Background: Buprenorphine offers a range of potential benefits for patients with serious illness. For patients who started long-term opioid therapy (LTOT) during their serious illness and are unable to taper opioids otherwise, it can facilitate patient-centered opioid tapering (1). Other patients may have developed opioid misuse behaviors or opioid use disorder (OUD) such that the harms of LTOT with full µ-agonist opioids (e.g., morphine or oxycodone) outweigh the benefits (2). Buprenorphine is a safer option for many of these patients and can be a life-saving therapy (3). Lack of familiarity, knowledge, and resources on initiating buprenorphine have been cited as significant barriers to use (4). This Fast Fact provides guidance on initiation using the traditional method via buprenorphine/naloxone sublingual (SL) film (Suboxone®), intended for patients currently taking a full µ-agonist opioid. While this method was developed for patients with OUD, it is also used for opioid-tolerant patients with chronic pain without OUD. Other methods of initiating buprenorphine are not addressed here, including the use of lower-dose formulations, FDA-approved for chronic pain but not OUD, such as the transdermal patch (see Fast Fact #268) and buccal film (Belbuca®).

Clinician and patient preparation: Effective April 2021, any Drug Enforcement Agency (DEA)-licensed clinician can apply for an X waiver to prescribe buprenorphine for OUD or opioid misuse for up to 30 patients without completing educational training or attestation of the ability to refer for counseling (6,7). Additional education from trusted sources including Substance Abuse and Mental Health Services Administration (SAMHSA), Providers Clinical Support System (PCSS), or American Society of Addiction Medicine (ASAM) is advised before clinicians begin prescribing buprenorphine (8-10). We also recommend identifying a mentor (such as an addiction specialist at your institution or through the PCSS Mentorship Program) and utilizing live support from National Clinician Consultation Center (11,12).

Clinical setting: Buprenorphine can be safely initiated in the inpatient setting, outpatient clinic, or in the patient’s home (13-15). Prior to initiation, determine the setting and protocol that fits your clinical workflow and patient situation (16). Prepare for buprenorphine initiation by arranging follow-up phone calls or in-person visits within one week of initiation as well as coordinating care to behavioral support as needed and facilitating medication access (e.g., prior authorization may be required) (13-15).

Patient education and shared decision-making: Patients should be educated on safe storage and SL administration with no food or water until completely dissolved (14). A discussion of treatment goals (i.e., reduction in pain, high risk behaviors, cravings) is essential. If a patient is reluctant to initiate buprenorphine, then it is important to acknowledge these conflicting emotions and to dispel stigma around chronic pain, addiction, and the medications used for treatment (see Fast Fact #429 on stigma).

Step 1: Discontinue full µ-agonist opioids: Buprenorphine has high affinity for the µ-opioid receptor and only partially activates it (18). At moderate and high doses (more than 1 mg/day), buprenorphine displaces full µ-agonist opioids from the receptor and causes severe withdrawal symptoms unless the patient is already in withdrawal. In that case, it stimulates the receptor enough to relieve withdrawal (15). Therefore, current guidelines recommend stopping full µ-agonist opioids before starting buprenorphine.

Step 2: Assess for opioid withdrawal: The onset of withdrawal symptoms typically takes at least 12 hours for patients on short-acting opioids, 24 hours for those on extended-release formulations, and 36 hours for those on methadone. Withdrawal tools such as the Clinician Opioid Withdrawal Scale (COWS) or the Subjective Opioid Withdrawal Scale (SOWS) rate the stage and severity of opioid withdrawal (19, 20). It is recommended to start buprenorphine when there is mild-moderate opioid withdrawal (COWS > 8 with at least one objective sign of withdrawal or SOWS > 17) (9).

Addressing patient comfort and minimizing the risk of precipitated withdrawal are key factors to success (17). Withdrawal symptoms should be treated with medications as needed during initiation (see Fast Fact #429 on stigma).
Precipitated withdrawal occurs when withdrawal symptoms increase in the first hour following buprenorphine initiation. If concerns arise about precipitated withdrawal, consult your identified mentor, or use the resources for live clinician support mentioned above.

**Step 3: Start buprenorphine:** Administer the initial dose of buprenorphine following the development of mild-moderate withdrawal symptoms; repeat doses may be needed every 1-2 hours on the first day. The effective dose will be titrated over the next several days to the clinically relevant target. The following protocol is adapted from *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction* from SAMHSA Treatment Improvement Protocols (22):

**Day 1:** Patient has already discontinued full μ-agonist opioids and developed mild-moderate withdrawal:
- Start 2 mg/0.5 mg buprenorphine/naloxone SL
- Reassess symptoms every 1-2 hours. If withdrawal persists, then repeat the same dose every two hours to a maximum of 8 mg/2 mg buprenorphine/naloxone SL on Day 1
- The preeminent goal of Day 1 is to relieve opioid withdrawal

**Day 2:** If continued pain or withdrawal despite 8 mg/2 mg buprenorphine/naloxone SL:
- Increase dose to 12 mg/3 mg as a once daily or split dose every 6-12 hours (patients with pain typically receive split dosing for better analgesia) (18)
- If continued pain or withdrawal, then add an additional 4 mg/1 mg dose two hours later
- Maximum dose on Day 2 is 16 mg/4 mg buprenorphine/naloxone SL

**Day 3-14:** Fine-tune the dose. If the patient’s therapeutic goals are met, the dose need not be adjusted.
- If continued pain or withdrawal, increase the dose by 2-4 mg buprenorphine per day
- On average, patients with OUD require 16 mg/4 mg - 24 mg/6 mg buprenorphine/naloxone SL daily (maximum FDA approved dose for OUD is 32mg/8mg buprenorphine/naloxone SL daily)
- For patients with pain without OUD, the dose is often lower than 16 mg/4 mg per day
- It often takes 1-2 weeks to achieve a stable dose (23)


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