrawal symptoms for people who use fentanyl, which likely increases the risk of treatment discontinuation post-discharge.

Macrodosing as an alternative approach to treating withdrawal and initiating buprenorphine has been described as part of the CA Bridge program in California for patients who had undergone reversal of opioid overdose with naloxone (1). The **protocol** suggests an initial dose of 16mg for patients in withdrawal post-naloxone followed by subsequent doses of 8–16mg for a total Day 1 dose of up to 32mg (2). The pharmacological explanation is that buprenorphine at high enough doses provides relief of withdrawal symptoms and blockade against full-agonist opioids still in circulation that have been temporarily displaced by naloxone. The same rationale can be applied to withdrawal from opioid use without naloxone reversal: at doses of 16mg or higher, there is enough buprenorphine to provide relief of withdrawal symptoms after the full-agonist opioids are displaced from the mu-receptors, whereas lower doses (2–8mg) displace other full-agonist opioids without providing relief. Essentially, higher initial doses effectively bypass precipitated withdrawal and achieve a full therapeutic dose within hours.

It should be noted that there have been no clinical trials to date comparing the effectiveness of high-dose initiation to other initiation protocols, and that 24mg is the maximum daily dose of buprenorphine recommended in the product monograph in Canada. Nonetheless, high-dose buprenorphine has been shown to be safe and well tolerated (3), and clinicians using this protocol in Ontario have reported success in the ED setting in patients post-overdose and those in withdrawal from fentanyl (4).

Macrodosing initiation could therefore result in more patients starting buprenorphine in the ED and more patients continuing with outpatient buprenorphine treatment. Another advantage of high-dose buprenorphine initiation is that it allows for the early administration of depot buprenorphine (Sublocade®), a monthly extended-release injectable buprenorphine treatment option (see **Depot Buprenorphine Information Sheet**) that provides higher and more constant serum buprenorphine levels than sublingual dosing (5) and eliminates the need for frequent pharmacy attendance.

PRECAUTIONS WITH BUPRENORPHINE MACRODOSING

Buprenorphine macrodosing protocols should be used only with patients who are known to have high opioid tolerance.

Preliminary evidence suggests that high-dose buprenorphine is very safe. The largest safety study to date (3) looked at adverse outcomes among 366 ED patients who were given high dose buprenorphine; there were no cases of respiratory depression, no cases of naloxone administration, and no cases of sedation. However, the California high-dose protocols have been used mainly in patients who presented to the ED with complications of illicit fentanyl or heroin use. Therefore, until there is more research and clinical experience with high-dose buprenorphine, we recommend that it be reserved for people with very high opioid tolerance, i.e., people who inject or smoke fentanyl.

Do not use macrodosing in patients with a severe illness, who are intoxicated, who have any altered mental status, or are in concurrent withdrawal from other substances.

See algorithm for more details. In particular, do not use macrodosing for patients who have reduced respiratory reserve due to pneumonia, COPD, or other causes (3). Macrodosing should not be used in those with overlapping withdrawal syndromes, such as patients withdrawing from benzodiazepines or alcohol along with opioids.

Do not use macrodosing in patients at high risk of opioid toxicity.

Buprenorphine is far less likely to cause respiratory depression than full opioid agonists. However, it can cause toxicity if administered in high doses or via injection, especially if additional risk factors are present. Risk factors for opioid-induced sedation include older age, concurrent use of alcohol or sedating medications, and underlying health conditions, including sleep apnea, COPD, cardiac disease, hypertension, and renal disease (6).

Take steps to avoid precipitated withdrawal and treat it promptly if it occurs.

Precipitated withdrawal can be frightening and uncomfortable, and it can cause patients to leave treatment. The following steps can minimize its occurrence and severity:

a. **For patients in withdrawal from fentanyl use (who have not had full naloxone reversal of an opioid overdose), do not administer buprenorphine until at least 18 hours have elapsed since the last fentanyl use, with COWS score of 13 or more.** Fentanyl is highly lipophilic and takes at least 18 hours before it has mostly left the serum. A high COWS score provides objective confirmation that the level of fentanyl in the system is low.
b. **For patients who have had a full naloxone reversal of an opioid overdose, administer buprenorphine as early as possible, while the naloxone is still active (the half-life of naloxone is 30 to 90 minutes).** Naloxone displaces fentanyl from the receptor. Buprenorphine can then displace the naloxone and fully occupy the empty opioid receptors. The high-dose buprenorphine relieves withdrawal symptoms while blocking fentanyl from reattaching to the receptor.
c. **Do not offer buprenorphine to patients who use methadone unless at least 72 hours have passed since their last methadone dose.** Methadone has a very long half-life and can persist in the serum for days.
d. **Give an initial dose of 16 mg buprenorphine (see algorithm).** If the patient experiences worsening of their withdrawal symptoms (i.e., precipitated withdrawal) give another 16mg buprenorphine. The usual maximum dose on Day 1 is 32mg.

Get consent.

Macrodosing buprenorphine initiation is off-label, even though there is an abundance of literature on the efficacy and safety of buprenorphine itself. The clinician should explain that the goal is to get onto a full dose of buprenorphine quickly and effectively treat withdrawal symptoms. There is a small chance that the patient will experience a temporary worsening of withdrawal symptoms; if this occurs, additional doses of buprenorphine should help to resolve these symptoms.

CONNECT THE PATIENT WITH OUTPATIENT TREATMENT

- Arrange for the patient to be seen as soon as possible at a RAAM clinic, community opioid agonist treatment clinic, or medical withdrawal management service. These services will provide ongoing outpatient treatment.
- Prescribe up to a week's supply of take-home buprenorphine.
- Give a take-home naloxone kit.
- Involve a peer worker or substance use navigator if available. They can provide support and assist with coordinating outpatient follow-up.

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