

ASAM Clinical Considerations: Buprenorphine Treatment of Opioid Use Disorder for Individuals Using High-potency Synthetic Opioids

Melissa B. Weimer, DO, MCR, DFASAM, Andrew A. Herring, MD, Sarah S. Kawasaki, MD, FASAM, Marjorie Meyer, MD, Bethea A. Kleykamp, PhD, and Kelly S. Ramsey, MD, MPH, MA, FACP, DFASAM

Abstract: Treatment of opioid use disorder (OUD) with buprenorphine has evolved considerably in the last decade as the scale of the OUD epidemic has increased along with the emergence of high-potency synthetic opioids (HPSOs) and stimulants in the drug supply. These changes have outpaced the development of prospective research, so a clinical consideration document based on expert consensus is needed to address pressing clinical questions. This clinical considerations document is based on a narrative literature review and expert consensus and will specifically address considerations for changes to the clinical practice of treatment of OUD with buprenorphine for individuals using HPSO. An expert panel developed 6 key questions addressing buprenorphine initiation, stabilization, and long-term treatment for individuals with OUD exposed to HPSO in various treatment settings. Broadly, the clinical considerations suggest that individualized strategies for buprenorphine initiation may be needed. The experience of opioid withdrawal negatively impacts the success of buprenorphine treatment, and attention to its management before and during buprenorphine initiation should be proactively addressed. Buprenorphine dose and dosing frequency should be individualized based on patients' treatment needs, the possibility of novel components in the drug supply should be considered during OUD treatment, and all forms of opioid agonist treatment should be offered and considered for patients. Together, these clinical

considerations attempt to be responsive to the challenges and opportunities experienced by frontline clinicians using buprenorphine for the treatment of OUD in patients using HPSOs and highlight areas where prospective research is urgently needed.

Key Words: buprenorphine, opioid use disorder, addiction, treatment (*J Addict Med* 2023;00: 00–00)

Treatment of opioid use disorder (OUD) with buprenorphine has dramatically expanded from restricted access in office settings to many nontraditional settings. The illicit drug supply has likely permanently transitioned to predominantly synthetic substances—both high-potency synthetic opioids (HPSOs) such as fentanyl and its analogs and stimulants.^{1,2} These changes have coincided with the exponential rise in overdose deaths, other novel components in the drug supply, high prevalence of polysubstance use, and high psychosocial vulnerability driving an unprecedented urgency to expand access to buprenorphine treatment through updating and optimizing treatment approaches to meet the needs of patients with OUD.²

This “Buprenorphine Clinical Consideration” is based on expert consensus and available evidence to address 6 key questions that address buprenorphine initiation and ongoing treatment among individuals with OUD chronically using HPSOs (Table 1). This document is not a Clinical Practice Guideline (CPG) and does not follow CPG rigorous methodology.³ Each key question and its narrative response focuses on current clinical challenges, summarizes literature to date, and concludes with clinical consideration statements.

METHODS

The American Society of Addiction Medicine (ASAM) Quality Improvement Council assembled a group of experts in OUD treatment to serve on the writing group for this document. A chair (M.B.W.) from ASAM's CPG Methodology Subcommittee was selected. The writing group members were chosen based on their experience (Appendix A, <http://links.lww.com/JAM/A431>). A separate group of experts were chosen as a peer review panel (Appendix A, <http://links.lww.com/JAM/A431>). The writing group and peer review panel developed the scope and key questions (Table 1). Broadly, key questions address buprenorphine initiation, stabilization, and long-term treatment for individuals with OUD who are chronically exposed to

From the Yale School of Medicine, Program in Addiction Medicine, New Haven, CT (MBW); Yale School of Public Health, New Haven, CT (MBW); Division of Addiction Medicine, Highland Hospital–Alameda Health System, Oakland, CA (AAH); Department of Psychiatry and Internal Medicine, Penn State Health, Hershey, PA (SSK); University of Vermont, Burlington, VT (MM); BAK and Associates, Baltimore, MD (BAK); NYS Office of Addiction Services and Supports (OASAS), Albany, NY (KSR).

Received for publication March 14, 2023; accepted June 16, 2023.

Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.journaladdictionmedicine.com).

Dr Weimer reports stock options with Path CCM and consulting for CVS Health.

Dr Kleykamp is an owner of BAK and Associates and a consultant for Palladian Associates, Pinney Associates, STATinMED, and Hayes, Inc/Symplr. Dr Herring, Dr Kawasaki, Dr Meyer, and Dr Ramsey report no conflicts of interest.

Supported by the American Society of Addiction Medicine staff Taleen Safarian, Amanda Devoto, PhD, and Maureen Boyle, PhD.

The authors report no funding source.

Send correspondence to Melissa B. Weimer, DO, MCR, DFASAM, Yale School of Medicine, Program in Addiction Medicine, 367 Cedar St, Harkness Hall A, 417A, New Haven, CT 06510. E-mail: melissa.weimer@yale.edu.

Copyright © 2023 American Society of Addiction Medicine

ISSN: 1932-0620/23/0000-0000

DOI: 10.1097/ADM.0000000000001202

TABLE 1. Buprenorphine Clinical Considerations Scope and Key Questions Components

Key Question Components	
Population	Individuals with severe OUD chronically exposed to HPSO Pregnant individuals with OUD chronically exposed to HPSO
Interventions	Buprenorphine initiation* Buprenorphine stabilization† Buprenorphine long-term treatment
Comparisons	Usual practice as specified in the ASAM 2020 Updated OUD National Practice Guideline (NPG)
Outcomes	Opioid withdrawal syndrome Precipitated opioid withdrawal‡ Opioid cravings Recurrence of opioid use Morbidity (eg, nonfatal overdose, premature hospital discharge, infections) All-cause mortality Opioid-related mortality
Timing Setting	Any All outpatient/ambulatory practice settings Emergency department and hospital-based practice§
Key Questions	<ol style="list-style-type: none"> 1. What specific clinical situations favor use of low or high-dose buprenorphine initiation strategies? 2. What strategies can address patient discomfort, including precipitated opioid withdrawal, if it occurs during buprenorphine initiation? 3. After buprenorphine initiation, what range of buprenorphine dosing and/or dosing strategies can be considered during stabilization and long-term treatment? 4. What are indications for injectable extended-release buprenorphine for OUD treatment compared with sublingual formulations? 5. How do other novel drug components affect buprenorphine initiation and stabilization? 6. What are OUD treatment alternatives after repeated unsuccessful attempts at buprenorphine treatment?

*Buprenorphine initiation is defined as the initial phase of OUD treatment when medication doses are adjusted for a patient to reach stabilization.³ The time to reach stabilization is individualized.

†Buprenorphine stabilization is defined as the period when a patient has attained “a medically stable, steady state in which the patient is adequately supported to prevent deterioration of their illness.”³

‡Precipitated opioid withdrawal (POW) is defined as the rapid onset of objective signs of opioid withdrawal syndrome (eg, pupillary dilation, gooseflesh, extreme restlessness, vomiting, or diarrhea) after an initial administration of buprenorphine and typically involves a rise of the Clinical Opioid Withdrawal Scale by >5 points.⁴

§Emergency department and hospital-based practice will apply to the initiation and management of opioid withdrawal syndrome only.

HPSO. The ASAM Quality Improvement Council and Board of Directors have approved this clinical document.

NARRATIVE LITERATURE SEARCH

A narrative literature search was performed of PubMed for English-language, human studies published from 2012 to 2022 (Appendix B, <http://links.lww.com/JAM/A431>). A structured literature search yielded 578 studies of which 41 met inclusion criteria (Appendix B, <http://links.lww.com/JAM/A431>). The writing group also evaluated 4 relevant studies published before 2012 and other highly relevant studies captured in a supplemental literature search.

Consideration Statements

KQ1: What Specific Clinical Situations Favor Use of Low- or High-Dose Buprenorphine Initiation Strategies?

Evidence Summary

Opioid withdrawal syndrome (OWS) before and during buprenorphine initiation can be a barrier to successful buprenorphine initiation.² The OWS experience is mediated by expectations, setting, and other reinforcers; its effective treatment is important for buprenorphine initiation.⁵ Herein, we discuss 2 emerging strategies for buprenorphine initiation that may be considered when standard-initiation strategies are not possible

or not preferred: low-dose buprenorphine with opioid continuation (LDB-OC) and rapid high-dose buprenorphine (HDB) initiation after opioid discontinuation (Table 2).

During LDB-OC, patients are administered or self-administer full agonist opioids (FAOs) during a multiday dose escalation of low-dose buprenorphine (0.25–1 mg) (Table 2).^{6,7} The continuation of FAO supports buprenorphine initiation by maintaining the level of mu-opioid receptor (MOR) activation needed to match a patient’s baseline opioid tolerance. Initially described among patients with chronic pain prescribed with FAO, the technique has been extended to patients with OUD using differing buprenorphine uptitration schedules and buprenorphine formulations.^{6–8} Administered FAOs for OWS and OUD are permitted in emergency departments (EDs) and hospital settings.⁹ However, under current federal law, it is currently understood that clinicians may not prescribe an opioid other than buprenorphine for treating OUD in outpatient settings. An important exception is that FAO may be prescribed to patients with OUD to treat pain. Thus, outpatient LDB-OC case reports have described patients with acute or chronic pain using prescribed FAO or patients with OUD using their own nonprescribed opioids during buprenorphine dose escalation.^{6–8}

There is a combined total from case reports of over 250 patients treated via LDB-OC strategies.^{6–8,10} No available data exist to recommend a specific dosing schedule for either FAO or buprenorphine. A systematic review of case reports and case series described similar success rates with standard initiation

Downloaded from <http://journals.lww.com/journalofaddictionmedicine> by BhDMf5ePHkav1ZEoum1tQIN4a+kULNEZ gbsIHd4XMI0hCjwCX1AWnYQp/IIQH333D00dR7V7V5F14C3VC4/OAVpD88K2+Y6H515KE= on 07/30/2023

TABLE 2. Clinical Decision Support for Buprenorphine Initiation Techniques Based on the Clinical Setting

Initiation Strategy*	Fastest Slowest		
	HDB†	Standard‡	LDB-OC§
Possible advantages	-Quick stabilization -Bridge access barriers to ongoing buprenorphine	-Most common and well-described technique	-Opioid abstinence not initially required
Need for opioid withdrawal?	Yes	Yes	No
Premedicate with adjuvant medications?¶	Consider	Yes	Yes
Initial starting dose¶ (buprenorphine SL formulation)	8–16+ mg	2–8 mg	0.25 mg–1 mg
Duration of initiation until stabilization	≤2 h	1–3 days	3–10 d (may be longer in certain situations)
Need for opioid continuation	No	No	Yes
Full agonist opioid continuation dose	None	None	Examples: Methadone 30 mg PO daily or Hydromorphone 4 mg PO every 4 hr or Self-directed illicit/nonprescribed opioid use High
Care coordination required	Moderate	Moderate	High

*See Appendix C (<http://links.lww.com/JAM/A431>) for example protocols of these strategies.

†HDB = high-dose buprenorphine; this is sometimes referred to as “macro dosing.”

‡Standard buprenorphine initiation is based on the ASAM NPG and typically occurs with medically managed instructions for home buprenorphine initiation.³

§LDB-OC = low-dose buprenorphine with opioid continuation; this is sometimes referred to as “micro dosing” or “microinduction” but the most clinically accurate term is used here.

¶Adjuvant medications include clonidine, hydroxyzine, acetaminophen, and NSAIDs (Appendix D, <http://links.lww.com/JAM/A431>).

¶¶This refers to the initial dose only. The total daily dose on day 1 and subsequent days is likely more than this initial dose.

and LDB-OC (95.6% and 96%, respectively), with most cases of LDB-OC occurring in the hospital.⁸

High-dose buprenorphine is another initiation strategy where opioid discontinuation is followed by rapid HDB (≥8 mg starting dose).^{11,12} This strategy is based on the premise that increasing initial doses of buprenorphine beyond 8 mg sublingual (SL) will result in increasing agonist MOR activation and strengthening opioid blockade—both conferring significant advantages. Typically, HDB expects a period of opioid abstinence, which is highly variable. Once at least mild withdrawal (COWS ≥8) has developed, buprenorphine is escalated rapidly to 16–32 mg SL in 1 or 2 initial doses, aiming to quickly reduce OWS. The high-loading dose may benefit patients with anticipated delays accessing buprenorphine. Most HDB approaches are described in urgent care centers or EDs.

A prospective cohort study of ED patients with >75% confirmed HPSO exposure reported precipitated OWS in <1% after receiving buprenorphine initial doses of 8 mg or greater.⁴ In addition, 2 retrospective cohort studies of HDB across 16 EDs reported no increased adverse events compared with standard initiation; however, 1 study occurred before widespread HPSO, and the other reported a low incidence of HPSO use.^{11,12}

Commentary

Patients with pain transitioning from FAO to buprenorphine, patients admitted to hospital, and patients enrolled in opioid treatment programs transitioning from methadone to buprenorphine may be ideal for LDB-OC. However, outside of these settings, United States federal law is currently understood to prohibit med-

ical prescription of FOA to support buprenorphine initiation. The decision to advise a patient to continue opioid consumption during buprenorphine initiation is complex with no consensus on the relative risks and benefits of this approach. For the purposes of facilitating OUD treatment, the Drug Enforcement Administration Code of Federal Regulations allows either direct administering up to a 3-day supply of an opioid, including methadone (“the 72-hour rule”), or dispensing (when approved by the Drug Enforcement Administration exception) a 3-day supply of an opioid, including methadone, from a hospital, clinic, or ED for the treatment of OWS, which may be considered to facilitate LDB-OC.^{9,13}

Patients experiencing OWS generally should proceed with standard buprenorphine initiation (see Table 2). If concern for undertreatment of OWS exists due to lack of positive response to standard buprenorphine initiation doses, chronic use of HPSO, or anticipated delay in access, HDB may be considered as a safe alternative, particularly in the urgent care, ED, or hospital setting.

Insurance or state regulations could be a barrier to any nonstandard buprenorphine initiation strategy.

Clinical Considerations

- Observational data suggest buprenorphine initiation is best individualized by setting and patient preference (Tables 2 and 3).
- LDB-OC in hospital settings appears to be well tolerated in observational data.
- More evidence is needed to determine the optimal strategy for LDB-OC in ambulatory settings for patients who are ineligible for medically prescribed FAO under current regulations.

Downloaded from <http://journals.lww.com/journaladdictionmedicine> by BhDMf5ePHkav1ZeEum1tQIN4a+KJLhEZ
gbsIH04XMIDhCjwCX1AWnYQp/IIQHHD3i3D00dRy7TVSFI4C3VCA4/AVpDDa8K2+Y66H515KE= on 07/30/2023

- In patients with chronic exposure to HPSO who initiate buprenorphine after opioid abstinence and development of OWS, rapid dose escalation has been observed to be safe, primarily in the ED setting.

KQ2: What Strategies Can Address Patient Discomfort, Including Precipitated Opioid Withdrawal, If It Occurs During Buprenorphine Initiation?

Evidence Summary

Patient discomfort after an initial dose of buprenorphine can be from various pharmacologic and nonpharmacologic causes: ongoing OWS, withdrawal from other substances, adverse effects such as nausea, or precipitated opioid withdrawal (POW). Risk factors for POW related to HPSO are unknown and vary by individual and substance exposure, although recent prospective data showed a <1% incidence of POW after buprenorphine initiation in the ED.⁴

For OWS after buprenorphine initiation, the most effective treatment remains administration of additional buprenorphine. After most MORs are bound with buprenorphine, opioid agonism is optimized.¹⁴ The ceiling for many agonist effects is unknown,¹⁵ whereas the ceiling effect for respiratory depression has been well demonstrated.¹⁵ Nevertheless, in patients with advanced age, acute medical illness, chronic lung disease, and those already sedated due to other drugs or medications, the risk of worsening sedation and/or respiratory depression should be considered.

Commentary

Patient comfort during buprenorphine initiation depends on the patient's balance of buprenorphine agonist effects and FAO effects.¹⁴ Patients in a deficit state, where the combined agonism of buprenorphine and the FAO is less than the patient's baseline tolerance, will feel opioid withdrawal.¹⁴

Mild to Moderate OWS

Some patients with OUD starting buprenorphine will have persistent or worsening OWS that responds to increasing buprenorphine doses. Case reports and anecdotal experience suggest improvement with rapid dose escalations to 24–32 mg SL per day during initiation.^{14,16,17} Given the relative safety profile, increasing the buprenorphine dose is the most reasonable first-line treatment of persistent OWS.

Although medically managed opioid withdrawal alone is not recommended, evidence supports use of alpha-2 agonists and symptom-directed adjunctive medications in ameliorating OWS.¹⁸ It is reasonable to premedicate with these medications to reduce the severity of OWS. Limited use of benzodiazepines can be considered with attention to the risk of respiratory depression (see Appendix D, <http://links.lww.com/JAM/A431>).

Severe OWS

Buprenorphine POW is complex involving both chronic neuroadaptations and acute MOR dynamics; the clinical picture is unpredictable, and risk factors are poorly understood. Severe

cases of POW unresponsive to buprenorphine and supportive medications warrant acute management in an ED or a similar level of care for close monitoring and medication titration.

The treatment goal is rapid maximization of buprenorphine MOR activation in combination with multimodal agents (Appendix D, <http://links.lww.com/JAM/A431>).¹⁸ A patient who has received <16 mg buprenorphine SL and then develops severe OWS may need additional doses of buprenorphine to reach at least 24–32 mg SL. Successful use of buprenorphine doses during initiation as high as 64 mg SL has been reported.¹⁷

Intractable POW that does not respond to the above measures has not been studied well but likely requires hospital-level interventions and monitoring with a combination of additional buprenorphine, FAO, and nonopioid adjunctive medications, such as benzodiazepines, ketamine, or dexmedetomidine (an intravenous alpha-2 agonist). Ketamine is a *N*-methyl-D-aspartate receptor antagonist that may potentiate the opioid system.¹⁹ Although more research is needed, these effects may treat POW at 0.3 mg/kg boluses administered over 10–15 minutes or via continuous infusions.¹⁹ Administration of high-affinity intravenous FAOs can be considered in addition to buprenorphine in select cases of POW; buprenorphine should be continued normally after POW resolution. Benzodiazepines and/or antipsychotics should be sparingly used and targeted to treat persistent agitation and/or anxiety.

Clinical Considerations

- For mild to moderate OWS during buprenorphine initiation, treatment with buprenorphine >24 mg SL on day 1 may be considered for patients with clinically apparent high opioid tolerance.
- For mild to moderate OWS during buprenorphine initiation, alpha-2 agonists and other symptom-targeted treatments may be helpful in addition to more buprenorphine.
- For intractable cases of OWS, treatment escalation involves transition to an ED or hospital for additional buprenorphine and consideration of high-affinity FAO, benzodiazepines, ketamine, or dexmedetomidine.

KQ3: After Buprenorphine Initiation, What Range of Buprenorphine Dosing and/or Dosing Strategies Can Be Considered During Stabilization and Long-Term Treatment?

Evidence Summary

Buprenorphine stabilization refers to the treatment period when individuals do not experience OWS and have minimal to no opioid cravings.²⁰ Buprenorphine long-term treatment refers to treatment after stabilization and is recommended as long as the patient benefits, which can be for years or a lifetime.

The ASAM NPG recommends titrating the buprenorphine dose “to alleviate symptoms” and to “be sufficient to enable patients to discontinue illicit opioid use.”²³ The ASAM NPG cites a buprenorphine dose limit of 24 mg/d based on “limited evidence regarding relative efficacy of doses higher than 24 mg/d.”²³ High-quality studies show improved treatment retention, reduced opioid use, and lack of adverse events at doses of buprenorphine 16–32 mg/d, and the need for doses up to 32 mg/d for some patients has been recognized since 2004.^{20–22}

No high-quality data inform the most effective buprenorphine dose for individuals with HPSO exposure; however, it is understood that individuals with HPSO exposure may have more difficulty achieving stabilization. Higher buprenorphine doses that approximate HPSO may be more effective. A recent human laboratory study of patients with OUD found that higher concentrations of buprenorphine (5 ng/mL) were most effective in protecting against fentanyl-induced respiratory depression.²³ Buprenorphine formulations and doses achieving the highest plasma concentrations are SL buprenorphine 24–32 mg/d and injectable extended release (XR) buprenorphine 300 mg.²⁴ Therefore, raising buprenorphine doses to 24–32 mg/d or using XR buprenorphine may help some individuals with extensive exposure to HPSO stabilize.

Rigorous data are lacking on long-term SL buprenorphine dosing of 24–32 mg/d for buprenorphine treatment.²⁵ One observational study found reduced opioid use for individuals treated with SL buprenorphine doses between 24 and 56 mg over 30 months.²⁶ Another observational study performed in opioid treatment programs found that individuals treated with 30–32 mg of buprenorphine were more likely to be retained in treatment at 24 weeks.²⁷ Most recent studies are short term and limited to case series of patients receiving single doses of buprenorphine²⁸ or case reports.²⁹

Higher buprenorphine stabilization doses may be needed during pregnancy. Pregnancy expands plasma volumes and adipose stores, and is associated with lower serum levels of buprenorphine related to elevated buprenorphine metabolism, particularly during the third trimester.³⁰ Buprenorphine doses >16 mg daily and frequent dosing (2–4 times daily) may be needed to achieve consistent effective buprenorphine plasma levels and prevent opioid withdrawal between doses.³¹

Commentary

Buprenorphine dosing during stabilization should be individualized. Although some insurance plans or states may have buprenorphine dose limitations, some patients may benefit from doses higher than 16–24 mg/d. Higher doses of buprenorphine (≥16 mg daily) appear necessary for rapid stabilization in individuals with HPSO exposure. Factors such as psychosocial vulnerability, concomitant stimulant use, or mental health conditions may further impede stabilization and necessitate higher doses and a higher level of care.²⁵ For highly vulnerable patients, consider the potential lifesaving benefit of using high buprenorphine doses during buprenorphine stabilization (>24 mg daily) and weigh this against potential harms. Then, document clinical reasoning when patients are prescribed buprenorphine doses >24 mg/d. Once individuals achieve durable stabilization and have no ongoing FOA use, doses within the range recommended by the ASAM NPG may be effective for long-term treatment.

Clinical Considerations

- Some patients with high opioid tolerance may require buprenorphine doses >24 mg/d during treatment stabilization.
- Physiological changes during pregnancy alter buprenorphine metabolism, necessitating adjusted buprenorphine dose and dosing intervals.

- Consider dose and frequency adjustments, psychosocial supports, and a higher level of care if individuals are unable to stabilize with buprenorphine.
- Consider a reassessment of higher (>24 mg/d) long-term doses once patients enter long-term treatment without ongoing use of opioids.

KQ4: What Are Indications for Injectable Extended-Release Buprenorphine for OUD Treatment Compared With Sublingual Formulations?

Evidence Summary

Extended release buprenorphine has been available since 2017 for the treatment of moderate to severe OUD.³² There are 2 formulations of XR buprenorphine: Sublocade and Brixadi.

At its highest doses (Sublocade 300 mg), studies show that XR buprenorphine achieves similar or higher buprenorphine plasma levels at steady state compared with 24 mg daily SL buprenorphine, although it may take up to 8–16 weeks to reach steady state (Appendix E, <http://links.lww.com/JAM/A431>).^{24,33} Plasma peak-to-trough fluctuations and first-pass metabolism are lower for XR versus SL buprenorphine.³³

Extended release buprenorphine is an option for individuals who struggle to stabilize. Compared with SL buprenorphine, XR buprenorphine has shown statistically significant reductions in opioid use^{34,35} and durable opioid blockade.^{36–38} In 1 trial with 30% of patients exposed to HPSO, no opioid overdoses occurred in the XR buprenorphine (Brixadi) group compared with 5 overdoses in the SL buprenorphine group.³⁵ A case series of 40 adults treated with XR buprenorphine (Sublocade) who had HPSO exposure, unstable housing, stimulant and other substance use, and mental health conditions found that 65% of patients discontinued opioid use.³⁹ Notably 55% of patients in that study required supplemental SL buprenorphine related to ongoing opioid withdrawal and cravings.³⁹ Some patients may prefer XR buprenorphine due to the need for decreased facility visits, greater autonomy for travel, and greater ability to adhere to treatment,⁴⁰ although others may dislike injections.⁴¹

The initiation of XR buprenorphine, like other buprenorphine initiation strategies, is evolving. Initial guidance recommended a 7-day period of SL buprenorphine lead-in, but the ASAM NPG states “only 1 dose of SL buprenorphine is needed before XR buprenorphine initiation,” and this has been described in case reports.^{3,4,16,35} Receipt of XR buprenorphine has also been described after both LDB-OC and HDB initiations.^{16,39,42}

Evidence is limited for XR buprenorphine for pregnant individuals.⁴³ One case series raises concern about the efficacy of XR buprenorphine (Sublocade) alone and describes that supplementation with SL buprenorphine may be needed in the first 1–3 months of treatment.⁴³ Sublocade contains an excipient with *N*-methyl-2-pyrrolidone with teratogenic effects in animal studies²⁴; Brixadi does not contain this substance in its weekly product, and a clinical trial in pregnant and postpartum individuals is ongoing.⁴⁴ Clinicians may consider XR buprenorphine, particularly Brixadi, for pregnant individuals.

Commentary

Extended release buprenorphine offers high plasma buprenorphine concentrations at steady state and continuous exposure, which may be essential for some individuals. In patients who have been previously unable to stabilize on buprenorphine, high opioid tolerance, and high stimulant co-use, same-day XR buprenorphine administration may be considered. Extended release buprenorphine requires monthly medical appointments and may be challenging in rural areas or for individuals receiving telehealth treatment.

Clinical Considerations

- Consider XR buprenorphine formulations for individuals unable to stabilize on SL buprenorphine formulations, particularly individuals who have had extensive HPSO exposure, unsafe living environments, and/or multiple opioid overdoses.
- Consider the administration of XR buprenorphine soon after successful buprenorphine initiation to achieve durable opioid overdose protection.
- Although XR buprenorphine is reaching steady state, consider the risks and benefits of additional SL buprenorphine, particularly for pregnant individuals.

KQ5: How Do Other Novel Drug Components Affect Buprenorphine Initiation and Stabilization?

The unregulated drug supply has become increasingly unpredictable and hazardous. Novel drug components are substances added to the expected drug to enhance or mimic the intended effects. In addition to HPSO, other synthetic opioids, designer benzodiazepines, synthetic cannabinoids, ketamine, xylazine, levamisole, prescription medications, and synthetic stimulants are encountered in the unregulated drug supply. People who use drugs may be aware that adulteration occurs, but unaware of which components and in what concentration. Drug checking provides actionable information, but access is limited.

The potential health consequences of exposure to unexpected drug components can be significant (Appendix F, <http://links.lww.com/JAM/A431>). Polysubstance overdose is the norm rather than an exception, and although naloxone administration remains vital, other supportive care is needed for many cases of polysubstance overdose.

Limited data exist on the effect of novel drug components on buprenorphine treatment. The ubiquity of HPSO has made

buprenorphine initiation more challenging. Similarly, some components, especially xylazine, may affect withdrawal presentations (eg, intense or protracted OWS), cause medical complications (eg, skin ulcers; severe anemia) that delay care or cause individuals to prematurely leave care.⁴⁵ Concomitant treatment with clonidine, gabapentin, or benzodiazepines could be considered for xylazine withdrawal.⁴⁶

Clinical Considerations

- Consider withdrawal from other substances when OWS does not respond as expected to ancillary medications and buprenorphine; utilize a higher level of care as needed.
- Consider other etiologies or overdose from other substances when an individual does not respond as expected to multiples doses of naloxone.
- Consider using comprehensive toxicology testing and drug checking to identify drug components; use this information to inform harm reduction and overdose prevention strategies.

KQ6: What Are OUD Treatment Alternatives After Repeated Unsuccessful Attempts at Buprenorphine Treatment?

Evidence Summary

The ASAM NPG recommends that “medications for treating OUD should be available for all patients. Clinicians should consider the patient’s preferences, past treatment history, current state of illness, and treatment setting when deciding between methadone, buprenorphine, and naltrexone.”³ Many patients may prefer buprenorphine, although repeated unsuccessful buprenorphine initiation attempts may require other MOUD options.

Commentary

Buprenorphine. Unsuccessful medically managed buprenorphine initiation can harm patients and place them at risk for overdose. If outpatient-based initiation strategies are unsuccessful, referral for medically managed inpatient initiation may be necessary. In the inpatient setting, clinicians may consider a LDB-OC approach, HDB, and ancillary medications (Table 3).^{10,47} Buprenorphine initiation in highly supportive environments, such as hospitals, can improve treatment retention.²⁵

TABLE 3. Considerations for Buprenorphine Initiation Approach Based on High-Tolerance and High-Potency Synthetic Opioid Exposure—Clinical Setting and Opioid Withdrawal

Situation	Outpatient	Emergency Department	Residential/Hospital Setting*
Opioid withdrawal, COWS ≥8 with 1 objective sign of opioid withdrawal	Standard initiation or HDB	Standard initiation or HDB	Standard initiation or HDB
Opioid withdrawal, COWS <8	Standard initiation or LDB-OC†	Standard initiation or LDB-OC†	Standard initiation or LDB-OC†
Pain + opioid withdrawal, COWS <8	Standard initiation or prescribed FAO for pain with LDB-OC	Standard initiation or prescribed FAO for pain with LDB-OC	Administered FAO + LDB-OC

*Includes medically managed levels of care such as ASAM 4th Edition Levels of Care 3.7 (medically managed rehab), 4.0 (hospital setting).

†LDB-OC = low-dose buprenorphine initiation with opioid continuation (prescribed versus nonprescribed). Requires an individualized determination of the risks and benefits of prescribed full opioid agonist within federal regulations versus continuation of an illicitly obtained full opioid agonist.

Downloaded from <http://journals.lww.com/journaladdictionmedicine> by BhDMf5ePHkav1zEumtn1QIN4a+kULHEZ
gbsIHd4XMI0hCjwCwCX1AWNvQp/IIQH3D3D0D0dRy7TVSFI4C3V3C4/OAVppDa8K2+Y6H515KE= on 07/30/2023

Methodone. Methodone is the first alternative medication recommended for individuals who elect not to start or continue buprenorphine. Patients with HPSO exposure may need closer monitoring, use of adjunctive medications during initiation, and faster up-titration of methadone.⁴⁸ Geographical, financial, or transportation challenges may complicate treatment access.

Extended-Release Naltrexone. Typically considered a second-line treatment for OUD, initiation is challenging for individuals with extensive HPSO use due to its prolonged elimination.⁴⁹ In a multisite clinical trial, individuals who tested positive for fentanyl were 11 times less likely to initiate XR naltrexone than buprenorphine or methadone.⁴⁹ This evidence, along with the higher risk of overdose off MOUD, makes XR naltrexone a dangerous alternative for treatment outside of a controlled setting. If a patient is highly motivated for starting XR naltrexone, a rapid conversion may be considered in a controlled environment.⁵⁰ Overdose prevention education and informed consent are vital due to the high risk of overdose while awaiting initiation of treatment and at discontinuation of XR naltrexone.

Clinical Considerations

- If a patient has been unsuccessful with buprenorphine initiation and continues desiring buprenorphine, consider a higher level of care and/or alternative initiation strategies.
- Consider methadone for individuals who are unable to stabilize safely and effectively on buprenorphine.
- Consider XR naltrexone initiation only in individuals in a highly structured, medically managed inpatient environment.

REFERENCES

1. Fiellin DA. Buprenorphine initiation in the era of high-potency synthetic opioids: a call for community-based participatory research to help learning health systems provide precision medicine for opioid use disorder. *J Addict Med.* 2022;16(6):e348–e349.
2. Sue KL, Cohen S, Tilley J, et al. A plea from people who use drugs to clinicians: new ways to initiate buprenorphine are urgently needed in the fentanyl era. *J Addict Med.* 2022;16:389–391.
3. The ASAM national practice guideline for the treatment of opioid use disorder: 2020 focused update. *J Addict Med.* 2020;14(2S Suppl 1):1–91.
4. D’Onofrio G, Hawk KF, Perrone J, et al. Incidence of precipitated withdrawal during a multisite emergency department–initiated buprenorphine clinical trial in the era of fentanyl. *JAMA Netw Open.* 2023;6(3):e236108–e236108.
5. Pantazis CB, Gonzalez LA, Tunstall BJ, et al. Cues conditioned to withdrawal and negative reinforcement: neglected but key motivational elements driving opioid addiction. *Sci Adv.* 2021;7(15):eabf0364.
6. Cohen SM, Weimer MB, Levander XA, et al. Low dose initiation of buprenorphine: a narrative review and practical approach. *J Addict Med.* 2022;16(4):399–406.
7. Moe J, O’Sullivan F, Hohl CM, et al. Short communication: systematic review on effectiveness of micro-induction approaches to buprenorphine initiation. *Addict Behav.* 2021;114:106740.
8. Spreen LA, Dittmar EN, Quirk KC, et al. Buprenorphine initiation strategies for opioid use disorder and pain management: a systematic review. *Pharmacotherapy.* 2022;42(5):411–427.
9. Administering or dispensing of narcotic drugs 21 C.F.R. § 1306.07. Available at: <https://www.ecfr.gov/current/title-21/chapter-II/part-1306/subject-group-ECFR1eb5bb3a23fdd0/section-1306.07>. Accessed March 1, 2023.
10. Adams KK, Cohen SM, Guerra ME, et al. Low-dose initiation of buprenorphine in hospitalized patients using buccal buprenorphine: a case series. *J Addict Med.* 2023. doi:10.1097/ADM.0000000000001146.

11. Herring AA, Vosooghi AA, Luftig J, et al. High-dose buprenorphine induction in the emergency department for treatment of opioid use disorder. *JAMA Netw Open.* 2021;4(7):e2117128.
12. Snyder H, Chau B, Kalmin MM, et al. High-dose buprenorphine initiation in the emergency department among patients using fentanyl and other opioids. *JAMA Netw Open.* 2023;6(3):e231572–e231572.
13. Exceptions to regulations 21 C.F.R. § 1307.03. Available at: <https://www.ecfr.gov/current/title-21/chapter-II/part-1307/subject-group-ECFR9876b995678379/section-1307.03>. Accessed March 1, 2023.
14. Greenwald MK, Herring AA, Perrone J, et al. Neuropharmacological model to explain buprenorphine induction challenges. *Ann Emerg Med.* 2022;80(6):509–524.
15. Huhn AS, Strain EC, Bigelow GE, et al. Analgesic effects of hydromorphone versus buprenorphine in buprenorphine-maintained individuals. *Anesthesiology.* 2019;130(1):131–141.
16. Mariani JJ, Mahony AL, Podell SC, et al. Open-label trial of a single-day induction onto buprenorphine extended-release injection for users of heroin and fentanyl. *Am J Addict.* 2021;30(5):470–476.
17. Ahmadi J, Jahromi MS, Ghahremani D, et al. Single high-dose buprenorphine for opioid craving during withdrawal. *Trials.* 2018;19(1):675.
18. Gowling L, Farrell M, Ali R, et al. Alpha₂-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database Syst Rev.* 2016;2016(5):–Cd002024.
19. Hailozian C, Luftig J, Liang A, et al. Synergistic effect of ketamine and buprenorphine observed in the treatment of buprenorphine precipitated opioid withdrawal in a patient with fentanyl use. *J Addict Med.* 2022;16(4):483–487.
20. Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04–3939. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2004.
21. Fareed A, Vayalapalli S, Casarella J, et al. Effect of buprenorphine dose on treatment outcome. *J Addict Dis.* 2012;31(1):8–18.
22. Bergen AW, Baurley JW, Ervin CM, et al. Effects of buprenorphine dose and therapeutic engagement on illicit opiate use in opioid use disorder treatment trials. *Int J Environ Res Public Health.* 2022;19(7):4106.
23. Moss LM, Algera MH, Dobbins R, et al. Effect of sustained high buprenorphine plasma concentrations on fentanyl-induced respiratory depression: a placebo-controlled crossover study in healthy volunteers and opioid-tolerant patients. *PLoS One.* 2022;17(1):e0256752.
24. Sublocade [package insert]. North Chesterfield, VA: Indivior Inc, 2018.
25. Kennedy AJ, Wessel CB, Levine R, et al. Factors associated with long-term retention in buprenorphine-based addiction treatment programs: a systematic review. *J Gen Intern Med.* 2022;37(2):332–340.
26. Di Petta G, Leonardi C. Buprenorphine high-dose, broad spectrum, long-term treatment: a new clinical approach to opiate alkaloid dependency. *Heroin Add Rel Clin Probl.* 2005;7(3):21–25.
27. Hser YI, Saxon AJ, Huang D, et al. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. *Addiction.* 2014;109(1):79–87.
28. Gross A, Jacobs EA, Petry NM, et al. Limits to buprenorphine dosing: a comparison between quintuple and sextuple the maintenance dose every 5 days. *Drug Alcohol Depend.* 2001;64(1):111–116.
29. Danilewitz M, McLean M. High-dose buprenorphine for treatment of high potency opioid use disorder. *Drug Alcohol Rev.* 2020;39(2):135–137.
30. Bastian JR, Chen H, Zhang H, et al. Dose-adjusted plasma concentrations of sublingual buprenorphine are lower during than after pregnancy. *Am J Obstet Gynecol.* 2017;216(1):64.e1–64.e7.
31. Lo-Ciganic W-H, Donohue JM, Kim JY, et al. Adherence trajectories of buprenorphine therapy among pregnant women in a large state Medicaid program in the United States. *Pharmacoepidemiol Drug Saf.* 2019;28(1):80–89.
32. Poliwooda S, Noor N, Jenkins JS, et al. Buprenorphine and its formulations: a comprehensive review. *Health Psychol Res.* 2022;10(3):37517.
33. Jones AK, Ngaimisi E, Gopalakrishnan M, et al. Population pharmacokinetics of a monthly buprenorphine depot injection for the treatment of opioid use disorder: a combined analysis of phase II and phase III trials. *Clin Pharmacokinet.* 2021;60(4):527–540.

34. Ling W, Shoptaw S, Goodman-Meza D. Depot buprenorphine injection in the management of opioid use disorder: from development to implementation. *Subst Abuse Rehabil*. 2019;10:69–78.
35. Lofwall MR, Walsh SL, Nunes EV, et al. Weekly and monthly subcutaneous buprenorphine depot formulations vs daily sublingual buprenorphine with naloxone for treatment of opioid use disorder: a randomized clinical trial. *JAMA Intern Med*. 2018;178(6):764–773.
36. Walsh SL, Comer SD, Lofwall MR, et al. Effect of buprenorphine weekly depot (CAM2038) and hydromorphone blockade in individuals with opioid use disorder: a randomized clinical trial. *JAMA Psychiatry*. 2017;74(9):894–902.
37. Laffont CM, Gomeni R, Heidbreder C, et al. Population pharmacokinetic modeling after repeated administrations of RBP-6000, a new, subcutaneously injectable, long-acting, sustained-release formulation of buprenorphine, for the treatment of opioid use disorder. *J Clin Pharmacol*. 2016;56(7):806–815.
38. Nasser AF, Greenwald MK, Vince B, et al. Sustained-release buprenorphine (RBP-6000) blocks the effects of opioid challenge with hydromorphone in subjects with opioid use disorder. *J Clin Psychopharmacol*. 2016;36(1):18–26.
39. Peckham AM, Kehoe LG, Gray JR, et al. Real-world outcomes with extended-release buprenorphine (XR-BUP) in a low threshold bridge clinic: a retrospective case series. *J Subst Abuse Treat*. 2021;126:108316.
40. Rolland B, Trojak B, Nourredine M, et al. Determinants of interest in extended-released buprenorphine: a survey among 366 French patients treated with buprenorphine or methadone. *Drug Alcohol Depend*. 2021;220:108492.
41. Neale J, Tompkins CNE, Strang J. Depot buprenorphine injections for opioid use disorder: patient information needs and preferences. *Drug Alcohol Rev*. 2019;38(5):510–518.
42. Seval N, Nunez J, Roth P, et al. Inpatient low-dose transitions from full agonist opioids including methadone onto long-acting depot buprenorphine: case series from a multicenter clinical trial. *J Addict Med*. 2023. Publish ahead of print.
43. Cleary EM, Byron RK, Hinely KA, et al. Subcutaneous buprenorphine extended-release use among pregnant and postpartum women. *Obstet Gynecol*. 2020;136(5):902–903.
44. Winhusen T, Lofwall M, Jones HE, et al. Medication treatment for opioid use disorder in expectant mothers (MOMs): design considerations for a pragmatic randomized trial comparing extended-release and daily buprenorphine formulations. *Contemp Clin Trials*. 2020;93:106014.
45. Friedman J, Montero F, Bourgois P, et al. Xylazine spreads across the US: a growing component of the increasingly synthetic and polysubstance overdose crisis. *Drug Alcohol Depend*. 2022;233:109380.
46. Ehrman-Dupre R, Kaigh C, Salzman M, et al. Management of xylazine withdrawal in a hospitalized patient: a case report. *J Addict Med*. 2022;16(5):595–598.
47. Thakrar AP, Uritsky TJ, Christopher C, et al. Safety and preliminary outcomes of short-acting opioid agonist treatment (sOAT) for hospitalized patients with opioid use disorder. *Addict Sci Clin Pract*. 2023;18(1):13.
48. Buresh M, Nahvi S, Steiger S, et al. Adapting methadone inductions to the fentanyl era. *J Subst Abuse Treat*. 2022;141:108832.
49. Cook RR, Torralva R, King C, et al. Associations between fentanyl use and initiation, persistence, and retention on medications for opioid use disorder among people living with uncontrolled HIV disease. *Drug Alcohol Depend*. 2021;228:109077.
50. Bisaga A, Mannelli P, Yu M, et al. Outpatient transition to extended-release injectable naltrexone for patients with opioid use disorder: a phase 3 randomized trial. *Drug Alcohol Depend*. 2018;187:171–178.