

Clinical Pearls for Buprenorphine Treatment

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Abstract

Buprenorphine, a highly effective yet underutilized medication for opioid dependence, is crucial to tackling the current global opioid epidemic. Multiple studies have identified the need for more clinical information to increase confidence in delivering buprenorphine treatment. This article provides a practical guide to assist in educating inexperienced buprenorphine prescribers on relevant subjects involved in inducting, stabilizing, maintaining, and discontinuing patients on buprenorphine. This guidance intends to serve as a useful resource, particularly in low-resource or rural settings, to empower practitioners in buprenorphine treatment to expand the numbers of prescribers necessary to assist in diminishing the unrelenting opioid crisis.

Keywords: Buprenorphine, Induction, Maintenance, Discontinuance, Clinical guidance

Introduction

Buprenorphine (BUP), approved in 2002 and available since 2003, is one of three FDA-approved medications to treat opioid use disorder. To prescribe BUP, training and a SAMHSA waiver are required to receive a DEA 'X' number. Caps are placed, allowing providers to prescribe BUP to 30, 100, or 275 patients depending upon the length of time prescribing BUP and type of the practitioner. Eighteen years after BUP hit the market and in the middle of a global crisis of opioid overdose, BUP remains an underutilized medication as a sizable number of practitioners are still not utilizing this prescriptive privilege [1] to help mitigate the current opioid epidemic.

Many providers have not obtained an X-waiver and not all X-waivered practitioners prescribe BUP; a majority of those who are waivered do not prescribe to capacity [2]. Studies have found that approximately 44% to 66% of X-waivered physicians actually prescribe BUP [3-9]. The gap in treatment demand versus treatment supply is estimated at 1.4-1.5 million people in 2012 [5]. Given the growth of the epidemic, this likely underestimates the current need.

Various reasons explain the hesitancy to prescribe BUP, including lack of knowledge, training, and experience including concerns of induction logistics and precipitating withdrawal; confidence in providers and staff; perceived complexity of patients with opioid use disorder; and lack of available resources and support. Another reason cited is a lack of access to expert consultation [2,4,6; 9-13]. Physician confidence has been associated with more favorable practices regarding treatment of substance use disorders [14]; therefore, multilevel educational interventions that include academic detailing and clinical mentoring, along with establishing strong practitioner collaborative networks, are effective strategies to increase physician likelihood of prescribing and to increasing patient capacity [15,16]. Legislation is pending in Congress to deregulate the BUP prescribing process and remove training requirements. The premise being that BUP is a safe and effective treatment for opioid use disorder and that more practitioners will prescribe if the training requirement is waived [17]. While this waiver of training may increase the

number of individuals willing to start prescribing, as in all aspects of medicine, some minimum level of training is needed for competency in providing clinical care.

This article provides practical, clinical instruction for medical personnel treating patients with opioid use disorder, specifically for inducting, stabilizing, maintaining, and discontinuing patients on sublingual and transmucosal BUP. It provides relevant information surrounding the clinical application of BUP in the absence of a readily available expert.

Buprenorphine

BUP is a partial opioid agonist at the mu (μ)-opioid receptor and an antagonist at the kappa (κ)-opioid receptor. This means that BUP can produce typical opioid effects and side effects such as euphoria (in opioid non-dependence) and respiratory depression; however, its maximal effects are less than those of full agonists like heroin and fentanyl. BUP produces agonist effects to enable opioid-dependent individuals to discontinue opioid use without experiencing withdrawal symptoms. Its effects reach a plateau, where the effects no longer continue to increase with further increases in dose, causing a "ceiling effect." BUP is able to block the effects of opioids and can precipitate withdrawal symptoms if administered to an opioid-dependent individual while an opioid is occupying the opioid receptors. Thus, BUP carries a lower risk of abuse, overdose, and side effects compared to full opioid agonists [18,19].

BUP has poor oral bioavailability, and swallowing the medication renders it 90% inactive after first-pass hepatic metabolism [20]. Sublingual administration circumvents this first-pass hepatic metabolism, with most studies demonstrating moderate sublingual absorption. BUP has a long half-life ranging from 20-73 hours. Sublingual BUP has an onset of effect between 30-60 minutes post-dose with peak effect observed at 1-4 hours. The duration of effect at a low dose (< 4 mg) ranges from 6-12 hours and 24-72 hours at a higher dose (>16 mg) [21].

Subutex® contains buprenorphine only. Suboxone® contains buprenorphine with a 4:1 ratio of naloxone (Narcan®). Naloxone is added to Suboxone to deter use by injection. Naloxone (NLX), an antagonist at the μ -opioid receptor has poor availability sublingually (approximately 3%), so when taken simultaneously with BUP, the BUP agonist effect dominates, therefore, withdrawal is not precipitated. When NLX is used intravenously (IV), subcutaneously or intramuscularly, its bioavailability reaches 98% [22]; thus, if BUP is crushed and injected, patients may develop some symptoms of withdrawal (e.g., abdominal pain and nausea). When explaining to patients, it can be said that NLX only 'activates' if injected. Oftentimes, patients incorrectly believe the NLX is the "blocker" rather than BUP.

That said, studies have reported that sublingual absorption of NLX is not negligible [23] but rather about 25%, [24] and increases with ongoing sublingual doses [25]. Several studies have reported that BUP/NLX used IV produced subjective effects of sublingual BUP but did not precipitate withdrawal [26-28]. These reports mitigate the assertion that IV BUP/NLX universally precipitates opioid withdrawal.

Opioid Agonist/Antagonist Properties

Because of the opioid agonist/antagonist properties in BUP, it typically is much less sedating than other opioids [21]. BUP itself is not a sedative, but some of its active metabolites are [29]. Despite that, BUP's effect on cognitive and psychomotor function was found to be comparable to placebo [30]. Studies have shown that BUP can decrease depression and anxiety [31-36]. These antidepressant and anti-anxiety properties are likely due to BUP being a potent κ -opioid antagonist, which also could contribute to its pain management properties, [21,37,38] or to some degree, due to a placebo effect [39].

Effectiveness of BUP vs. Methadone on Opioid Receptors

BUP is quite efficient. Data suggest that a 16 mg dose of BUP fills between 79%-95% of opioid receptors [40], likely because of high binding affinity. In comparison, a therapeutic methadone dose fills about 1/3-1/2 of the opioid receptors [41,42]. Regardless of the number of receptors occupied, the goal

of treatment is to support abstinence rather than only fill enough receptors to prevent withdrawal. It is essential to use an ample dose of BUP to achieve opioid blockage to assuage the reinforcing subjective and physiological effects of opioid use [43]. This may mean a dose of greater than 16 mg may be warranted in individuals who continue to use opioids [44] or metabolize BUP quickly. Dosages higher than 24 mg have not been demonstrated to provide any clinical advantage [25]. Higher doses of buprenorphine can suggest that the patient is not appropriately administering the medication sublingually (e.g., swallowing and the medication is lost to hepatic metabolism) or a sign that the patient wants a higher dose to divert tablets illicitly.

Buprenorphine is a Blocker

BUP displays high affinity (attraction to the opioid receptor), non-selective binding to multiple opioid receptors (δ , κ , and particularly the μ receptor) [45-47]. BUP is also slow to reach full binding effect, has a long duration of action [48], and dissociates very slowly [49]. Simply put, because BUP binds tighter and longer to multiple opioid receptors, it can block other opioids from occupying opioid receptors. When individuals use short-acting opioids after BUP administration, even more potent opioids, they are less likely to feel effects, such as euphoria [50]. However, the effect of BUP is time- and concentration-dependent upon the dose, therefore, high doses of other opioids can alter BUP placement.

How Buprenorphine Works

When individuals use BUP too soon after using a full opioid (e.g., heroin, methadone, oxycodone, morphine) and not enough withdrawal has occurred, BUP can precipitate withdrawal by displacing opioids from the receptor because of its high binding affinity. It then occupies more receptors yet produces a lesser effect than other opioids (low intrinsic activity) [21,25]. This is why it is crucial when initiating BUP to have empty opioid receptors (patient is in partial withdrawal at a minimum) and to start with a lower dose on the initiating day. Day 1 of induction is meant to fill the empty receptors only. The dose on the first day may not last 24 hours, but too high of an initial dose can precipitate withdrawal.

Induction, Maintenance, and Taper

Clinical Induction

The medically monitored initiation of BUP therapy is called induction. Abstinence of short-acting opioids should be a minimum of 12 hours (48-72 hours for long-acting opioids), but it is essential to inform patients to abstain long enough so that they present in visible, mild to moderate withdrawal as patients know the length of time it typically takes to enter withdrawal (often more than 12 hours). High potency synthetic opioids (such as fentanyl and its derivatives) may precipitate withdrawal even with abstinence of 72 hours from the last opioid use. The ability of BUP to displace fentanyl from opioid receptors along with fentanyl accumulation in fat and muscle tissues from repeated use may at least partially account for the precipitated withdrawal. More extended abstinence periods or alternative approaches (e.g., supplemental methadone, tramadol, clonidine, or hydroxyzine) may be utilized until BUP can be initiated [51].

A modified induction for individuals using Fentanyl has been reported by administering four, 2 mg sublingual doses of BUP/NLX at dose intervals ranging from 85 to 385 minutes without precipitating withdrawal [52]. Other inpatient buprenorphine or BUP/NLX inductions from full agonists without

periods of abstinence have been demonstrated utilizing microdosing at multiple dosing intervals over the course of several days [53,54].

A brief orientation before induction helps patients understand the basics of how BUP functions (Figure 1), why partial opioid withdrawal is necessary, and the consequences of induction if withdrawal is feigned or started too soon. Naloxone exposure is higher with the transmucosal formulation (versus sublingual), so sublingual dosing on Day 1 is recommended to minimize exposure to naloxone and thus withdrawal [55]. If no office visit is scheduled for Day 2, it is recommended that that provider contact the patient to ascertain how the remaining Day 1 ensued and how (s)he is feeling. Below are suggestions for Inductions Day 1 and Day 2 (Figure 2-4).

Unobserved or 'Home' Induction

Home inductions have gained popularity as the number of BUP naïve individuals is diminishing with significant numbers of induction-experienced patients increasingly requiring less instruction or observation. It can be challenging to coordinate being in withdrawal with an induction appointment time, even if in the morning. It is inconvenient to attend medical appointments for two consecutive days; therefore, home inductions provide an accommodating alternative to office dosing if both provider and patient feel comfortable doing so. Home inductions can be safe and effective with retention rates similar to office inductions [56]. The provider needs to be available for patient questions or concerns during this time and to see the patient if needed. It is recommended that the provider contact the patient on Day 2 to determine if the induction went smoothly or the next steps if induction was not seamless. Random urine toxicology screens should be administered to assure ingestion of BUP rather than diversion. See Figures 5a and 5b for a Home Induction template.

Single Dosing and Steady State

BUP is approved by the Food and Drug Administration to be administered sublingually as a single daily dose. In most patients, a maintenance dose of BUP is attained in 2-4 days with a steady-state blood level achieved in 3-7 days [25]. It is necessary to assess the patient weekly for the first two weeks to assure proper dosing that alleviates both cravings and withdrawal.

Side Effects

BUP side effects are similar to those of other opioids, but considerably less intense in comparison; side effects such as nausea, vomiting, headache, drowsiness, dizziness, sweating, miosis, anticholinergic-like effects (constipation, dry mouth, urinary retention, memory loss), insomnia, sexual side effects, and lowering of the seizure threshold. BUP may cause central nervous system depression, hypotension, orthostatic hypotension, and QT prolongation [25,57].

Buprenorphine Excess

The most common effects of BUP excess are similar to withdrawal symptoms usually with a headache, [58] nausea (vomiting), or sedation typically later in the day. For example, if the patient doses at 8 am, (s)he may experience a headache daily around 4 pm; nausea tends to be earlier. People often do not associate that these symptoms could be due to the BUP ingested hours prior. It is important to educate patients of these symptoms to inform the prescriber should any occur so that a dose decrease may be considered. Package inserts may provide updated side effects and symptoms of buprenorphine excess.

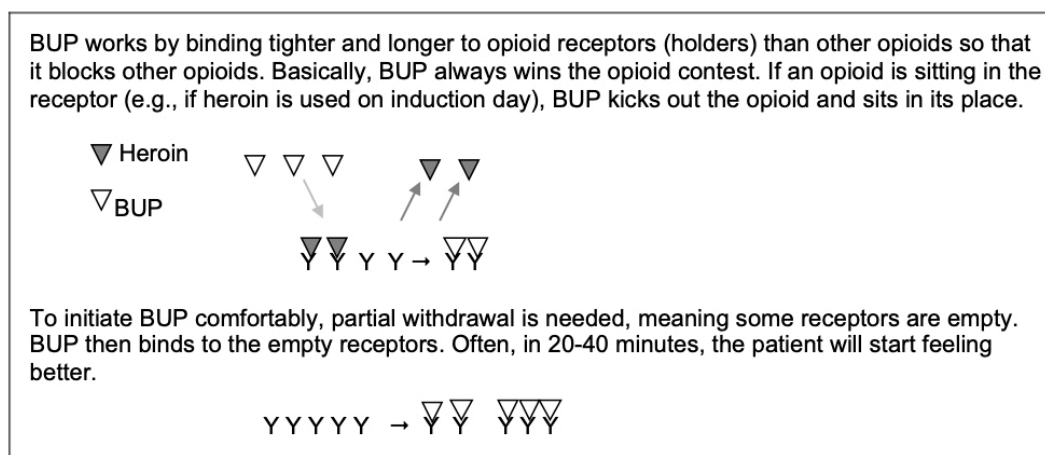


Figure 1: Explanation to patients: why partial withdrawal is important for induction.

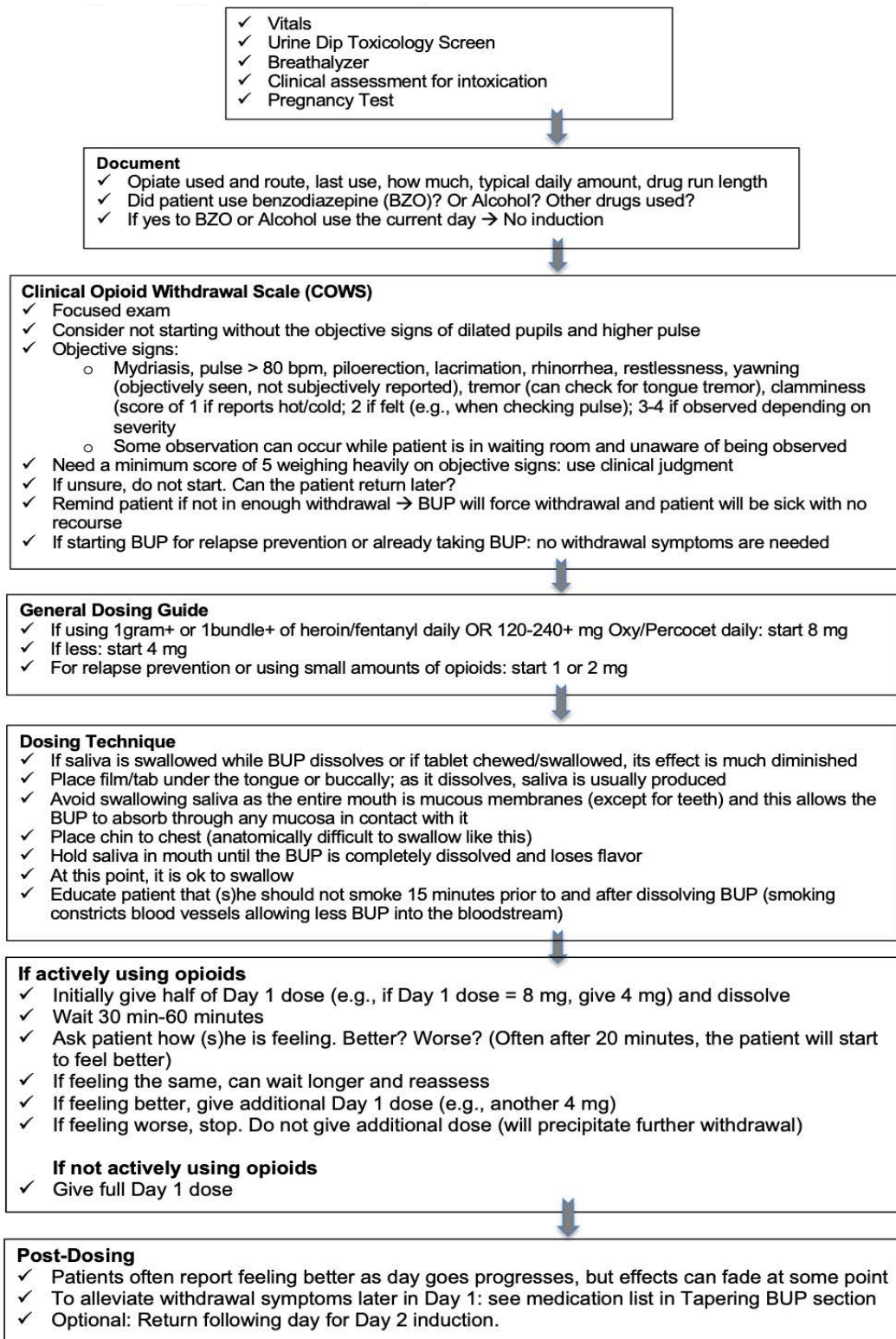


Figure 2: Suggestions for induction on day 1.

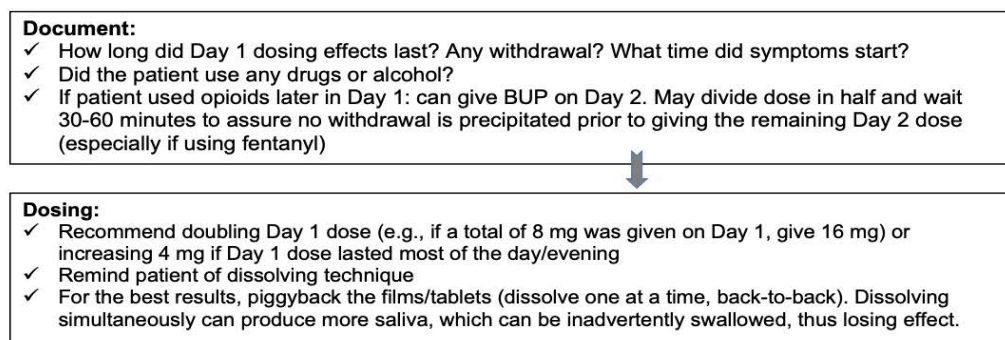


Figure 3: Suggestions for induction on day 2 (Optional).

Orientation Topics
Typically on Day 1 or 2 while dissolving:

- How opioid use leads to tolerance and then dependence
- Full opioids vs. buprenorphine
- How buprenorphine works: Why partial withdrawal is important in induction
- How buprenorphine blocks opioid effects such as euphoria
- Buprenorphine is not typically sedating like methadone and other opioids
- Proper buprenorphine dissolving techniques
- Signs/symptoms of buprenorphine excess
- Difference between Suboxone® and Subutex®
- Inform provider prior to medical procedures
- Dangers of mixing opioids including buprenorphine with benzodiazepines and alcohol
- Take-home or prescription schedule
- Clinic expectation and rules
- Two parts to addiction: physical and psychological

Figure 4: Orientation topics.

When to start Suboxone

- ✓ Use the list of withdrawal symptoms below to see if you are ready to start Suboxone
- ✓ Wait until you have **at least 5 - 6 symptoms**
- ✓ See directions below on how to take your pulse (heartbeats per minute)
- ✓ If you don't have at least 5 symptoms, wait a bit longer and review the symptoms again
- ✗ If you start Suboxone too soon, it will cause more withdrawal and you will be really sick! It is worth waiting to have more withdrawal symptoms naturally.

Symptoms	Do I have this?
Pulse is at least 80 beats per minute	Yes
I have hot/cold flashes	Yes
I have stomach cramps or nausea	Yes
I have diarrhea	Yes
I have goosebumps	Yes
I am yawning a lot	Yes
I am sweating a lot	Yes
My bones/joints/muscles ache more than usual	Yes
My hands are shaking	Yes
My nose is running	Yes
My eyes are watering	Yes
My pupils are large	Yes
I feel restless and am unable to sit still	Yes
I have no appetite	Yes



How to check for Pulse

- ✓ Place 2-4 fingers below your thumb in the wrist groove
- ✓ Press lightly
- ✓ Find heartbeat
- ✓ Count number of beats in 30 seconds.
- ✓ Multiply this by 2

Example: 40 beats in 30 seconds x 2 = 80

My pulse: _____

How To Take Suboxone

- ✓ Before taking Suboxone, **drink water**
- ✗ **Do not smoke** 15 minutes before or after dissolving Suboxone (smoking causes blood vessels to become small and less Suboxone can get into your bloodstream)
- ✓ Place film or tablet under your tongue
- ✓ Place your **chin to touch your chest** (it is difficult to swallow like this) and hold your saliva while you dissolve
- ✗ **Do not swallow** when saliva is produced
- ✗ **Don't eat or drink** anything or talk until the film has dissolved
- ✗ **Try not to talk** while dissolving
- ✗ **Once Bup is dissolved** and some taste goes away, **swallow.**

Figure 5a: Home induction template for patients (Part 1).

Plan

- ✓ Time of last heroin / pain pill: _____
- ✓ Wait at least 12 hours.
- ✗ If you are taking methadone, you must skip **at least** one day of dosing.
- ✓ Even if it has been more than 12 hours, when you have **at least** 5 symptoms from the list above, you can start Suboxone.
- ✓ Start with _____ film under your tongue. Place your chin to touch your chest and don't swallow.
- ✓ Wait at least 30 minutes after the film has dissolved.
- ✓ If you feel the same, wait a bit longer. If you feel a little better, then place an additional _____ film under your tongue and dissolve without swallowing.
- ✗ If you feel worse or sick, **DO NOT TAKE MORE.**
- ✓ On Day 2, take _____ film(s). If it is two films, dissolve one. When that has finished, place another film in your mouth and dissolve (piggybacking films). Taking two at once causes more saliva to be produced, which increases chances of swallowing the Suboxone and losing some effect.
- ✓ Continue this dose until your next appointment.

Problems or Questions

- ✓ Call _____ at phone #: _____ especially if you feel sick or feel your dose is not right.
- ✓ Go to the emergency room if you cannot reach someone, have problems, feel very ill or feel it is an emergency (you can also call 911 for an emergency).

Next Steps

- ✓ Your next appointment time to see the medical provider is: _____.
- ✓ Your counseling appointment with _____ is: _____.

DON'Ts

- ✗ DON'T use Suboxone when you are high—it can make you very sick (sudden withdrawal)
- ✗ DON'T use Suboxone with alcohol — this combination is not safe
- ✗ DON'T use Suboxone with benzos (Xanax, Klonopin, Valium, Ativan, etc.) unless prescribed by a medical provider who knows you are taking Suboxone
- ✗ DON'T use Suboxone while taking painkillers. Please talk to your medical provider first
- ✗ DON'T use Suboxone if you are taking more than 30 mg of methadone
- ✗ DON'T swallow Suboxone – much more gets into your bloodstream by dissolving under your tongue
- ✗ DON'T lose your Suboxone – it cannot be refilled early

Figure 5b: Home induction template for patients (Part 2).

Taste

Buprenorphine is bitter. If patients find the taste unbearable, a piece of candy or tic-tac can be placed on the dorsal surface (top) of the tongue to offset the taste. However, the patients need to be sure not to suck on the tic-tac as sucking triggers swallowing, which reduces the absorption of BUP. Another alternative is to place the film buccally between the cheek and gum to increase the distance from the taste buds.

Twice-Daily Dosing

Individuals may be rapid metabolizers (phenotype P4503A4 [CYP3A4*1B]) requiring higher doses of BUP or twice daily dosing. It has been suggested that the recurrence of urges or cravings to use may be a psychological effect of long-term, multiple daily dosing of short-acting opioids. Twice daily dosing for these individuals mirrors their drug-use pattern and allows them to feel better psychologically about BUP effectiveness [59]. Along these lines, but yet different to cravings and urges, prescribers of BUP will attest that patients report BUP can cause an increase in energy [60]. Because of this, twice daily dosing can introduce two issues with PM dosing. BUP has been associated with difficulty sleeping [61,62]; therefore, PM dosing may interfere with sleep. In addition, patients' report experiencing a "bump" in the PM after dosing with BUP. Twice daily dosing can then encourage a continuance of drug use behaviors by taking BUP to assist with increased energy. Once-daily dosing can be encouraged to resolve these issues.

Two and Three Times a Day Dosing: Pain Control

BUP has been studied for the treatment of cancer and noncancer pain; neuropathic, bone, and heat pain; pain related to nerve growth factor injections, musculoskeletal, visceral, and cold pressor pain as well as for chronic headaches [21,63]. The analgesic action of BUP is, on average, 6-8 hours (range 4-9 hours), so to address pain management and for optimum analgesic effect, it is recommended that sublingual or buccal BUP be administered 3-4 times a day [64,65]. However, Neumann et al. reported a statistically significant decrease in pain (P = 0.043) with sublingual BUP/NLX in once-daily administration with an average daily dose of 14.93/3.73 mg [66]. Since sublingual doses of 16 mg bind to 79% to 95% of the μ opioid receptors, doses higher than 24-32mg do not produce any greater opioid effect [40,67]. Opioid treatment programs can justify the use of BUP (and methadone) for pain control by documenting that it is being used to assist with pain issues while treating for opioid use disorder.

Alternate Day Dosing

It is recommended to dose with BUP daily. Due to BUP's slow dissociation from the receptor (or long half-life), alternate-day dosing can be considered in individuals with negative toxicology screens who have stabilized on daily BUP. Alternate-day dosing can be advantageous in an opioid treatment program where take-home medication privileges are subject to federal regulations or program policies, and when daily clinic attendance is a hindrance to treatment.

Studies recommend for dosing every other day doubling the daily dose. For example, if the dose is 16 mg, then every other day the patient would receive 32 mg [68]. Patients who attend clinic three times weekly, on Monday and Wednesday should receive twice the daily dose, and then on Friday receive a triple dose [67] or a dose 50% higher than the Wednesday dose [69]. For example, if the dose is 12 mg, the patient would receive 24 mg on Monday and Wednesday, and then receive 36 mg on Friday. Alternate dosing also reduces the risk of diversion associated with take-home doses and can be cost-effective [21].

Sublingual/Transmucosal Buprenorphine Formulation Bioavailability

Bioavailability is the amount of medication to reach the systemic circulation. Variability among individuals in transmucosal BUP pharmacokinetics is high, perhaps due to individual variability in absorption [70]. Table 1 details buprenorphine/naloxone dose conversions for sublingual and transmucosal formulations.

Suboxone Film®: A study showed that compared to the tablet, a single dose of 8/2 mg film produced 20% higher systemic BUP exposure and 28% peak BUP concentration; however, the pharmacokinetic data did not provide a firm conclusion that the efficacy of Suboxone 8/2 mg films are equivalent to, or better than, the efficacy of Suboxone tablet. The 2/0.5 mg film showed better bioavailability to the 2/0.5 mg tablet with a 22% higher peak BUP concentration with the film. The BUP/NLX disintegration times were measured at 1- 6 minutes for the film, with dissolving time for the tablets between 7-12.4 minutes [71,72].

Zubzolv® Tablets: This BUP/NLX formulation was found to have higher bioavailability, better taste, and faster sublingual dissolve time than a reference sublingual Suboxone tablet [73], with a 12% lower NLX exposure. The median dissolve time was observed at 5 minutes [74].

Bunavail® Film: This BUP/NLX formulation uses a BEMA® (bio-erodable muco-adhesive) technology applied to the buccal mucosa. It has a higher bioavailability than all other transmucosal products [71] found to be almost double that of the Suboxone tablets [55]. Dissolution time was about 30 minutes or less in this study [71].

Methadone to Buprenorphine Transition

It is recommended to decrease methadone (MTD) slowly at a pace that allows the patient to remain comfortable and stable. Ideally, individuals in an outpatient setting should be on MTD 30 mg or less and remain on 30 mg for at least one week prior to transferring to BUP [75]. Transitioning at higher doses of MTD or rapidly tapering MTD to 30 mg to transition typically causes discomfort due to the long elimination half-life (30 ± 7.7 hours) [76] and accumulation of MTD in the system. However, a multisite prospective cohort study of 33 patients reported effective transitions of patients to BUP on less than 50 mg MTD [77].

Patients need to discontinue MTD for 48-72 hours (up to 96 hours) before BUP is initiated. This means that if the patient doses on Monday, Tuesday is 24 hours post-dose, and Wednesday is 48 hours; therefore, if found to be in enough withdrawal, the patient can start BUP on Wednesday after missing one day of MTD dosing. For doses higher than 30 mg of MTD, patients should remain off MTD and other opioids for longer than 48 hours. As the time interval between the last MTD dose and the first BUP dose increases, the likelihood of precipitating withdrawal decreases [78].

When transitioning from a long-acting opioid (i.e., MTD) to BUP, it is recommended to use BUP monotherapy (Subutex) for the first day (or two) as a small amount of NLX could cause precipitated and prolonged withdrawal [25,79]. Studies have shown that up to 50% of individuals transferring from monotherapy to BUP/NLX experienced side effects, predominantly gastrointestinal, fatigue, sweating, and headache [79,80]. It is thought that pseudo-allergies are frequently reported as well, including headaches, nausea, diaphoresis, agitation, and general dysphoria [79].

Titration on Day 1 should remain 4 mg or less to avoid precipitated withdrawal [81]. After a thorough COWS assessment with objective signs (particularly dilated pupils and higher pulse), it is recommended to administer 2 mg of BUP during the office visit, then monitor for a minimum of 30-45 minutes to ensure

withdrawal is not precipitated. To increase the length of time since last MTD dosing, this author recommends providing the patient a take-home dose of 2 mg dose to take should the patient feel withdrawal symptoms later in the day or evening. For Day 2, double the dose of Day 1. Rapid titration to a stable dose compared to slow and medium rate titrations have demonstrated statistical superiority. [81] A case series reports inpatient inductions of individuals on methadone to BUP/NLX without any abstinence on doses as high as 100 mg methadone utilizing microdosing in multiple dosing intervals over the course of several days [82].

When transitioning from MTD to BUP, this author has noted that during the first week (usually day 3 or 4), the BUP dose sometimes needs to be increased temporarily for 1-2 weeks due to continued withdrawal symptoms. It is important to check-in with the patient to assess for this. In the first month, weekly visits to monitor are helpful to determine if/when the BUP dose needs to be lowered. Patients will typically report headaches, but also can express having nausea, or sedation later in the day as symptoms that would indicate lowering the dose.

Buprenorphine to Methadone Transfer

Because BUP is already on board occupying opioid receptors with a higher affinity than MTD, MTD can be administered the day after BUP ingestion with no period of abstinence. The patient will not experience precipitated withdrawal. Because of the tight-binding (high affinity) and slow dissociation of BUP, the patient may not feel the full MTD dose as BUP will block a portion of the MTD dose, particularly on the first day of MTD dosing.

Tapering Buprenorphine

It is recommended that patients taper to discontinue BUP at a comfortable pace. As in tapering of all treatments for opioid use disorder, it is critical that the patient has a sustainable support system beyond treatment with the opioid agonist. Patients who taper off medication and discontinue the social intervention of seeing a therapist or medical provider are at risk of relapse if they lack an ongoing sober community that can provide support.

Some prefer to decrease in 2 mg increments for a period of time, although for doses higher than 8 mg daily, it may be comfortable to reduce 4 mg at a time. If at any point, tapering becomes uncomfortable, pausing the taper or decreasing more slowly is suggested. The author suggests then tapering by alternating doses daily. For example, take 8mg one day and then 6 mg (3/4 film/tablet) the following day, alternating like this daily for a given time (e.g., one month); then take 6 mg daily for a period of time (e.g., one month), followed by alternating again at a lower dose 6 mg one day, then 4 mg (1/2 film/tab) the next, and so on. Once at 1 mg daily, dosing 1 mg every other day for a length of time can conclude the taper.

Some prescribers give BUP monotherapy on doses of 4 mg or less with the thought that the NLX causes agitating symptoms that mimic withdrawal (see Methadone to BUP Section above for explanation); thus, patients often find monotherapy more comfortable and easier in the tapering process [79]. Patients report that they may feel one or more mild withdrawal symptom(s) for 3-6 days when initially reducing the dose. At some point, withdrawal symptoms may be unavoidable; however, BUP withdrawal symptoms have generally been reported to be less than that of other opioids [75].

Medications may help alleviate withdrawal symptoms the patient is experiencing. Dopamine system modulation has been implicated in opioid withdrawal and can be a target for some opioid withdrawal symptoms [83]. Avoid all medications that have addictive potential such as benzodiazepines. Medications that may be helpful are:

- Insomnia: hydroxyzine, trazodone, mirtazapine, quetiapine, melatonin, diphenhydramine
- Myalgias/Arthralgias: NSAIDs, acetaminophen
- Anxiety: hydroxyzine, clonidine
- Akathisia: pramipexole, hydroxyzine, clonidine
- GI motility: dicyclomine
- Nausea: ondansetron, promethazine, metoclopramide, meclizine, diphenhydramine

Table 1. Sublingual/Transmucosal dose conversion chart for buprenorphine/naloxone.

Suboxone SL Tablet	Suboxone SL FILM	Zobzolv SL Tablet	Bunavail Buccal Film
2 mg/0.5 mg	2 mg/0.5 mg	1.4 mg/0.36 mg	
4 mg/1 mg	4 mg/1 mg		2.1 mg/0.3 mg
8 mg/2 mg	8 mg/2 mg	5.7 mg/1.4 mg	4.2 mg/0.7 mg
12 mg/3 mg	8 mg/2 mg + One 4 mg/1 mg or Two 2 mg/0.5 mg Films		6.3 mg/1 mg

- Overall/Multiple Symptoms: quetiapine [84], hydroxyzine, clonidine, lofexidine.

Lofexidine is equivalent in efficacy to clonidine with fewer adverse effects for the management of opioid withdrawal symptoms; however, the cost may be prohibitive [85].

BUP Cessation and Naltrexone

BUP has been shown to deposit into 13 major tissues in the body following sublingual dosing [86] and has an active metabolite, norbuprenorphine that can induce withdrawal if challenged with naltrexone.[87] Due to the elongated action of BUP and its metabolite; withdrawal symptoms can linger after BUP cessation. The abovementioned medications can assist with any protracted withdrawal symptoms.

The most frequent patient concerns regarding BUP cessation are often related to relapse to illicit opioid use and withdrawal [88] and thus, remain on BUP due to these fears [89]. A medication that may mitigate these fears is naltrexone (NTX). It is a non-opioid, long-acting competitive antagonist at opioid receptors that does not activate the opioid receptor. NTX displaces opioids, occupies opioid receptors, and then blocks other opioids as well as the euphoric effects of opioids. Its half-life is 3.9-10.3 hours with a slow terminal elimination half-life of 96 hours [90]. An individual must be opioid-free for 7-10 days before starting NTX [91] (the author recommends 14 days, especially after MTD cessation). A low dose of NTX has been shown to attenuate withdrawal intensity and noradrenaline release following the opioid taper [92]. A literature review of perspectives and outcomes of discontinuation of BUP maintenance therapy reported the two studies with the best outcomes included a transition to NTX maintenance after successful completion of BUP taper [93,94]. NTX implants and intramuscular injections have been shown to reduce opioid cravings and use [95,96], though the orally administered NTX did not, primarily due to poor treatment retention [97].

Special Topics

Pregnancy

Monotherapy BUP is recommended with pregnancy and is classified as category C. Recently, studies have shown safety with no adverse effects in taking BUP/NLX [98,99], but this is not the current guideline to date. Induction in pregnancy should occur as with a non-pregnant female. Dose increases in pregnancy may or may not be needed. More frequent dosing to twice a day may be necessary as dose-adjusted BUP plasma concentrations are significantly decreased during pregnancy compared with non-pregnancy [100]. BUP does cross the placenta and was shown to have less than 10% of maternal dose transferred to the fetal circuit, with only 5% of perfused BUP metabolized to norbuprenorphine [101]. The current recommendation for C-sections is that BUP not be discontinued but rather to override the BUP blockade if opioid medications are necessary. Postpartum BUP with three- and four- times daily dosing may be used for more analgesic effect along with other analgesics [102].

Newborns should be monitored for drowsiness, respiratory depression, adequate weight gain, and developmental milestones [103]. A randomized, double-blind control study of BUP reported significantly less neonatal abstinence syndrome (NAS) with neonates requiring 89% less morphine and, on average, 58% less hospital time to receive medication for NAS than did those babies exposed to MTD. However, the pregnant mothers taking BUP showed higher rates of attrition due to greater dissatisfaction with BUP [104].

Due to low BUP levels in breast milk and its poor oral bioavailability in infants, breastfeeding is encouraged if mothers are stable on BUP or MTD, not using illicit drugs, and have no other contraindications [102,105]. If breastfeeding is stopped abruptly, observe infants for withdrawal signs [106]. Currently, limited information exists regarding birth defects and long-term outcomes in children who received prenatal BUP.

Hypogonadism

Hypogonadism is associated with the use of long-acting opioids [107]. Although BUP appears less likely than MTD to be associated with hypogonadism, cases of hypogonadism in BUP-treated men have been reported, which improved with dose reductions or testosterone replacement [108]. Transfer to BUP is one option for the management of hypogonadism in men on MTD [109].

Medical Procedures

It is important for patients on BUP to inform providers when having medical procedures for the following:

- To notify the surgeon/practitioner that the patient is taking BUP and may require more opioid analgesics during the procedure than anticipated, whether BUP is or is not discontinued. Opioid-dependent individuals

may require higher doses of opioids due to tolerance and opioid-induced hyperalgesia than opioid-naïve individuals [110]. Alternatively, opioids may wish to be avoided if possible.

- To ascertain if BUP should be continued or discontinued for the procedure, dependent upon practitioner preference, procedure, post-procedure pain management, and patient stability [111-114]. If BUP is discontinued for the procedure, the patient should stop BUP 2-3 days prior so that the opioid analgesics will be more effective [111,114,115]. It typically takes up to three days to experience withdrawal symptoms when discontinuing BUP [116,117], so educating the patient about the delay of withdrawal may reduce anxiety surrounding the discontinuation of BUP days before the procedure.
- To coordinate post-procedure pain management if needed and to inform the patient when and how to restart BUP without precipitating withdrawal if discontinued for the procedure.
- To ascertain if midazolam will be administered during or before the procedure. Midazolam can have a severe interaction with BUP causing respiratory depression [60,118]. If midazolam is used, the patient should discontinue BUP two days before the procedure, or the provider may opt to use another medication.

Transdermal BUP has demonstrated an additive or synergistic effect when combined with other opioids (morphine, tramadol, oxycodone, hydromorphone) [119-121]. Lower doses of BUP as with the transdermal system leave opioid receptors unsaturated, which allow significant receptor openings for other opioids to bind without any safety-relevant issues [120-122].

BUP and Other Psychotropic Agents

Sedatives/Hypnotics: Respiratory depression, coma, and even death have occurred when combining BUP with sedatives; therefore, it is important to remind patients that caution should be exercised when mixing opioids, including BUP with benzodiazepines, alcohol, or any CNS depressant, as this can be dangerous [123].

Benzodiazepines (BZO): A randomized control trial demonstrated that supra-therapeutic doses of benzodiazepines co-administered with therapeutic doses BUP can remove BUP's 'ceiling effect' on respiratory depression [124]. The BUP-BZO combination, however, appears safer than MTD-BZO for respiratory distress [123,125]. Adding to lethality, the BZO drug class can cause anterograde amnesia. The sedative effects of BZOs increase the likelihood of overdose with opioids; adjunct anterograde amnesia can further increase overdose potential as patients forget how much of any medication or substance they have used and consume more.

Alcohol: Studies have shown that BUP has reduced alcohol cravings and thus use [126]. Due to this, BUP may be helpful in coexisting use.

Cocaine: Studies have shown that BUP reduces cocaine cravings and thus use, which may assist with reducing concomitant cocaine use [127,128]. It should be noted that cocaine lowers plasma concentrations of BUP [129].

Two Components to Addiction: Physical and Psychological

Addiction has two components: physiological, in which BUP assists, and psychological. It is essential to explore the reasons for drug use in efforts to diminish or resolve those reasons while receiving medication-assisted treatment. Addressing mental health issues, learning healthier coping and recovery skills, and how to better emotionally self-sustain may increase abstinence. For example, if a patient used drugs to self-medicate anxiety, treating the anxiety, exploring the root cause, improving life skills, and resolving it may reduce the potential for future relapse or lure back to drug use as this reason for use is diminished or resolved.

Conclusion

The advent of BUP is the most significant advance in medication-assisted treatment since methadone. Utilizing BUP in the treatment of opioid use disorder and in preventing opioid overdose is pivotal as treatment can be a matter of life and death. Various reasons explain the hesitancy to prescribe BUP, including an overall lack of knowledge, expertise, and comfort concerning BUP prescribing, resulting in less than expected prescribers. Providing instructional modalities with clinical application and removing barriers to BUP utilization is paramount so that medical providers feel empowered in prescribing BUP, thus multiplying the number of active BUP prescribers. Legislation to eliminate restrictions on BUP prescribing such as the required training and X-DEA number, as well as the removal of patient caps particularly for advanced practice providers, can significantly affect the uptake and utilization of BUP in this accelerating opioid pandemic.

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