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Practice-Based Guidelines: Buprenorphine in the Age of Fentanyl

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Purpose

To provide practical clinical practice-based guidance, based on available research combined with emerging clinical experience, on the use of buprenorphine in the treatment of individuals using fentanyl and other highly potent synthetic opioids.

Key Points

Fentanyl and other high potency synthetic opioids (F/HPSO) are increasingly present in US drug supplies, currently accounting for the majority of substance-related overdose/poisoning deaths. While some regional prevalence differences persist, F/HPSO are now almost universally present throughout the US in illicit drug samples.

Relatively little rigorous research has been undertaken on the physiological consequences of chronic F/HPSO use and how its use may impact treatment. The clinical landscape therefore has progressed beyond the current research base, making the establishment of standards of care more challenging.

Despite the increasing prevalence of F/HPSO in illicit drug supplies, opioid use disorder remains a highly treatable condition with the use of three FDA-approved medications with excellent evidence to support their efficacy: buprenorphine, methadone, and naltrexone.

Emerging experience suggests that chronic F/HPSO exposure may result in greater tolerance/physiologic dependence than other full agonist opioids. Moreover, due to the high lipophilicity of F/HPSO individuals may experience persistent serum opioid levels beyond what would be predicted by pharmacologic half-life alone, necessitating longer washout times prior to buprenorphine initiation. Therefore, careful assessment of opioid withdrawal remains the most important clinical tool in preventing the possibility of precipitated opioid withdrawal.

Precipitated withdrawal remains the most concerning potential negative outcome of buprenorphine initiation. However, current evidence is lacking to support the belief that precipitated withdrawal is more common or more severe in individuals who have been using F/HPSO.

The standard buprenorphine initiation protocol remains the most studied initiation protocol and clinical experience supports the efficacy of this protocol in individuals who have been using F/HPSO. Longer washout periods and higher buprenorphine maintenance doses may be needed in some of individuals who have been using F/HPSO. Adjunctive medications can be helpful in ensuring that patients can tolerate the potentially longer washout periods that may be needed in some patients who have been using F/HPSO.



Alternative buprenorphine initiation protocols are emerging and may provide additional pathways for buprenorphine initiation in individuals who have been using F/HPSO, but these protocols are currently largely relegated to specialty medical settings with a high degree of clinical monitoring. The lack of significant large-scale research on these alternative protocols is insufficient to suggest superiority of these alternative protocols over the standard buprenorphine initiation protocol.

Definitions/Acronyms

Opioid Use Disorder (OUD)

Opioid use disorder is a health condition characterized by the ongoing problematic use of opioids that results in clinically significant distress or impairment. The DSM-5 enumerates 11 specific diagnostic criteria, the presence of 2 or more of which characterize this disorder. Broadly, OUD is characterized by: cravings, loss of control over intake; continued use despite negative consequences; significant negative personal, social and occupational consequences; and significant physiologic consequences (tolerance/physiologic dependence and withdrawal). Of note, physiologic consequences alone are not sufficient to establish a diagnosis of OUD. Severity is rated depending on the number of diagnostic criteria met: mild (2-3), moderate (4-5), or severe (6 or more)

Opioid Withdrawal (OW)

In this practice guideline, this refers to the syndrome of physiological and psychological symptoms (e.g., nausea, vomiting, diarrhea, anxiety, insomnia, myalgias, pupillary dilation, diaphoresis, rhinorrhea, tearing, piloerection, yawning) resulting from discontinuation or reduction of opioids in individuals who have become physiologically dependent on opioids (i.e., tolerant). OW can be the result of natural metabolism of any exogenous opioid occupying mu-opioid receptors, or precipitated opioid withdrawal (POW, see below) which is instigated by introduction of buprenorphine or an opioid receptor antagonist (i.e., naltrexone or naloxone) that rapidly displaces agonist or partial agonist opioids occupying those receptors.

Precipitated Opioid Withdrawal (POW)

A subset of OW wherein the symptoms are brought about by rapid displacement of opioids actively occupying the mu-opioid receptors, often via systemic introduction of other chemicals that have higher affinity for the mu-opioid receptors but produce lower activation of those receptors (e.g., naloxone or naltrexone (mu-receptor antagonists with no intrinsic mu-opioid receptor activation) or buprenorphine (partial intrinsic mu-opioid receptor activation) administered to individuals currently physiologically dependent on full-agonist opioids such as heroin and fentanyl). While the withdrawal syndrome consists of the same symptoms as OW, the rapidity of onset of these symptoms may result in a subjectively more severe OW experience, and is typically quantified as a rapid escalation in clinical opiate withdrawal score (COWS) of 10 or greater.

Medications for Addiction Treatment (MAT)

Any medication used for the treatment of addiction.



Medications for the Treatment of Opioid Use Disorder (MOUD)

A subset of medications that are specifically used for the treatment of opioid use disorder. FDA-approved MOUD include: buprenorphine, buprenorphine-naloxone, extended-release buprenorphine for injection (BUP-XR) methadone, naltrexone, extended release naltrexone (XR-naltrexone).

Fentanyl and Other Highly Potent Synthetic Opioids (F/HPSO)

The term that will be used to represent the emerging array of high-potency full agonist opioids increasingly found in illicit drug supplies in the US. While some regional variations in prevalence of F/HPSO may persist, F/HPSO are becoming increasingly widespread throughout the US.

Buprenorphine Initiation

The process of initiating buprenorphine for the treatment of opioid use disorder. Often also called buprenorphine “induction.”

Standard Buprenorphine Initiation

Most extensively researched and most commonly employed approach to buprenorphine initiation that involves the patient experiencing OW followed by careful introduction of buprenorphine titrated to a dose that relieves withdrawal symptoms, minimizes cravings, and then blocks the effects of other exogenously administered agonist opioids. This process can be successfully achieved in as little as a single day, but may take several days to achieve steady-state.

Buprenorphine Maintenance Treatment

Refers to the ongoing treatment of OUD using a steady daily dose (or long-acting injectable formulation) of buprenorphine. The goal of buprenorphine maintenance treatment is continued prevention of OW, reduction in cravings, ongoing blockade of mu-opioid receptors, and psychosocial stability that enables further reduction in non-physiologic symptoms of OUD and reduction in opioid overdose. The duration of buprenorphine maintenance treatment is patient-specific, and may be of indefinite duration.

Overdose Education and Naloxone

All patients with OUD are at risk for experiencing overdose and this risk persists during initiation and maintenance treatment with buprenorphine, regardless of the method employed. All patients with OUD should receive overdose education and be provided with naloxone kits. Psychosocial counseling should be made available on site or in the community, including a discussion of the value of social supports.

Additional PCSS Trainings and Resources Related to the Definitions Above:

Medications for Opioid Use Disorder:

<https://education.sudtraining.org/URL/medicationsforOUD>

Preventing Opioid-Involved Overdose with Education and Naloxone:

<https://education.sudtraining.org/URL/PreventingOpioidInvolvedOverdose>



Limitations/Scope

The focus of these guidelines is specifically on the use of buprenorphine (buprenorphine mono-product, buprenorphine-naloxone, and long-acting injectable buprenorphine) in the treatment of individuals with opioid use disorder in which fentanyl or other highly potent synthetic opioids is either an intentional or unintentional component of the opioid mix that is being consumed.

Buprenorphine-containing products are not the only medications that can be used to treat opioid use disorder. Methadone and naltrexone are also US Food and Drug Administration (FDA) approved medications with established evidence bases for the treatment of opioid use disorder. These clinical practice-based guidelines do not aim to establish superiority or inferiority of buprenorphine-containing products against these other FDA-approved medications for the treatment of opioid use disorder, nor do these guidelines aim to establish criteria for patient appropriateness for each of these medications.

It is important to acknowledge at the conclusion of these practice-based guidelines that the buprenorphine products discussed here represent one of three FDA-approved medications for the treatment of OUD. Individuals with OUD should be presented with all three medication treatment options as part of standard informed consent. Patient-specific factors may make one medication option more or less attractive to individual patients. However, the presence or absence of exposure to F/HPSO **alone** is not sufficient for determining which medication option is appropriate. Both the available research and clinical experience currently fail to establish universal medication recommendation guidelines based solely on the use of F/HPSO. The purpose of these clinical practice-based guidelines is not to review the use of methadone and/or naltrexone in individuals using F/HPSO, but mention of the limited emerging evidence base is nonetheless warranted here.

With the increasingly widespread availability of fentanyl and other highly potent synthetic opioids, the clinical landscape is evolving more rapidly than the research base. This divergence creates a gap between what has been rigorously studied and what is being seen and needing to be treated clinically. Given the unprecedented risks of overdose and death posed by fentanyl and other highly potent synthetic opioids, it is imperative to provide practical practice-based guidance to clinicians who aim to treat individuals using these substances, even in the absence of rigorous scientific studies on which guidance can be firmly anchored.

Further complicating the formulation of these practice-based guidelines is the expectation that F/HPSO will be continually synthesized in new ways that introduce novel chemical alterations. These chemical changes may result in an evolving heterogeneous array of pharmacologically diverse compounds which may result in unique clinical buprenorphine initiation challenges.



Over-arching Premises

Buprenorphine containing products **are effective** treatments for opioid use disorder in individuals who are using fentanyl or other highly potent synthetic opioids.

The phenomenon of rapid widespread availability and use of F/HPSO in the US has led to questions as to the optimal clinical management. There are inconsistent clinical and research reports as to the possibility of an increased risk of POW in F/HPSO using individuals. A review of this phenomenon is currently underway through the NIDA Clinical Trials Network (CTN), but those results are not yet available. In the absence of large scale data supporting a higher likelihood of POW in individuals who are taking F/HPSO and initiating buprenorphine, the standard buprenorphine initiation protocol remains the most widespread and evidenced-supported strategy for initiating buprenorphine in these individuals.

The major concern of starting buprenorphine in individuals exposed to fentanyl is the possibility of precipitated opioid withdrawal (POW). POW is neither life-threatening, nor is it untreatable or unmanageable, should it occur. However, POW, during clinical induction of following periods of lapse to use of full opioid agonists such as heroin or F/HPSO, can discourage patients from continuing buprenorphine and other treatments for OUD.

Based on emerging clinical experience, due to the potential of unique risks of POW in individuals exposed to fentanyl and other highly potent synthetic opioids, buprenorphine initiations in these individuals may require some additional considerations. However, these considerations remain rooted in the same principles that have guided buprenorphine initiations since buprenorphine was first introduced for the treatment of OUD.

To best prevent POW, research evidence and clinical experience continue to support an approach in which individuals embarking on buprenorphine treatment first achieve adequate OW, as is undertaken in a standard buprenorphine initiation protocol.

Adjunctive medications targeting specific OW symptoms can be particularly helpful in this approach, as they can effectively minimize OW-related distress and thereby increase the likelihood of buprenorphine initiation success. Specifically, adjunctive medications may enable the patient to tolerate a longer washout period and may also provide symptom relief in the event of POW. Prior to the advent of F/HPSO, adjunctive medications were rarely used in most standard buprenorphine initiations. However, clinical experience increasingly suggests that longer washout periods may be needed in individuals taking F/HPSO in order to achieve adequate vacancy of mu-opioid receptors to prevent POW. Therefore, adjunctive medications (e.g., alpha-2 agonists, analgesics, antihistamines) may prove to be an increasingly valuable tool in ensuring successful buprenorphine initiations.

If OW is not tolerable to the patient, or if other patient-specific factors make a standard initiation protocol unfeasible, alternative initiation pathways have been proposed and reported (discussed in further detail below): cross over buprenorphine initiation, low- or high-dose buprenorphine initiation or choice of using the full agonist methadone.

Alternative buprenorphine initiation protocols are themselves consistent with our current understanding of buprenorphine pharmacology and pharmacodynamics, although the evidence base for these protocols is not as robust as the evidence base for standard buprenorphine initiation protocols.



Efficacy of buprenorphine maintenance treatment of individuals who have used F/HPSO prior to buprenorphine initiation does not appear to be negatively impacted. Anecdotally, however, during maintenance treatment some patients report difficulty with significant cravings for opioids beyond what would be normally expected or was experienced prior to the widespread availability of F/HPSO. Some providers and patients report preference for methadone in individuals who have been taking F/HPSO, which may be the result of the relatively easier transition process to methadone and the added structure and contact provided through opioid treatment programs (OTP) rather than pharmacologic differences between buprenorphine and methadone. Clinicians have also reported that higher doses of methadone than needed before the increase of F/HPSO use may be needed to achieve stabilization. Research on this specific phenomenon is lacking. Similarly, clinicians have also noted that some individuals transitioning from F/HPSO may require higher maintenance doses of buprenorphine (e.g., 24-32mg or higher daily).

Audience

The focus of these clinical practice-based guidelines is for primary healthcare setting providers. While buprenorphine initiations may occur in a wide range of clinical settings such as opioid treatment programs, inpatient medical wards and emergency departments, the vast majority still occur in outpatient settings. It remains an area of active and ongoing investigation whether alternative approaches may have more clinical utility in different specialty settings, but randomized controlled trial evidence is lacking that demonstrates alternative approaches are superior or even equivalent to standard buprenorphine initiations in any setting.

Nonetheless, it is imperative that providers continue to treat OUD using buprenorphine products and are not dissuaded from treating OUD by concerns related to perceived challenges posed by the presence of F/HPSO.

Additional PCSS Trainings and Resources Related to Integrating OUD into Different Clinical Settings:

- Integrating Opioid Use Disorder Treatment in Clinical Care: <https://education.sudtraining.org/URL/IntegratingOUDTreatment>
- Treatment of Opioid Use Disorder in the Emergency Department: Should it be a choice? <https://education.sudtraining.org/URL/TreatmentofOpioidUseDisorderintheEmergencyDepartment>

Principles/Physiology

Fentanyl and Other Highly Potent Synthetic Opioids (F/HPSO)

Although F/HPSO have been found in the street drug supply, the scientific understanding of the impact of these substances on the brain and other organs and resulting medical and psychiatric syndromes is limited.

From a pharmacodynamic perspective it is important to highlight that one feature common to F/HPSO is their



Table 1. The Effects of Fentanyl and Other High-Potency Synthetic Opioids as Compared to Heroin

Properties	Fentanyl and HPSO: difference from heroin/morphine
Pharmacological effects (acute)	<p>Greater “efficacy” than morphine at the MOR (greater ability to activate opioid receptors but similar binding affinity at those receptors.)</p> <p>Fentanyl and HPSO preferentially affect respiratory drive over analgesia resulting in rapid, profound, and prolonged respiratory depression</p>
Pharmacological effects (chronic)	<p>High levels of tolerance and physical dependence potentially greater than typical for someone using large amounts of daily heroin</p> <p>Much more variable onset of withdrawal (up to 2-4 days after cessation)</p>
Toxicity/therapeutic index	<p>More rapid respiratory suppression</p> <p>Pronounced noradrenergic toxicity (laryngospasm, wooden chest)</p> <p>Higher doses of naloxone appear to be more effective</p>
Pharmacokinetics	<p>Lipid soluble – resulting in faster onset of effect (euphoria and respiratory suppression) but a shorter duration of action as fentanyl and HPSO leave the brain rapidly</p> <p>Fentanyl and HPSO are redistributed to fatty tissues and have prolonged metabolite elimination $\frac{1}{2}$ life (up to 3-4 weeks)</p>
Drug-taking behavior	<p>Fentanyl and HPSO are short-acting which may incline users toward more frequent use, putting them at greater risk for overdose, as blood levels may continue to climb with cumulative dosing, and as concentrations increase in fatty tissue</p>
Toxicology testing	<p>Many commonly used medications cross react with Fentanyl and HPSO on immunoassay screening tests leading to false positives and need to confirm positive screens with more accurate confirmatory tests</p>



high potency. Potency refers to the amount of a drug needed to produce a certain effect, with high potency meaning that relatively less amount of the drug is needed to achieve the same desired effect as a less potent drug. Consequently, high potency drugs like F/HPSO have smaller margins for error when calculating dose—small over-estimations of dose, for example, may result in toxicity or death.

Another noteworthy emerging pharmacodynamic feature of F/HPSO is their lipophilicity, which refers to a drug's ability to be dissolved in (or suspended in) fatty tissue. Highly lipophilic drugs, such as many F/HPSO, can accumulate in these fatty tissues and function as a reservoir of the drug contributing to higher-than-expected blood levels sometimes long after the drug is discontinued as it slowly elutes back out of the fatty tissues.

Individuals using F/HPSO potentially differ from individuals using other opioids in several ways, such as: 1) acute and chronic pharmacological effects (opioid and non-opioid), 2) toxicity range and the “therapeutic index,” 3) pharmacokinetics (absorption (t_{max}) and elimination half-life), 4) drug-taking behaviors with related consequences. Table 1 summarizes these differences which impact several aspects of clinical care for individual who regularly use F/HPSO.

Precipitated Opioid Withdrawal (POW)

Buprenorphine is a high-affinity partial mu-opioid receptor agonist opioid. Affinity refers to firmness with which a drug binds to a receptor; consequently, drugs with greater affinity will preferentially displace those with lower affinity. Different opioids have different affinities for the mu-opioid receptor, with relative affinities of several noteworthy opioids as follows: buprenorphine > fentanyl > methadone. Due to its high receptor affinity, buprenorphine can effectively and rapidly displace other *mu-opioid* receptor agonists, including fentanyl. Buprenorphine's partial agonism refers to its characteristic “ceiling effect,” meaning that no matter how much of the drug that an individual takes the individual will not achieve specific effects beyond a certain “ceiling” threshold. The partial agonist property of buprenorphine results in a lower activation of the *mu-opioid* than other full agonists.

A successful buprenorphine initiation (that is, an initiation that does not result in the experience of significant withdrawal after the first few doses of buprenorphine) requires that a portion of *mu-opioid* receptors are vacated and available for buprenorphine binding. In order to achieve this goal, individuals should therefore wait for the agonist to leave the receptor (i.e. washout) which invariably results in a mild degree of withdrawal. When buprenorphine is then administered it occupies the available receptors increasing the net opioid activity, thereby relieving withdrawal and craving.

Administering a large dose of buprenorphine (a high-affinity partial agonist) **before** *mu-opioid* receptors are adequately vacated results in a displacement of the high-potency agonist from the receptors and a rapid, precipitous decrease in mu-opioid receptor activity and (consequently) severe opioid withdrawal (i.e., precipitated opioid withdrawal).

Therefore, POW risk is lessened if the patient is already in a moderate opioid withdrawal (with most agonist already metabolized and not occupying receptors) prior to buprenorphine initiation, and the initial dose of buprenorphine is low enough. In such cases, the partial opioid agonist activity of buprenorphine will mitigate the overall opioid deficit and provide withdrawal relief.



The magnitude of tolerance/physiologic dependence is directly proportional to the dose, duration of use, and potency of the exogenous opioid being consumed. Similarly, the greater the tolerance/physiologic dependence developed, the more significant the withdrawal experience may be when the mu-opioid receptors are vacated. Prolonged heavy use of F/HPSO may therefore produce more profound tolerance/physiologic dependence than other full agonist opioids given the extremely high potency of these compounds. In addition, F/HPSO may accumulate in fatty tissues (similar to what is observed with chronic methadone administration) thereby prolonging the amount of time required for adequate washout from mu-opioid receptors and increasing the risk of POW if administration of buprenorphine is undertaken too soon. This may account for some of the challenges that some providers and patients describe in buprenorphine initiations in individuals exposed to chronic F/HPSO. While these phenomena do not lessen the effectiveness of the standard buprenorphine initiation approach, alternative buprenorphine initiation protocols have been proposed and implemented in certain clinical settings, and will be introduced below (i.e., high dose, cross over dose, and low dose protocols).

Principals of Evaluation

In addition to well-established guidelines for evaluation of patients, clinicians may also consider assessing for the following factors:

- 1) Assess for known or possible exposure to F/HPSO
- 2) Overdose history, and history of overdose in individuals with whom they use opioids
- 3) Toxicology screening: Toxicology screening is standard of care for patients being evaluated and treated for substance use disorders. However, toxicology screening should be used as a clinical tool that is part of a comprehensive evaluation and treatment approach, not as either a punitive tool or the definitive measure of an individual's need for treatment or the measure of their success in treatment. Urine toxicology testing is not alone diagnostic of OUD or any other SUD. The role of toxicology screening in addiction treatment is discussed in greater detail elsewhere. It is important to note that many routinely available toxicology screening tools do not detect F/HPSO. As a result, clinicians should be aware of the limitations of the particular toxicology screens that they use or aim to use. While the emphasis of this guide is in F/HPSO, clinicians should be mindful that there may be other containments that could influence clinical management of induction into medications for opioid treatments, i.e. sedatives, benzodiazepines, cocaine, xylazine and stimulants.

Additional PCSS Trainings and Resources Related to Principals of Evaluation:

- Lab Testing in Assessment of Substance Use Disorders:
<https://education.sudtraining.org/URL/LabTestinginAssessmentofSUD>
- Preventing Opioid-Involved Overdose with Education and Naloxone:
<https://education.sudtraining.org/URL/PreventingOpioidInvolvedOverdose>
- Screening, Assessment, and Treatment Initiation for SUD:
<https://education.sudtraining.org/URL/screeningassessmentandtreatmentinitiation>



Approaches to Buprenorphine Initiation

Initiation Upon Experience of Opioid Withdrawal:

Standard buprenorphine initiation

In-office observed initiation that assures there is a moderate/severe (Clinical Opioid Withdrawal (COWS) >12) opioid withdrawal before the first dose of buprenorphine is administered. This may also be accomplished at home with individuals who are able to self-monitor OW symptoms (i.e., “at home initiations”). Initiation is accomplished using a buprenorphine product (either buprenorphine monoproduct or buprenorphine-naloxone combination product) initially administered typically at either 2 mg doses every 2 - 4 hours until OW symptoms resolve and cravings are minimized. To achieve this goal, typical total daily doses of buprenorphine range from 12 to 24 mg. While earlier protocols suggested accomplishing this target over several days, clinical experience and research support being able to achieve this goal sometimes in as little as one day. However, some patients and providers may nonetheless prefer a multi-day implementation of this protocol.

Alternative/emerging buprenorphine initiations (variations of standard protocol)

NOTE: The standard initiation protocol remains the most widely researched and clinically implemented initiation protocol in the US. Data and clinical experience regarding alternative buprenorphine initiation pathways (i.e., the cross-over protocol, see below) is relatively lacking.

Low Dose

There are variations to this approach, but in a sample protocol, patients work toward a goal of a 24-hour washout, aiming for a mild-moderate severity withdrawal level (i.e., COWS score between 8 - 12). Adjunctive medications (e.g., alpha-2 agonists, analgesics, antihistamines) are often used during the washout period to reduce the symptoms of emerging withdrawal and allow patients to wait the whole 24 hours (if possible). This approach is based on the hypothesis that a very-low dose of buprenorphine will displace only a small amount of the residual full agonist on the mu-receptors (and possibly reverse the receptor adaptations maintaining physiological dependence/tolerance) and begin to relieve the OW symptoms through mu-receptor reactivation.

Buprenorphine dosing is advanced gradually in small increments over the initial day of treatment, thereby minimizing the risk of POW. This protocol typically uses an initial buprenorphine dose of 0.5 mg, followed by 0.5 mg doses given every 2 hours until the total 2 mg is achieved. Dosing is then advanced to 2 mg doses administered every 2 - 3 hours until the total 6-8 mg dose is given. Additional doses of adjunctive medications can be given during the 1st day dose titration.



High Dose

In this protocol, a standard 16-24 hours washout is used, aiming for an upper mild severity withdrawal level (COWS > 12) before initiating buprenorphine. The first buprenorphine dose is usually 2 mg followed by a rapid titration (e.g. up to 24 mg within a few hours regardless of the withdrawal severity) with monitoring for excessive sedation. This approach is based in the hypothesis that a higher buprenorphine dose will maximize buprenorphine's agonist activity to rapidly treat the withdrawal state. In this approach, patients with a higher tolerance/physiologic dependence (as is hypothesized to potentially occur in the setting of F/HPSO use) are predicted to require higher doses of buprenorphine to maximize the agonist effects of buprenorphine. Adjunctive medications may be used before and during the buprenorphine titration. A variation on this technique more commonly employed in the emergency department setting is to begin when COWS > 7 (irrespective of washout period) with a buprenorphine dose of with 8 - 12 mg, and to titrate up to a total of 32 mg (or more) if necessary.

Initiation Prior to the Experience of Significant Opioid Withdrawal:

Cross-over (sometimes referred to as “micro dosing” protocol)

In this protocol, no washout period is required before initiating buprenorphine. The risk of POW is theoretically minimized by administering extremely low doses of buprenorphine (0.25 mg or lower), which are slowly titrated over the period of several days to a target 8 - 12 mg/day. At the same time as the buprenorphine dose is gradually increased, the patient continues to take a full dose of an agonist (e.g. prescription opioid while in the hospital). This approach is based on the expectation that the risk of POW will be very low as the buprenorphine dose is slowly increased while at the same time reversing the receptor adaptations maintaining physiological dependence. At buprenorphine doses of 8 - 12 mg, the full agonist can be stopped. Adjunctive medications are usually not utilized (or used less) in this protocol.

One significant limitation of this approach is that the protocol requires the patient to follow a complicated, sometimes multi-day titration that may still result in the experience of POW if the titration is attempted too quickly.

Transitioning from a high potency full agonist (F/HPSO) to a partial agonist (buprenorphine) can result in POW due to the net reduction of opioid agonism. With time, and additional doses of buprenorphine, the patients opioidergic system will equilibrate to the new level of opioid agonism, and withdrawal symptoms will resolve. Ultimately, POWS resolves with additional doses of buprenorphine, time passing to allow the opioidergic system to adjust, and in some cases, adjunctive medications.

Another significant limitation of this approach is that many individuals will continue using F/HPSO during the (often) several-day initiation period, which carries a significant overdose risk. Moreover, to achieve the necessary very low doses of buprenorphine promoted in this protocol, formulations of buprenorphine are used that are not specifically FDA-approved for treatment of OUD (i.e., low-dose buccal film or transdermal buprenorphine patches). As a consequence of these limitations, this approach is currently primarily relegated to inpatient acute-care settings.



Table 2. A Comparison of Buprenorphine Induction Approaches

	Standard	Low-dose	High-dose	Micro-dose with cross taper
Post-agonist washout duration	16h (short acting) 48→72h (long acting)	24 - 36h	16→24h	No washout Usual dose of agonist continued
First dose of buprenorphine	2 mg	0.5 - 1 mg	2→16 mg	0.25→0.5 mg
First day total dose of buprenorphine	8→12 mg	8 mg	16→32 mg	0.5→1 mg
Adjunctive medications	As needed	Standing doses up to maximum tolerability	As needed	None

XR-Buprenorphine for Injection Induction

Two XR-BUP formulations for the treatment of OUD in the US have been approved by the FDA; Brixadi™ and Sublocade™. Brixadi™ has been approved by the FDA but is not yet commercially available in US. The Brixadi™ induction protocol used in the pivotal trial leading to FDA-approval was a standard buprenorphine induction approach where participants in withdrawal received a sublingual dose of buprenorphine 4 mg followed by 16 mg of subcutaneous (SC) buprenorphine in a weekly injection (estimated equivalent of 8mg/day). The FDA-approved prescribing information for Sublocade™ indicate that a standard sublingual buprenorphine be performed with a maintenance dose of at least 8 mg/day for one week, followed by a SC injection of 300 mg (estimated equivalent of 12-16 mg/day). However, there are several small case series reporting on the use of Sublocade™ in fentanyl users where a single-day induction onto 300 mg SC is achieved after 4-24 mg SL buprenorphine.

Additional PCSS Trainings and Resources Related to Approaches to Buprenorphine Initiation:

- Comparing Methods of Buprenorphine Induction in Patients Using Fentanyl (clinical roundtable discussion): https://youtu.be/_OgS2eZpKxU
- Buprenorphine Induction (clinical guidance): <https://pcssnow.org/wp-content/uploads/2021/12/PCSS-GuidanceBuprenorphineInduction.Casadonte.pdf>



Management of Precipitated Opioid Withdrawal

Increasing buprenorphine dosing:

Patients may interpret the feeling of going from a high potency opioid like a F-HPSO to the partial agonist buprenorphine as POW. However, they will not be left without a level of opioid agonist with buprenorphine thus allowing the system to equilibrate and eventually alleviate the patients' experience of POWs. This can be augmented by a small additional dose of buprenorphine, adjunctive medications and/or assurance, by the provider of the impending stabilization.

Adjunctive medications

In some instances POW may self-resolve as the system re-equilibrates and stabilizes after introduction of buprenorphine. Adjunctive medications can provide targeted relief of OW symptoms while the system stabilizes and can also therefore enhance the likelihood that the patient is not lost to follow up and/or returns to illicit opioid use.

- Alpha 2 agonists
 - Clonidine
 - Lofexidine
 - Tizanidine
- Analgesics
 - Ibuprofen
 - Acetaminophen
- Antispasmodics
 - Bentyl
 - Cyclobenzaprine
- Anxiolytics
 - Hydroxyzine
 - Benzodiazepines*
 - Gabapentin
- Hypnotics
 - Trazodone
 - Z-drugs
 - Mirtazapine
 - Doxepin
 - Quetiapine
- Antiemetics
 - Ondansetron
 - Prochlorperazine
- Anti-Diarrheal
 - Loperamide

*Benzodiazepine and Z-drugs are controlled substances and have risks for patients with OUD, and should therefore be used sparingly, especially in the outpatient setting.



Individualized Care

It is important that decisions regarding treatment of OUD, including the various forms of MOUD, are made collaboratively and without stigmatizing language between provider and patient. In order for patients to make informed decisions appropriate to their needs, providers should be equipped with information about the relative advantages and disadvantages of the various treatment options and should be able to communicate these effectively with their patients. Information about buprenorphine initiations and treatment may be distorted in the community, and providers should be able to ground discussions with patients in current evidence-based approaches coupled with clinical experience. Importantly, assuring patients that while there is a risk of POW when initiating buprenorphine this risk is low relative to the risks of continued use and that standard initiation protocols remain the best researched and most widely used strategy for initiating this treatment, even with the widespread emergence of F/HPSO.

Frequently Asked Questions

Is methadone more effective than buprenorphine in the treatment of individuals with OUD who have been using F/HPSO?

Although research would be helpful to determine predictors of success for each patient, there is limited evidence that methadone is superior to buprenorphine in terms of ease of initiation and the treatment delivery system resulting in greater retention in treatment in patients who have been using F/HPSO. Given the observations in the field of worsening retention in the context of increasing F/HPSO use and the increased risk of fatal overdose with the misuse of high potency opioids, optimizing treatment retention is paramount. Therefore, it is suggested that patients with F/HPSO be informed about the benefits and risks of all medications. When prescribing buprenorphine to patients with poor or partial response, the prescriber should consider referring the patient to an OTP, if available and feasible, for methadone maintenance, to potentially achieve and improved response.

Should alternative buprenorphine initiation protocols (i.e., cross-over or “micro dosing”) be preferentially used for individuals who have been using F/HPSO?

While alternative initiation protocols may eventually prove to be efficacious for some individuals who have been using F/HPSO, these protocols typically require specialty medical settings (e.g., emergency departments or inpatient medical settings) and the research base is currently lacking to suggest that alternative initiation protocols are superior to the standard buprenorphine initiation protocol outside of these settings.

Is precipitated opioid withdrawal (POW) more likely to occur in individuals who have been using F/HPSO?

Current research is lacking—but clinical experience suggests this is the case—that POW is more common in individuals who have been using F/HPSO. The key to prevention of POW is that individuals achieve adequate opioid withdrawal prior to initiation of buprenorphine (COWS > 12). Some individuals who have been using F/HPSO may require longer washout periods than those who have been using short acting lower potency full agonist opioids. Adjunctive medications are an important and under-utilized tool that can help ensure patients tolerate the potentially longer washout period and any POW that occurs. However, patients with OUD using



F/HPSO are at risk for overdose, and the clinical management setting and approach for buprenorphine induction needs to be individualized based on the balancing of risks present.

If a patient experiences POW, is the preferred management discontinuation of the buprenorphine initiation and/or hospitalization?

POW typically can be safely managed in an outpatient setting through the use of targeted adjunctive medications and/or additional doses of buprenorphine. In some instances, POW will resolve as buprenorphine reaches serum steady state, although adjunctive medications may be needed in the interim to increase the likelihood of treatment retention. POWs is unconformable and potentially distressing for patients; providing psychoeducation and reassurance is critical for achieving a good clinical outcome.

Additional PCSS Trainings and Resources Related to the Frequently Asked Questions:

- Methadone: <https://pcssnow.org/medications-for-opioid-use-disorder/methadone/>
- Managing Common Psychiatric Conditions in Primary Care: <https://education.sudtraining.org/URL/ManagingCommonPsychiatricConditionsinPrimaryCare>
- Fentanyl and Opioid Use Disorder: <https://youtu.be/898EsYSq7m0>
- Methadone and Buprenorphine-Associated Drug-Drug Interactions: <https://education.sudtraining.org/Public/Catalog/Details.aspx?id=6DdlmMf3FxlP1z1XUpomHQ%3d%3d>

PCSS Mentoring

PCSS Discussion Forum, an online discussion forum moderated by addiction specialists where health professionals can post questions and receive answers from clinical experts and other colleagues: <https://pcssnow.org/mentoring/#forum>

One-on-One Mentoring: Provides individualized, one-on-one guidance via email, phone, or in-person, (if feasible) to discuss specific clinical issues. Members are “matched up” with one of our mentors in their region. This is the most in-depth of the three PCSS mentoring tools.

Ask a Clinical Question: A simple and direct way to receive an answer related to Substance Use Disorder, Opioid Use Disorder, and other related topics. Designed to provide a prompt response to clinical questions via email.

To learn more: <https://pcssnow.org/mentoring/>



Additional PCSS Resources

Buprenorphine Induction (clinical guidance):

<https://pcssnow.org/wp-content/uploads/2021/12/PCSS-GuidanceBuprenorphineInduction.Casadonte.pdf>

Clinical Roundtable Discussions: <https://pcssnow.org/mentoring/clinical-roundtable/>

Clinically Relevant Drug Interactions: Buprenorphine or Methadone with Other Frequently Prescribed Drugs:

https://pcssnow.org/wp-content/uploads/2021/08/PCSS-Clinically-Relevant-Drug-Interactions-Buprenorphine-or-Methadone-with-Other-Frequently-Prescribed-Drugs_2021.pdf

Comparing Methods of Buprenorphine Induction in Patients Using Fentanyl (clinical roundtable discussion):

https://youtu.be/_OgS2eZpKxU

Fentanyl and Opioid Use Disorder: <https://youtu.be/898EsYSq7m0>

Harm Reduction and Recovery Support Services: Complementing and Supporting Pharmacotherapy for Substance Use Disorders:

<https://education.sudtraining.org/URL/HarmReductionandRecoverySupportServices>

How Adding a Clinical Pharmacist Improves Access to Addiction Care:

<https://education.sudtraining.org/URL/HowAddingaClinicalPharmacistImprovesAccesstoAddictionCare>

Integrating Opioid Use Disorder Treatment in Clinical Care: <https://education.sudtraining.org/URL/IntegratingOUDTreatment>

Lab Testing in Assessment of Substance Use Disorders:

<https://education.sudtraining.org/URL/LabTestinginAssessmentofSUD>

Managing Common Psychiatric Conditions in Primary Care:

<https://education.sudtraining.org/URL/ManagingCommonPsychiatricConditionsinPrimaryCare>

Medications for Opioid Use Disorder:

<https://education.sudtraining.org/URL/medicationsforOUD>

Methadone: <https://pcssnow.org/medications-for-opioid-use-disorder/methadone/>

Methadone and Buprenorphine-Associated Drug-Drug Interactions:

<https://education.sudtraining.org/Public/Catalog/Details.aspx?id=6DdlmMf3FxlP1z1XUpomHQ%3d%3d>

Monitoring of Liver Function Tests in Patients Receiving Naltrexone or Extended-Release Naltrexone:

<https://pcssnow.org/wp-content/uploads/2014/10/PCSS-MAT-NTX-Liver-Safety-Guideline1.pdf>



Naltrexone: A Step-by-Step Guide:

<https://pcssnow.org/courses/naltrexone-step-step-guide/>

Preventing Opioid-Involved Overdose with Education and Naloxone:

<https://education.sudtraining.org/URL/PreventingOpioidInvolvedOverdose>

Screening, Assessment, and Treatment Initiation for SUD:

<https://education.sudtraining.org/URL/screeningassessmentandtreatmentinitiation>

Screening for Substance Use in Primary Care: Screening Tools and Guidance for Implementation

<https://education.sudtraining.org/URL/ScreeningforSubstanceUseinPrimaryCare>

SUD 101 Core Curriculum (23 Modules):

<https://pcssnow.org/education-training/sud-core-curriculum/>

SUD for the Healthcare Team (4 modules):

<https://education.sudtraining.org/URL/SUDfortheHealthcareTeam>

Telehealth for Opioid Use Disorder Toolkit: Guidance to Support High-Quality Care

<https://pcssnow.org/telehealth-for-opioid-use-disorder-toolkit-guidance-to-support-high-quality-care/>

Transfer from Methadone to Buprenorphine:

<https://pcssnow.org/wp-content/uploads/2014/03/PCSS-MATGuidanceTransferMethadonetoBup.Casadonte.pdf>

Treatment of Opioid Use Disorder in the Emergency Department: Should it be a choice?

<https://education.sudtraining.org/URL/TreatmentofOpioidUseDisorderintheEmergencyDepartment>

Video: Preparation and Injection of Extended-Release Naltrexone (Vivitrol)

<https://pcssnow.org/resource/video-preparation-injection-extended-release-naltrexone-vivitrol/>



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