FAQ: Low-dose Buprenorphine Induction in the Setting of Chronic Pain Management and Opioid Use Disorder

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1. What is buprenorphine microdosing/microinduction, now called low-dose buprenorphine induction (LDBI)?[1]

Buprenorphine is a first-line pharmacotherapy option for patients with opioid use disorder (OUD) and has become popular in recent years as an option for chronic pain management. Traditionally, the conversion from full mu agonists to buprenorphine has required patients to taper and discontinue their previous opioid and experience withdrawal symptoms before initiating buprenorphine as a means to prevent precipitated withdrawal. Buprenorphine microinduction, or low-dose buprenorphine induction (LDBI), has emerged in recent years as a method to convert patients to buprenorphine that reduces the risk of precipitated withdrawal and bypasses the need for prolonged opioid tapers. LDBI involves administering small doses of buprenorphine (0.25–2 mg/day of sublingual or 5–20 mcg/h of transdermal buprenorphine) while the full opioid agonist is continued. Both the dose and frequency of administration of buprenorphine are gradually increased until a therapeutic dose is achieved. At that point, the full opioid agonist is discontinued without the need for a slow taper. This process may take place over a 3- to 10-day period in the outpatient setting but may be done more quickly in the inpatient setting.

a. Pharmacology[2]

Buprenorphine is a partial agonist at the mu opioid receptor, meaning it does not fully bind to the receptor. Additionally, it has an effect at the kappa and delta opioid receptors. The partial interaction at the mu receptor is sufficient to reach an analgesic threshold with a ceiling effect for respiratory depression. Interaction at the kappa and delta receptors leads to decreased constipation, dysphoria and abuse potential while also reducing mental depression. Buprenorphine is a full-agonist at the opioid receptor-like 1, which may also contribute to analgesia. Buprenorphine has high binding affinity at the mu-opioid receptor and is slow to dissociate.

b. Why are low doses of buprenorphine used?[1]

Opioid withdrawal occurs when mu opioid receptor occupancy by full agonists is reduced. Sublingual maintenance doses of buprenorphine for OUD of 2, 16, and 32 mg/day have been shown to reduce mu opioid receptor binding availability by 41%, 80%, and 84%, respectively. Therefore, it's plausible that small doses of buprenorphine (0.25-1mg/day) only displace a small percentage of receptors and the threshold to induce withdrawal is not met.

2. When should LDBI be considered?

Buprenorphine is indicated for the management of moderate to severe chronic pain that requires a continuous, around-the-clock opioid analgesic for an extended period. It should be considered if the patient is assessed as high risk for traditional oral opioid therapy – this includes patients on high dose chronic opioid therapy (i.e., patients struggling with reducing dose or tapering off other opioids), those with mental health comorbidities (including substance use disorders) or medical comorbidities (sleep apnea, COPD, significant CVD, renal/hepatic impairment), or geriatric patients as they may be more susceptible to adverse reactions related to traditional opioids. It should also be considered if the patient has documented difficulty swallowing or poor/unpredictable gastrointestinal absorption (e.g., short bowel; nausea, vomiting).

3. How is LDBI induction done?

a. Prescribing information for buprenorphine products recommends either holding or tapering the full-agonist before buprenorphine initiation.[3] LDBI is an off-label approach.
b. Low dose buprenorphine induction initiates a low dose of buprenorphine while continuing full mu-agonists. The full mu-agonists are then tapered. The timeframe varies depending on the setting and patient factors. Rapid LDBI is often the approach used in OUD to get patients to therapeutic doses quickly.[2,4]
    i. The specific buprenorphine products list daily oral morphine equivalents (OME) ranges for each dose and product.[5-7] Patients on higher daily OMEs may require higher dose products labeled for OUD (if your state regulations allow).
c. Rotating for chronic pain[4]
    i. Consider reducing the long-acting opioid while covering with short-acting opioid to allow for gradual reduction of short-acting doses.
    ii. Start buprenorphine at a very low dose.
        1. Buprenorphine patch: apply 5 or 10 mcg/hr patch on Day 1. Steady state is reached by day 3, patients can have breakthrough full-opioid agonists. The patch can be increased every 72 hours. The max dose is 20 mcg/hr patch applied every 7 days. If this is insufficient to provide pain control, switch to another buprenorphine product. [5]
        2. Buprenorphine buccal film: start with 150 mcg once or twice a day. Steady state is reached by the 6th dose (~3 days). The dose can be increased in 150 mcg BID increments (300 mcg/day total), every 4 days.[6]
        3. Buprenorphine sublingual (OUD labeled products) for patients on higher doses: start with 0.5 mg to 1 mg once or twice a day. Steady state is reached in about 3-4 days. The dose may be increased every 3 days.[7]

iii. Counsel the patient:
    1. May be able to reduce short-acting as needed opioids by day 2-3.
    2. Check in with the patient every 3-4 days and taper the long-acting or scheduled opioids based on utilization, maintaining short-acting as needed doses.
iv. Patients may continue full opioid agonist for as needed analgesia.

d. Rotating for OUD[2]
    i. A sample induction is shown below.
    ii. The faster timeframe has been used mostly in the inpatient setting to rapidly transition but may be considered in the outpatient setting after discussion with the patient. The timeframe can be adjusted as tolerated by the patient.
    iii. Once at 16 mg/day of sublingual buprenorphine, full opioid agonists can be stopped without risk of withdrawal.

Day	SL Buprenorphine	Full Opioid Agonists	SL Buprenorphine (rapid plan)	Full Opioid Agonists
1	0.5 mg (¼ film/tablet) once	Continue, no dose adjustments or slowly taper opioids. Should see fewer cravings or doses of opioids being used as buprenorphine doses increase.	0.5 mg (¼ film/tablet) every 6 hours	Continue, no dose adjustments or slowly taper opioids. Should see fewer cravings or doses of opioids being used as buprenorphine doses increase.
2	0.5 mg (¼ film/tablet) BID		1 mg (½ film/tablet) every 6 hours	
3	1 mg (½ film/tablet) BID		2 mg (1 film/tablet) every 6 hours	
4	2 mg (1 film/tablet) BID		8 mg BID	Stop full opioid agonists
5	4 mg BID			
6	8 mg BID	Stop full opioid agonists		

4. What are the limitations/challenges to LDBI in practice?

a. Prescriber willingness - prescribers may not be familiar with low dose buprenorphine induction or may not feel comfortable prescribing buprenorphine due to lack of training and experience with the medication.
b. Insurance coverage - the product may not be covered by insurance, may require other products to be trialed and failed prior to being covered, or require a prior authorization based on specific formulation and indications for use.
c. Potential precipitated withdrawal symptoms - the intended utility of low dose buprenorphine induction is to negate withdrawal symptoms, but the possible potentiation of withdrawal may not be entirely minimized. The rate of precipitated withdrawal varies depending on dosage form and dosing strategy. A study evaluating tolerability of switching from a full mu-agonist to buccal buprenorphine at approximately 50% of the full agonist dose reported no increased risk of opioid withdrawal.[8] An observational cohort study using data from an ongoing clinical trial reported precipitated withdrawal of 0.76% in patients seeking buprenorphine treatment in emergency departments across the United States.[9]
d. Patient health literacy – induction regimens, especially those using sublingual buprenorphine, often require partial tablets or films slowly increased over a few days. The specific protocol detailing the induction may be challenging in select patient populations. Specific instructions, counseling, educational services, and frequent provider follow-up are needed to ensure compliance and success during induction.
e. Side effects[10] – the side effect profile is similar to full opioid agonists, though they are often less frequent and severe. Below are the most commonly reported side effects based on dosage form:
    a. Buccal film – nausea, dental effects – after dissolved take a large sip of water and swish around mouth then swallow, wait at least 1 hour before brushing teeth, maintain good oral hygiene and have regular follow up with a dentist
    b. Sublingual – headache, insomnia, nausea/vomiting, abdominal pain, diaphoresis, constipation, dental effects (see above for management)
    c. Transdermal patch – nausea, headache, dizziness, drowsiness, constipation, application-site pruritis (apply low dose topical steroid approximately 2 hours prior to application of the patch)
f. Cutting films – even though the package insert states the film should not be cut and should be administered whole, clinical practice often requires the films to be split. An exploratory study was published in 2019 evaluating cutting methods, content uniformity, and stability of split films. The cutting methods evaluated included ruler/razor cut, scissor cut, fold/rip, and fold/scissor cut. All four methods were found to be acceptable for splitting the films into half, but not quarter fractions.[11]

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