California Health Care Foundation

Buprenorphine: Questions and Answers

This document supplements the California Health Care Foundation webinars **Expanding Access to Buprenorphine in Primary Care Practices** and **Is Buprenorphine for Pain a Safer Alternative to High-Dose or Long-Term Opioid Use?** The clinical information contained in this document is meant as a guideline and is not intended to replace medical judgment. It is based on information covered in the webinars, and was reviewed by addiction specialists Howard Kornfeld, MD; James Gasper, PharmD; and Andrew Herring, MD.

CLINICAL QUESTIONS

Induction Options

Which patients should be induced in clinic versus at home? "Induction" is the term used for the process of switching to buprenorphine from other opioids; it typically requires 12-24 hours of withdrawal symptoms before buprenorphine can be started. Clinical trials on buprenorphine were performed with observed (in-office) inductions, and many clinic protocols are based on this practice. However, home induction is increasingly used, both to improve clinic workflow and to increase convenience for the patient. Some clinics do home inductions exclusively (HealthRIGHT 360); others adapt the strategy to the needs of the patient, using home inductions for stable patients and clinic inductions for those needing closer monitoring (e.g., psychiatric instability).

What are induction clinics? Induction clinics relieve primary care practices of the intensity and frequency of visits for patients newly starting on buprenorphine. These separate clinics can devote time and staff resources to intake, assessment, evaluation of options, education, induction, and early monitoring. The patients can be transferred back to primary care when they are stable on monthly prescriptions. This approach has been used successfully for over 10 years in San Francisco at the Office-Based Opioid Treatment Induction Clinic. A similar "hub and spoke" model is used in Vermont, where complex patients go to the hub (an opioid treatment program) and stable patients are managed at spokes (primary care practices).

Published Studies

- A randomized, controlled study from Sweden compared detox plus placebo to detox plus maintenance buprenorphine: 4 out of 20 (20%) died of overdose in the first year in the placebo group, compared to no deaths in the buprenorphine group.
- Patients on opioid maintenance therapy (buprenorphine or methadone) are less likely to contract hepatitis C and HIV.
- More than 9 of 10 people continue to use opioids after an overdose event. An overdose should be a signal of a very high-risk patient, immediately triggering a plan to taper to a safer regimen of prescribed opioids, offer take-home naloxone, and consider addiction treatment (buprenorphine or methadone) where appropriate.
- The POATS trial evaluated short- and long-term buprenorphine treatment. Of those tapered off at 12 weeks, 9% reported abstinence compared to 50% of those continuing treatment. Patients using buprenorphine were more than twice as likely to report abstinence at 18 months compared to those who were not (80% versus 37%); the difference persisted at 42 months (80% versus 51%).

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What is a buprenorphine or fentanyl patch induction? When a patient has a diagnosis of pain, a buprenorphine or fentanyl patch can bridge a patient from their current opioid treatment to sublingual buprenorphine, without requiring the patient to experience 12-24 hours of withdrawal symptoms. *Buprenorphine and fentanyl patches are FDA-approved for pain and cannot be used for pure addiction.*

The following guidelines are based on Dr. Howard Kornfeld's research and practice,[i] [ii] and are not intended to replace medical judgment. Patients should be assessed every 1-2 days, and adjustments made as needed. Expert advice is widely available (see box).

Where can clinicians get training and support?

Buprenorphine trainings are found on several websites. The training is 8 hours and can be done in person, online, or a combination. The buprenorphine waiver training can be valuable to any clinician (medical or behavioral), since it covers the basics of opioid addiction and how buprenorphine works.

At this point, only physicians can get a DEA waiver to prescribe buprenorphine for addiction. However, any DEA-licensed clinician can prescribe buprenorphine for pain. Nurses, nurse practitioners, and physician assistants can manage patients on buprenorphine for addiction if a physician writes the prescriptions and oversees care.

Training opportunities: SAMHSA, American Academy of Addiction Psychiatry, American Osteopathic Academy of Addiction Medicine, and Providers' Clinical Support System (PCSS). Some sites also offer other tools and resources. PCSS offers online mentorship, and Project ECHO offers video telementoring and case review 2 hours per month.

The Clinicians Consultation Center at UCSF offers a warmline with expert clinical advice Monday through Friday, 7 AM to 3 PM PST. **Substance Use Warmline: (855) 300-3595**

Buprenorphine transdermal (patch) induction

Step 1. Taper off methadone. Because methadone exits the body slowly, especially at high doses, most addiction treatment protocols advise a gradual taper to ≤30 mg of methadone, then abstinence for 48 hours or longer, before administration of sublingual buprenorphine. Unlike patients with addiction alone, patients with a pain diagnosis can use buprenorphine patches and other opioids for an easier transition and fewer withdrawal symptoms.

First, convert methadone to a different long-acting opioid (morphine, oxycodone, hydromorphone, hydrocodone, or oxymorphone). Due to individual variability, use caution when calculating the morphine equivalent dose: Use 30%-50% less than the dose calculated by any conversion calculator, and only give a small number of pills at a time. .

- *<50 mg methadone?* Use long-acting opioid for 3-4 days before starting the buprenorphine patch.
- *50-100 mg methadone?* Replace half of methadone with long-acting opioid for 3-4 days, then replace the other half for 3-4 days (overlapping or cross-taper).
- *>100 mg methadone?* Use the cross-taper method in three or more steps.
- After appropriate time on long-acting opioid, proceed to step 2.

Step 2. Buprenorphine patch induction for patients on long-acting opioids.

Before the induction day, prescribe the following medications and ask the patient to bring all to the office:

- Buprenorphine patches (one 20 mcg/hour, two 10 mcg, or four 5 mcg patches. One box contains four; pharmacists can dispense less than a box. Each patch lasts one week).

- Buprenorphine sublingual 2 mg #12-60 (amount depending on patient stability. The buprenorphine mono product — without naloxone — is cheaper, but should not be used when there is concern about inappropriate use).
- 4 days of short-acting opioids (30%-50% less than the current long-acting opioid dose). Options include immediate release forms of morphine, oxycodone, hydrocodone, or hydromorphone.

Tell the patient to stop taking long-acting opioids the night before the induction. Short-acting opioids can be used as needed for pain.

Simultaneously (on the first day of the induction):

a. Discontinue long-acting opioids the night before.
b. Place 20 mcg/hour of buprenorphine patch (10 mcg/hour for very low dose conversions). Keep patch on for 3-4 days.
c. Continue short-acting opioids as needed for pain.

Step 3. Start sublingual buprenorphine.

a. After 3-4 days on the patch, discontinue the short-acting opioids the night before starting sublingual buprenorphine. Keep the patch in place.
b. Give 1 mg (half-tablet) buprenorphine in the office; have the patient wait for 30 minutes to observe the effect before going home (observed induction is recommended for pain patients). The patient can take another 1 mg dose later that day.
c. Increase dose by 2-4 mg every 3 days as needed to control pain and cravings, to a maximum of 24 mg. Some physicians titrate up at a faster pace; however, many patients do well on lower doses.
d. The slow onset of the buprenorphine delivered through the patch system should prevent precipitated withdrawal. Once higher doses of sublingual buprenorphine are tolerated, discontinue the patch.

Fentanyl transdermal (patch) induction

1. Transition patients from their current opioid regimen to fentanyl 25 or 50 mcg; continue for 3-7 days.
2. Discontinue any short-acting opioids (if used) at least 24 hours prior to sublingual buprenorphine.
3. Remove fentanyl patch, and give 1-2 mg sublingual buprenorphine; observe for 20 minutes.
4. Increase to 8 mg if needed to manage withdrawal symptoms on the first day, and up to 24 mg over 3-7 days, as needed.

Behavioral health and other addiction treatments

What behavioral health treatments are required by the DEA waiver? The standard of care for opioid use disorder is for patients to be offered both medications and behavioral health treatment. The waiver requires physicians to offer referrals to behavioral health services, but patients are not required to accept them, and the services are not required to be onsite or in-person. Two trials are reassuring in areas with insufficient community behavioral health resources: One randomized controlled trial showed that buprenorphine is effective even without behavioral counseling[iii] and a 2016 American Society of Addiction Medicine review found mixed support in the literature for behavioral health interventions for opioid addiction.[iv] Nevertheless, most experts recommend a

comprehensive (medical and behavioral) approach where available. Addiction is a chronic illness that requires lifestyle changes. Behavioral and social therapies, as a supplement to medication treatment, can increase success in recovery.

How long do patients have to be in treatment before they are considered drug-free? Patients participating in treatment, taking buprenorphine, and avoiding other illicit substances are considered clean and sober by addiction specialists. Addiction specialists now consider opioid use disorder to be a chronic disease, and this perspective informs treatment. Instead of cutting people off of treatment when relapses or slips occur, an appropriate response would be to increase the intensity of monitoring.

> *"Providers and staff have to get used to a totally different perspective. When a patient is on pain meds, we don't refill early, and we try to cut doses down. When someone is on buprenorphine for addiction, we will work with them, including refilling early and raising doses when needed, because illicit drug use while on buprenorphine may not mean the treatment is failing. Rather, it may mean the dose is not sufficient to manage craving and withdrawal symptoms, or that the patient needs more behavioral health support. Likewise, we don't cut people off when they use marijuana or other drugs. Buprenorphine treats opioid use disorder – it doesn't treat marijuana use disorder. We don't cut off one treatment because the patient has more than one problem."*
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> *— Gary Pace, MD, medical director, Alexander Valley Medical Center*

How does buprenorphine compare to methadone? Buprenorphine and methadone have both been proven effective in opioid addiction.[v] Methadone has been shown to have a slightly higher retention rate in treatment; it is unclear if this is due to the medication or due to the wrap-around behavioral health services and the close monitoring that occurs in methadone programs. Methadone is better suited for patients who have psychiatric instability, severe poly-drug abuse, or functional instability needing close monitoring. The advantage of buprenorphine is that it is available in primary care, can be given to stable patients with follow-up once a month or every three months, and its partial agonist properties make it protective against overdose death. For a recent review of the evidence for treatment options, see the Vancouver Health Authority Opioid Addiction Guidelines, which recommends buprenorphine as first-line treatment, and methadone when a patient is unable to manage buprenorphine.

Conversion, tapers, and dosage

How should I convert from buprenorphine to another opioid? Buprenorphine is a very potent opioid. Out of caution, a factor of 30:1 to 90:1 (morphine milligram equivalents to buprenorphine) is used when converting from other opioids to buprenorphine. Conversion from buprenorphine to other opioids must be approached cautiously, at a much lower conversion ratio. Buprenorphine leaves the body slowly. If a full agonist treatment is used, it should be started at a low dose and increased gradually, as the buprenorphine wears off. For the treatment of addiction with buprenorphine, the target maintenance dose is 16 mg per day and does not use a conversion factor – the dose is based on the need to control cravings and prevent relapse, and the opioid dose used during active addiction is not relevant.

When should patients be tapered off of buprenorphine? Although buprenorphine can be used in short-term detoxification programs, addiction experts increasingly discourage this approach, and encourage continuing buprenorphine long-term.[vi] Patients who stop buprenorphine during the first few months of their treatment experience high rates of relapse,[vii] even with intensive behavioral support. In a 2015 long-term treatment trial, only 9% of patients remained abstinent after buprenorphine taper, while 80% of patients reported abstinence at 18 months and 42 months if they continued daily buprenorphine treatment.[viii] Without long-term treatment, people often return to the drug to which they were addicted, and the dose (or fraction of the dose) their bodies tolerated prior to treatment can lead to overdose death. Detoxification and tapering with buprenorphine is still superior to providing no medication assisted treatment at all, and can be considered in circumstances where timely follow up for continuation of buprenorphine is not available, or the patient specifically desires detoxification.

How do you taper off of buprenorphine? When tapering, smaller doses of tablets can be used by dividing the 2mg tablets into smaller segments. If a patient has addiction but no pain diagnosis, the smallest fraction that can be realistically achieved is ½ (1 mg) and ¼ (0.5 mg) of a tablet. Since swallowed buprenorphine has much lower bioavailability, swallowed buprenorphine tablets could be used at the latter stages of a taper. If the target condition is pain, then buprenorphine can be compounded by a specialty pharmacy to create low doses, or low doses of the buccal and patch formulations can be used. For example, one month of each strength of the buprenorphine patch (20, 15, 10, 7.5, and then 5 mcg/hour) is one effective method of gradually tapering buprenorphine to zero in a pain patient.

Should patients be discontinued from buprenorphine treatment if they are using marijuana, methamphetamine, or other drugs? Marijuana use has not been shown to worsen outcomes for patients on buprenorphine for opioid use disorder.[ix] The California Society of Addiction Medicine recommends continuing buprenorphine, and working with the patient to treat marijuana use disorder, if present. Patients may have more than one addiction: Buprenorphine may successfully treat opioid use disorder, while patients continue to need behavioral treatments for other active addictions to drugs such as methamphetamine or cocaine. Patients with active poly-drug use may benefit from the intensive treatment of an opioid treatment program, if available. If such programs are not available, these patients will be less likely to overdose, contract an infection, or have another negative outcome on buprenorphine than they would be on other opioids or street alternatives (a common pathway when opioids are abruptly discontinued).

What dosage formulations are available? Buprenorphine is schedule 3 (refills can be called in or faxed).

Formulation	Doses Available	Indication
Transdermal patch (Butrans)	buprenorphine: 5, 7.5, 10, 15, and 20 mcg/hour, every 7 days	Pain
Low-dose buccal film (Belbucca)	buprenorphine: 75, 150, 300, 450, 600, 750, 900 mcg, twice daily	Pain
High-dose buccal film (Bunavil)	buprenorphine/naloxone, daily: 2.1mg/0.3mg, 4.2mg/0.7mg, and 6.3mg/1mg	Addiction Off-label for pain
Sublingual tablets (Subutex, Suboxone, Zubsolv)	Dosed daily for addiction; divided doses for pain buprenorphine: 2mg, 8mg buprenorphine/naloxone: 2mg/0.5mg, 8mg/2mg; 1.4mg/0.36mg, 2.9mg/0.71mg, 5.7mg/1.4mg, 8.6mg/2.1mg, 11.4mg/2.9mg	Addiction Off-label for pain
Sublingual film (Suboxone)	buprenorphine/naloxone: 2mg/0.5 mg, 4mg/1mg, 8mg/2mg, 12mg/3mg	Addiction Off-label for pain
Implant	80 mg (equivalent to <8 mg sublingual daily)	Addiction Off-label for pain
Compounded	Many options	Pain

Buprenorphine for Pain (outpatient and inpatient)

Under what circumstances can buprenorphine be prescribed for pain? Any buprenorphine formulation can be used for a patient with a pain diagnosis by any DEA-licensed clinician without a waiver. The DEA clarified[x] that "limitations and requirements [relating to addiction treatment] in no way impact the ability of a practitioner to utilize opioids for the treatment of pain when acting in the usual course of medical practice. Consequently, when it is necessary to discontinue a pain patient's opioid therapy by tapering or weaning doses, there are no restrictions with respect to the drugs that may be used. This is not considered 'detoxification' as it is applied to addiction treatment."

If a patient has addiction but no pain diagnosis, the physician must have a DEA waiver and can only prescribe tablets and sublingual film (either buprenorphine alone, or buprenorphine with naloxone).

What are the advantages of buprenorphine compared to other opioids for pain? Buprenorphine provides excellent pain control, with no ceiling effect below 300 mg morphine equivalents. It has an excellent safety profile, due to a ceiling effect on respiratory suppression. Onset of action is 30-60 minutes, and it typically provides 8 hours of pain relief (so is usually given in divided doses when used for pain). Buprenorphine, unlike other long-acting opioids, has relatively few drug/drug interactions, and does not accumulate in patients with renal impairment. Due to long half-life, partial agonism at the mu receptor, and antagonism at the kappa-receptor, common medical problems seen with other long-acting opioids are less frequently seen with buprenorphine;[xi] these include sleep apnea, low testosterone, sexual dysfunction, osteopenia, opioid-induced hyperalgesia, mood disorders (depression and anxiety) and dysregulation of the hypothalamic pituitary adrenal axis. A growing body of

literature is finding improved pain relief on buprenorphine after conversion from other long-acting opioids.[xii] [xiii] [xiv] [xv]For example, one study of 35 patients found a mean decrease in pain score from 7.2 to 3.5, with 34 out of 35 patients reporting a pain decrease.[xvi] A Cochrane meta-analysis found buprenorphine superior to other opioids for pain relief in cancer (5 out of 11 studies) or equivalent (3 out of 11 studies).[xvii]

How do I convince patients to make the switch from other opioids to buprenorphine? Education about the medical side effects of opioids used over a long period of time often helps patients understand the rationale for change. Patients may be unaware that some medical problems are due to chronic opioid use, and that these issues may resolve after the transition: sedation, mood disorders (depression and anxiety), sleep apnea, erectile dysfunction are some of the more distressing problems for patients. Education about hyperalgesia and the common experience of withdrawal symptoms between doses, may convince patients to make the change. Some patients can be tapered off of anti-depressants and neuroleptic drugs. Other patients are motivated by the fact that buprenorphine is schedule 3 (refills can be called in), which decreases the hassle factor for patients.

Can buprenorphine be used in the elderly? For elderly patients already on long-term opioids, transitioning to buprenorphine lowers the risk of accidental overdose and potentially lowers the risk of medical complications (e.g., sleep apnea and hypogonadism). For this reason, buprenorphine may be a safer choice for elderly patients on daily opioid treatment. For elderly patients *not* currently taking opioids, the lowest dose of the buprenorphine-naloxone sublingual tablet formulation (2 mg) can be equivalent to 60-180 mg oral morphine a day, depending on the patient's metabolism, and would be too high a dose. Buprenorphine products in the form of a transdermal patch or buccal film come in much lower doses and can be therefore used in patients with no opioid tolerance.

How should patients on buprenorphine be managed in the hospital? Some hospital protocols still require buprenorphine to be discontinued, but this approach is not evidence-based. Continuing buprenorphine, with additional analgesia when needed, has been shown to be an effective way of managing inpatient and peri-operative pain.[xviii] Additional doses of buprenorphine, or other opioids, can be given simultaneously with maintenance buprenorphine for good pain relief. In small cohorts, continuing buprenorphine lowered length of stay with better or equal pain control.[xix] Another advantage of this approach is preventing the need for another induction to get back on buprenorphine.

Can patients be induced on buprenorphine in the emergency department? Gail D'Onofrio, MD, MS, from Yale University conducted a randomized controlled trial of starting buprenorphine in the ED for addiction and found that those given buprenorphine had twice the 30-day retention rate (78%) in treatment compared with referral (37%). Buprenorphine is a safer pain medication for patients with active or historical substance use, and can be used IV or IM while in the emergency department, or for take-home doses after discharge. Some California emergency departments are beginning to do buprenorphine inductions while the patient is in the ED, or giving patients instructions for home induction, combined with expedited referral to outpatient treatment. CHCF is connecting emergency physicians interested in piloting this treatment; contact CHCF's Director of High-Value Care Kelly Pfeifer, MD, at kpfeifer@chcf.org for more information.

Should buprenorphine be used for pain in the emergency department (ED)? Buprenorphine for pain can be used in the ED by clinicians without a waiver (sublingual, buccal, transdermal, IV, or IM). Advantages to buprenorphine as a first-line opioid analgesic include a lower abuse potential, lower risk for respiratory depression, better efficacy among patients with chronic pain, and long duration. As with all opioid analgesics, buprenorphine should be used sparingly for pain after both non-pharmacologic inventions and non-opioid analgesics have failed. Buprenorphine can be administered or prescribed for pain by any clinical provider with DEA opioid prescribing authority.

GENERAL QUESTIONS

Where can patients find buprenorphine-waivered physicians?

SAMHSA treatment finder: https://findtreatment.samhsa.gov/

How do you get buprenorphine approved by insurance or Medi-Cal? What is a TAR?

Medi-Cal does not require prior authorization (Treatment Authorization Requests or TARs) when using buprenorphine for addiction. When prescribers write their x-number on the prescription pad, and write "Dx: Opioid Dependence," then the prescription will be covered by Fee-For-Service (FFS) Medi-Cal without an authorization review. Not all pharmacies realize that these prescription claims should *not* be sent to the managed Medi-Cal plan. Prescribers starting to use buprenorphine should reach out to local pharmacies and confirm that they stock buprenorphine, and that pharmacists know the procedure for billing state Medi-Cal directly.

In contrast, ***Medi-Cal requires a TAR for buprenorphine when used for pain without addiction.*** The prescriber can write the justification on the prescription, such as "chronic pain due to ____ diagnosis; at high risk, currently on ____ regimen; buprenorphine is indicated for pain and for a more favorable safety profile." The pharmacist will use this information to complete a TAR and send to FFS Medi-Cal for review.

Medicare Part D plans are required as of April 2016 to cover buprenorphine, but may require justification (in the form of prior authorization). Information written on the prescription to justify its use will expedite the pharmacy's ability to obtain authorization.

Commercial insurance plans have different rules about buprenorphine coverage for pain and addiction, and may require a call or completion of an authorization form by the prescriber.

What is the Drug Medi-Cal Organized Delivery System Waiver? The Drug Medi-Cal Organized Delivery System (DMC-ODS) changes the way Medi-Cal substance use services are delivered. Instead of providers contracting directly with the state, for counties that "opt-in," providers will contract with the county. The county will be responsible for offering the continuum of care for patients with substance use disorder, modeled after the American Society of Addiction Medicine criteria. The program is launching in phases: Bay Area (Phase I), Southern California (Phase II), Central Valley (Phase III), Northern California (Phase IV), and the Tribal Delivery System (Phase V). For more information, see the Department of Health Care Services website.

How do federal regulations and California state law affect documentation requirements in primary care? Both federal regulations (at 42 C.F.R. Part 2) and California law (Cal. Civil Code Section 56.11) include restrictions on disclosure of patient information related to substance use disorder treatment that are stricter than those for other health information. The applicability of these rules varies depending on the type of provider and the sources of funding. For more information, see *Fine Print: Rules for Exchanging Behavioral Health Information in California;* and resources from the American Society of Addiction Medicine and SAMHSA.

ENDNOTES

[i] Dr. Kornfeld is a nationally known researcher and addiction and pain specialist with a practice in Marin County. He is on faculty at UCSF and was the founding medical director of an integrated pain and addiction clinic at Highland Hospital for low-income patients.

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[xvi] Daitch et al., "Conversion from High-Dose Full-Opioid Agonists to Sublingual Buprenorphine Reduces Pain Scores and Improves Quality of Life for Chronic Pain Patients," Pain Medicine 2014; 15:2087-2094.

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