

About Buprenorphine

What is buprenorphine?

Buprenorphine (BUP) is a unique schedule III opioid used for the treatment of acute and chronic pain, opioid withdrawal, and maintenance treatment of opioid addiction. The most common formulations are sublingual (alone or in combination with naloxone: Suboxone), transdermal (10mcg/hr = about 0.5mg/day), and intravenous (Buprenex).

How long has buprenorphine been around?

Since the 1970's. Initially, buprenorphine was used as an intravenous, perioperative, analgesic. It was used later because of its long-action ability to block the euphoric effects of heroin. Safety profile sublingual buprenorphine was developed for opioid substitution treatment in the 1990s and was approved for use in the US in 2002. Most recently, buprenorphine is increasingly used for the treatment of chronic pain.

How long does buprenorphine take to act and when does it peak?

Sublingual buprenorphine takes 15 minutes to act when held under the tongue and peaks in one hour. A typical 0.3mg IV buprenorphine begins to work immediately after an IV push with peak effect in 5-10 minutes.

What is the difference between buprenorphine and Suboxone®?

Suboxone is the trademark name for buprenorphine + naloxone. The naloxone component is an abuse deterrent that is inert when the tablet is taken sublingually. The naloxone is only active if the tablet is injected.

Are there contraindications for buprenorphine?

If a patient dependent on opioids takes buprenorphine when they have opioid in their system, the buprenorphine will rapidly block the effects of their opioid causing what is termed "precipitated withdrawal." The severity of this effect varies from mild discomfort to severe distress. This is why there is a washout period for opioid tolerant patients before starting buprenorphine. Once significant withdrawal has begun the administration of buprenorphine produces relief of withdrawal, anxiety, and analgesia. Some patients with significant liver disease (ALT > 5x normal) may not be able to take buprenorphine long-term. Avoid in patients with hypersensitivity to buprenorphine or naloxone.

Is there a need for an Alpha 2 agonist such as Clonidine?

No, nothing else is needed. However, adjunct medications such as clonidine, zofran, and loperamide can be helpful in some cases. We avoid routine use of benzodiazepines.

How long do people use buprenorphine?

It depends.

An ED patient might receive a few doses buprenorphine to treat withdrawal and then go right back to using street opioids. Most patients with opioid use disorder don't establish long-term abstinence on the first go around. The hope is that, having a positive experience with buprenorphine treatment can be a motivation to pursue long-term treatment.

The evidence is clear: the more weeks of stability on buprenorphine that a person with opioid use disorder can string together, the more their mortality risk goes down. We see patients stop and start frequently and that's common. Each medical encounter is an opportunity to make another attempt at long-term recovery.

Once patients have stabilized on buprenorphine patients should be continued on it indefinitely. When patients stop their maintenance buprenorphine or methadone, all cause mortality more than doubles. (Sordo L, Barrio G, Bravo M, Indave B, Degenhardt L, Wiessig L, Ferri M, Pastor-Barriuso R. Mortality Risks During and After Opioid Substitution Treatment: Systematic Review and Meta-Analysis of Cohort Studies. *BMJ* 2017; 357:j1550.) The underlying concept is that the neural architecture of the brain is changed by addiction and it takes years to recover. When patients are in recovery they develop whole new patterns of behavior, stress response, and reward seeking that then get "hardwired" into the brain. This process cannot be rushed and has very little to do with patient motivation or insight.

Buprenorphine in the ED

What forms of buprenorphine should we have on the formulary?

At minimum, sublingual tablet formulations of buprenorphine should be available to be administered and/or prescribed from the ED. The most common formulations are sublingual (alone or in combination with naloxone: Suboxone), transdermal (10mcg/hr = about 0.5mg/day), and intravenous (Buprenex).

When do you administer buprenorphine in the ED?

Buprenorphine will displace other drugs from opioid receptors, replacing the high-intensity stimulation from drugs like heroin or oxycodone with stable drug levels over 2-3 days, eliminating craving and withdrawal symptoms. Starting BUP when patients have moderate withdrawal symptoms provides immediate relief, stopping withdrawal discomfort without causing euphoria or sleepiness. Do NOT start BUP on opioid-dependent patients who are not in withdrawal. For these patients, the BUP causes withdrawal, and decreases patients' desire to stay on BUP or to try BUP again.

How does a clinician give buprenorphine in the ED?

Generally start with 4-8 mg as sublingual tablet (Suboxone or Subutex) under the tongue. IV BUP (0.3mg) can be used for patients unable to tolerate sublingual tablets. If the tablets are swallowed, very little BUP gets absorbed. Repeat doses up to 32mg SL can be administered depending on the clinical situation. It is okay to administer BUP in low-acuity, "fast-track" type areas of the ED. A single 8 mg dose will have peak effect by about 1 hour and control withdrawal symptoms 6-12 hours. Transdermal buprenorphine will generally be too weak to prevent withdrawal symptoms and is best used for patients with chronic pain. See *ED-BRIDGE Guide to Emergency Buprenorphine Treatment*.

How should an ED discharge a patient?

Always offer a naloxone prescription or kit.

- **Option 1. No DEA X waiver**

Prescribe comfort meds (e.g. clonidine, loperamide, ondansetron, NSAIDS) and recommend follow-up at treatment center. It is legal in all states to offer return ED visits for BUP administration for 3 days in a row if necessary.

- **Option 2. DEA X waiver**

Give bridge script to last until outpatient visit: e.g., 8mg Suboxone, SL tabs; Take 1 tab under the tongue twice a day for withdrawal symptoms; Dispense #6-7

How do you get cooperation from patients?

Communication with patients

Talk to patients broadly and openly about addiction to break down stigma on the part of patients and clinicians. Daily discussion of addiction helps break down stigmatized attitudes and promote a non-judgmental medical approach.

Communication with colleagues

Getting the word out to the larger health system and the community that the ED is a setting for getting help, versus hiding addiction and hoping to “score,” may be a potential benefit to beginning an ED MAT program. Public signage, patient handouts should be considered as part of communications plan.

Provide an overview of buprenorphine treatment and what it entails, discussing risks, benefits and expectations. Widespread patient education about the neurobiological model of addiction, buprenorphine treatment and the treatment program can be provided to any patient receiving opioids. For patients identified with addiction, individually tailored educational materials can then be used.

Does use of buprenorphine by emergency physicians lead to cases of precipitated withdrawal or drug seeking?

A study by Berg *et al*,¹ suggests that concerns about harm (precipitated withdrawal or drug-seeking) are likely unfounded. In a retrospective chart review of 158 patients treated at a single ED with buprenorphine for opioid withdrawal, the authors found no instances of precipitated opioid withdrawal (a potential medical complication of buprenorphine), and a greater than 50% reduction (17% vs. 8%) in return-rate to the same emergency department for a drug-related visit within one month, compared to return-visit rate for usual care (no pharmacologic management or supportive therapies such as anti-nausea medications and sedatives).

How do you treat people in denial about addiction, chronic pain?

Buprenorphine can always be used to treat withdrawal. Anyone with an opioid use disorder who is opioid dependent and desires to get off full agonist opioids (oxycodone, hydrocodone, heroin) should be considered for buprenorphine. Typically, dosing is more frequent such as 4mg SL 3-4 times per day. Most insurance plans will only cover buprenorphine if opioid dependence is diagnosed. Whenever possible coordinate care with outpatient providers.

What is the cost of Buprenorphine?

Buprenorphine sublingual tablets without naloxone is approximately \$5 and parenteral formulations are approximately \$10; sublingual tablets with naloxone, patches and buccal film are much more expensive.

What are the limitations on buprenorphine from the DEA?

Providers cannot see over 120 patients at the same time. The DEA is only counting active prescriptions, so an ED provider who is not following patients long term would not be expected to be affected by this limit. At any given time, an ED provider would only be expected to have a few active prescriptions at the same time.

What is the 72 hour (3 day) rule?

The 72-hour rule is intended to provide an emergency option for treating withdrawal as someone is getting established in treatment. It does not allow for prescribing but does allow repeat administration for three consecutive days for a given patient. The clock "resets" only after a patient has connected with a treatment program. If they relapse, they get another 72-hour emergency option. It does matter who is administering the meds. (See <https://www.samhsa.gov/programs-campaigns/medication-assisted-treatment/legislation-regulations-guidelines/special>).

For example:

¹ Berg ML, Idrees U, Ding R, Nesbit SA, Liang HK, and McCarthy ML. Evaluation of the use of buprenorphine for opioid withdrawal in an emergency department. *Drug Alcohol Depend.* 2007;86(2-3):239-44. doi:10.1016/j.drugalcdep.2006.06.014.

- Allowed: Patient "John" comes in acute withdrawal on Friday and gets buprenorphine for acute withdrawal. Then returns Saturday and Sunday to the ED and is administered suboxone during the visit without any take home script. On Monday he sees an addiction specialist.
- Allowed: If there is no suboxone on inpatient formulary: patient "John" comes in acute withdrawal on Friday and gets morphine for acute withdrawal. Then returns Saturday and Sunday to the ED and is administered oral morphine during the visit without any take home script. On Monday he sees an addiction specialist.
- Not allowed: Patient John sees provider Jane who does not have an X waiver, and gets a three day prescription for suboxone.
- Not allowed: Patient John misses his appointment on Monday and returns to the ED asking for suboxone. He cannot be administered or prescribed suboxone by a NON WAIVERED provider.
- Probably okay: John is seen on Friday, a butrans patch is placed and then is seen on Monday by an addiction specialist. The specialist then takes over the prescribing.
- Not okay: John keeps the patch on for longer than 3 days.

Patients

What patient group will have the greatest benefit from buprenorphine treatment?

Patients at risk for death from opioid overdose should be prioritized; risk factors include:

- Injection heroin and non-medical pain reliever abuse
- History of overdose and/or substance abuse
- History of mental illness
- > Morphine 100 mg equivalents/day
- Medicaid/low income patients
- Frequent emergency department visits
 - > 3 in the last year;
 - ED visits with disposition of leaving without treatment or against medical advice
- Multiple opioid prescriptions in last year and multiple prescribers. However, any patient who meets DSM 5 criteria for opioid use disorder should be strongly considered for starting buprenorphine.

What does the buprenorphine patient look like?

There are multiple kinds of patients that can benefit from a buprenorphine treatment.

Starting a patient on buprenorphine lowers mortality from opioid addiction 7-fold. It is strongly recommend to start BUP in ED after overdose (OD), due to 10% risk of fatal OD within 12 months in these patients. Patients in opioid withdrawal or who desire to stop using opioid pills or heroin can work well for this program.

Another type of patient that can be more tricky is an individual with chronic pain. If they have a prescribing doctor, encourage them to go talk with that clinician.

With these patients, we encourage starting a conversation about potential transition to buprenorphine, to reduce overdose risk and possibly improve pain control. However, patients should generally be directed to discuss this option with their opioid prescriber prior to starting buprenorphine.

Can buprenorphine be given to individuals on benzodiazepines?

Yes. Buprenorphine is far safer than using street opioids. However, buprenorphine can potentiate the effects of sedatives like alcohol and benzodiazepines (but less than other opioids). Assess risk and benefit with these high-risk patients. The risk of overdose is highest when patients have binge use of alcohol and benzodiazepines. Patients should be encouraged to decrease/stop use of these substances, but often benefits of starting buprenorphine outweigh risks as the combination of illicit opioids+sedatives is riskier than buprenorphine+sedatives. See the FDA statement for further guidance: <https://www.fda.gov/Drugs/DrugSafety/ucm575307.htm>

Will Buprenorphine work for people on methadone?

Patients who are on methadone (or on other chronic opioids) should not be started on buprenorphine while on these medications. Patients on methadone may ultimately consider transition from methadone to buprenorphine, but should do so in consultation with their methadone clinic. Starts on buprenorphine for patients who took methadone within the last week is high risk for precipitated withdrawal and should only be done in consultation with an expert.

Are screening labs needed to start BUP in the ED?

No. Offer women of childbearing age a pregnancy test. We encourage screening for HepC and HIV.

What if a patient comes back who is running out of buprenorphine?

This is a case-by-case decision. Ideally ED prescriptions are short (3-7 days) with follow-up prescriptions at the outpatient treatment site. In general, most EDs will advise patients that no refills will be offered. But, individual cases can be complicated and ED providers need to use clinical judgement in regards to refilling prescriptions.

Is there a risk of diversion with prescribing buprenorphine in the ED?

Yes. Buprenorphine is bought and sold on the street routinely. Most diverted buprenorphine is used for its intended purpose – avoiding dope-sickness and cravings. People who have experienced “street” buprenorphine have longer retention times in treatment, perhaps because they have experienced what buprenorphine does to increase stability and therefore are even more motivated when it comes to treatment.² A reasonable balance is check the patient drug monitoring database (CURES) to confirm the patients opioid prescriptions and to provide a brief prescription(less than 7 days). This allows time for follow-up appointments to be made with the outpatient clinic to continue buprenorphine prescribing and OUD treatment.³

² Cunningham et al. Prior Buprenorphine Experience Is Associated With Office-Based Buprenorphine Treatment Outcomes. *J Addict Med* 2013;7: 287–293

³ D'Onofrio G, O'Connor PG, Pantalon MV, Chawarski MC, Busch SH, Owens PH, Bernstein SL, and Fiellin DA. Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial. *JAMA*. 2015;313(16):1636-44. doi:10.1001/jama.2015.3474

Are providers required to have an X-waiver to administer buprenorphine in the ED and provide a prescription until follow-up is established?

There is a key difference between **administration** and **prescription**.

Administration of buprenorphine in any form is allowed for any ED provider.

A **prescription** of buprenorphine, on the other hand, is restricted. An x-waiver is needed for any prescription for SL buprenorphine for addiction. Note that anyone can prescribe buprenorphine for pain, but other than Medi-Cal, insurance often needs a TAR for the indication of pain.

Workarounds include:

A) Per title 21, §1306.07 section (c), the non-waivered prescriber can administer bupe in the ED and then the patient can return for 3 consecutive days to get bupe as they wait for an appointment.

B) For healthy (ASA 1&2), young (less than 65 yrs old) patients in moderate to severe withdrawal (at least one objective sign of withdrawal and COWS \geq 8), a loading dose can be used. Loading protocol = 8mg SL, assess in 30-45min, if feels better and no hypersensitivity, give 16-24mg SL. This will provide 72 hours of relief from withdrawal.

Is a DEA X waiver required to start a buprenorphine program in the ED?

No. A waiver is not required to administer buprenorphine, but having a clinician with an X-waiver is recommended so prescribing buprenorphine is an option on discharge.

For patients who are admitted for medical indication who are also on Suboxone for addiction prior to admission:

Are attending physicians able to order Suboxone for maintenance throughout admission without the X-waiver? Does the hospital require licensing and certification for inpatient rehab to start Suboxone for patients who are admitted for a medical reason?

Any MD can use any narcotic — buprenorphine, methadone, morphine, etc. — for the treatment of withdrawal (or prevention of - i.e. MAT) during the ED and inpatient course of treatment for a primary admission. There is no special certification required.

Title 21, §1306.07 section (b):

“If the primary admitting diagnosis is a different medical issue (other than opioid use disorder and withdrawal), the withdrawal can be treated as a part of their routine medical care. In this case, the facility is not acting as an inpatient rehab, and therefore no special certification is required.”

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Results from Buprenorphine Treatment

Will treatment with buprenorphine reduce mortality among patients with opioid addiction?

In a recent study of over 150,000 National Health Service patients treated for opioid dependence, followed for a total of 442,950 patient years, treatment of opioid dependence with buprenorphine was found to reduce risk for opioid overdose death by one half versus patients with no treatment or psychosocial treatment only.⁴

In a study of 33,923 Medicaid patients diagnosed with opioid dependence in Massachusetts, mortality during the four-year study period (2003-2007) was double among patients receiving no treatment versus patients treated with buprenorphine. Additionally, patients treated with buprenorphine experienced a 75% reduced mortality versus patients treated with psychosocial interventions alone.⁵

Among the highest risk patients who inject heroin, treatment with methadone or buprenorphine for at least 5 cumulative years, is associated with a reduction in mortality from 25% at 25 years to 6%. The association between treatment and improved survival is likely multifactorial and mediated through reduced risk of HIV infection, improved social functioning, reduced criminality, and establishing long-term contact with health professionals.^{6,7,8,9,10,11,12,13} Importantly, survival benefit is not affected by cessation of injection drug use.³

⁴ Pierce M, Bird SM, Hickman M, Marsden J, Dunn G, Jones A, and Millar T. Impact of treatment for opioid dependence on fatal drug-related poisoning: a national cohort study in England. *Addiction*. 2016;111(2):298-308. doi:10.1111/add.13193.

⁵ Clark RE, Samnaliev M, Baxter JD, and Leung GY. The evidence doesn't justify steps by state Medicaid programs to restrict opioid addiction treatment with buprenorphine. *Health Aff (Millwood)*. 2011;30(8):1425-33. doi:10.1377/hlthaff.2010.0532.

⁶ Kimber J, Copeland L, Hickman M, Macleod J, McKenzie J, De Angelis D, and Robertson JR. Survival and cessation in injecting drug users: prospective observational study of outcomes and effect of opiate substitution treatment. *BMJ*. 2010;341(jul01 1):c3172-c3172. doi:10.1136/bmj.c3172.

⁷ Mattick RP, Breen C, Kimber J, and Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2014;2:CD002207. doi:10.1002/14651858.CD002207.pub4.

⁸ Fugelstad A, Stenbacka M, Leifman A, Nylander M, and Thiblin I. Methadone maintenance treatment: the balance between life-saving treatment and fatal poisonings. *Addiction*. 2007;102(3):406-12. doi:10.1111/j.1360-0443.2006.01714.x.

⁹ Bell J, Trinh L, Butler B, Randall D, and Rubin G. Comparing retention in treatment and mortality in people after initial entry to methadone and buprenorphine treatment. *Addiction*. 2009;104(7):1193-200. doi:10.1111/j.1360-0443.2009.02627.x.

¹⁰ Gowing L, Farrell M, Bornemann R, and Ali R. Substitution treatment of injecting opioid users for prevention of HIV infection. *The Cochrane Library*. 2004.

¹¹ Amato L, Davoli M, Perucci CA, Ferri M, Faggiano F, and Mattick RP. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *J Subst Abuse Treat*. 2005;28(4):321-9. doi:10.1016/j.jsat.2005.02.007.

¹² Sporer KA. Strategies for preventing heroin overdose. *BMJ*. 2003;326(7386):442-4. doi:10.1136/bmj.326.7386.442.

¹³ Ward J, Hall W, and Mattick RP. Role of maintenance treatment in opioid dependence. *Lancet*. 1999;353(9148):221-6. doi:10.1016/S0140-6736(98)05356-2.

Title 21 Code of Federal Regulations

PART 1306 — PRESCRIPTIONS

GENERAL INFORMATION

§1306.07 Administering or dispensing of narcotic drugs.

(a) A practitioner may administer or dispense directly (but not prescribe) a narcotic drug listed in any schedule to a narcotic dependant person for the purpose of maintenance or detoxification treatment if the practitioner meets both of the following conditions:

- (1) The practitioner is separately registered with DEA as a narcotic treatment program.
- (2) The practitioner is in compliance with DEA regulations regarding treatment qualifications, security, records, and unsupervised use of the drugs pursuant to the Act.

(b) Nothing in this section shall prohibit a physician who is not specifically registered to conduct a narcotic treatment program from administering (but not prescribing) narcotic drugs to a person for the purpose of relieving acute withdrawal symptoms when necessary while arrangements are being made for referral for treatment. Not more than one day's medication may be administered to the person or for the person's use at one time. Such emergency treatment may be carried out for not more than three days and may not be renewed or extended.

(c) This section is not intended to impose any limitations on a physician or authorized hospital staff to administer or dispense narcotic drugs in a hospital to maintain or detoxify a person as an incidental adjunct to medical or surgical treatment of conditions other than addiction, or to administer or dispense narcotic drugs to persons with intractable pain in which no relief or cure is possible or none has been found after reasonable efforts.

(d) A practitioner may administer or dispense (including prescribe) any Schedule III, IV, or V narcotic drug approved by the Food and Drug Administration specifically for use in maintenance or detoxification treatment to a narcotic dependent person if the practitioner complies with the requirements of §1301.28 of this chapter.