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

**PRESENTED BY:**
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# ACRONYMS

| | | | |
|---|---|---|---|
| **ASAM** | American Society of Addiction Medicine | **MOUD** | Medications for opioid use disorder |
| **COWS** | Clinical Opioid Withdrawal Scale | **NPG** | National practice guidelines |
| **FAO** | Full agonist opioids | **NTP, OTP** | Narcotic treatment program **OR** opioid treatment program |
| **HDB** | High-dose buprenorphine | **OWS** | Opioid withdrawal symptoms |
| **HPSO** | High potency synthetic opioids | **OUD** | Opioid use disorder |
| **LDB-OC** | Low-dose buprenorphine with opioid continuation | **SAMHSA** | Substance Abuse and Mental Health Services Administration |
| **MAT** | Medication-assisted treatment **OR** medications for addiction treatment | **SDOH** | Social determinants of health |

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# ASAM CLINICAL CONSIDERATIONS
# NOVEMBER/DECEMBER 2023

REVIEW

OPEN CME/MOC Editor's Choice

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

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**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;17: 632–639)

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

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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/Symple. Dr Herring, Dr Kawasaki, Dr Meyer, and Dr Ramsey report no conflicts of interest.

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**TABLE 1.** Buprenorphine Clinical Considerations Scope and Key Questions Components

| Key Question Components | |
|---|---|
| Population | Individuals with severe OUD chronically exposed to HPSO<br>Pregnant individuals with OUD chronically exposed to HPSO |
| Interventions | Buprenorphine initiation*<br>Buprenorphine stabilization†<br>Buprenorphine long-term treatment |
| Comparisons | Usual practice as specified in the ASAM 2020 Updated OUD National Practice Guideline (NPG) |
| Outcomes | Opioid withdrawal syndrome<br>Precipitated opioid withdrawal‡<br>Opioid cravings<br>Recurrence of opioid use<br>Morbidity (eg, nonfatal overdose, premature hospital discharge, infections)<br>All-cause mortality<br>Opioid-related mortality |
| Timing | Any |
| Setting | All outpatient/ambulatory practice settings<br>Emergency department and hospital-based practice§ |
| Key Questions | 1. What specific clinical situations favor use of low or high-dose buprenorphine initiation strategies?<br>2. What strategies can address patient discomfort, including precipitated opioid withdrawal, if it occurs during buprenorphine initiation?<br>3. After buprenorphine initiation, what range of buprenorphine dosing and/or dosing strategies can be considered during stabilization and long-term treatment?<br>4. What are indications for injectable extended-release buprenorphine for OUD treatment compared with sublingual formulations?<br>5. How do other novel drug components affect buprenorphine initiation and stabilization?<br>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.

buprenorphine initiation, stabilization, and long-term treatment for individuals with OUD who are chronically exposed to 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

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 im-

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In November/December 2023, ASAM released **ASAM Clinical Considerations: Buprenorphine Treatment of Opioid Use Disorder for Individuals Using High-Potency Synthetic Opioids.**

🔗 **Publicly available at this link**



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# METHODOLOGY

- The ASAM Quality Improvement Council:
  - Assembled a group of experts in OUD treatment to serve as the writing group.
  - Assembled a separate work group to serve as a review panel.
  - The ASAM Quality Improvement Council and Board of Directors have approved this clinical document.
  - Reviewed 578 English language articles found in PubMed.
    - Human studies between 2012-2022.
    - 41 studies meet inclusion criteria.

Sources: https://journals.lww.com/journaladdictionmedicine/fulltext/2023/11000/asam_clinical_considerations__buprenorphine.2.aspx

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# HIGH POTENCY SYNTHETIC OPIOIDS (HPSO)

| Name | Human, Veterinary, Neither or Both? | Relative potency compared with morphine |
|---|---|---|
| Fentanyl and derivatives | Both | 50–100 |
| Sufentanil | Human | 1000–4000 |
| Acetylfenatnyl | Neither | 15.7 |
| Carfentanil | Veterinary | 10,000 |
| Ocfentanil | Neither | 90 |
| Nitazines | | |
| Isotonitazine | Neither | 1000 - 2000 |

Sources: Shafi et al 2022; https://www.drugsandalcohol.ie/38001/

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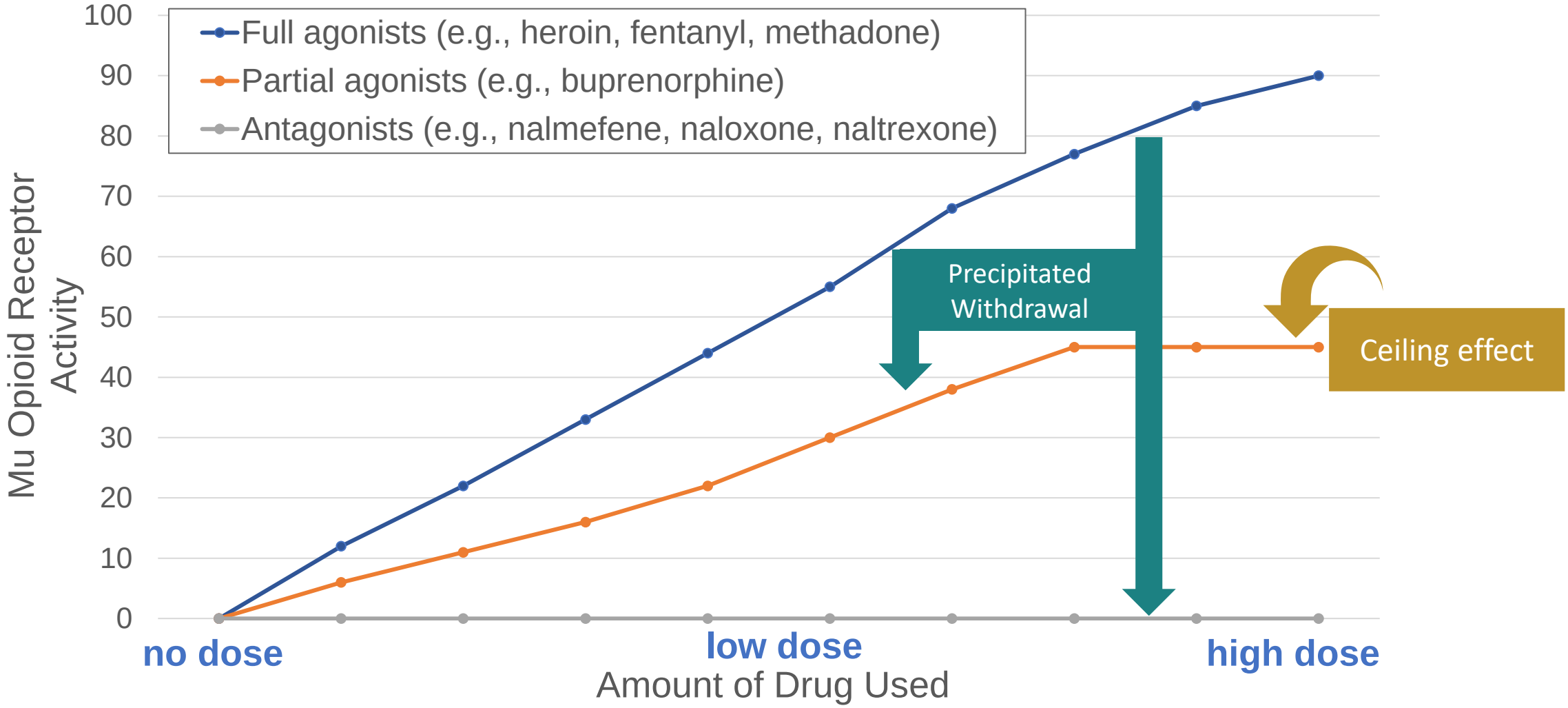
# FULL, PARTIAL, OR NO OPIOID EFFECT

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# WHAT SITUATIONS FAVOR USE OF LOW OR HIGH-DOSE BUPRENORPHINE INITIATION STRATEGIES?

**"Observational data suggest that buprenorphine initiation is best individualized by setting and patient preference."**

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

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# WHAT SPECIFIC CLINICAL SITUATIONS FAVOR USE OF LOW INITIATION STRATEGIES?

## Low-dose buprenorphine with opioid continuation (LDB-OC):

- Patients are administered (or self-administer) full agonist opioids (FAO) at the same time they gradually escalate buprenorphine, starting with low-dose buprenorphine.
- Consider for patients with:
  - Pain.
  - Admitted to hospital.
  - Transitioning from methadone to buprenorphine at opioid treatment program.
- Outside of hospitals and OTPs it is not legal to prescribe FAOs in the US.
- Therefore, if outpatient, this applies to people using their own opioids.

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# LOW DOSE BUPRENORPHINE WITH OPIOID CONTINUATION (LDB-OC)

- Case reports, case series, observational studies and 1 feasibility study of greater than 924 patients with OUD and/or pain.
- Different strategies have been used, and there is no available data to recommend a specific dosing strategy.
- Systematic review described similar success rates.
  - 95.6% traditional initiation group and 96% in the LDB-OC successfully rotated to sublingual buprenorphine.

Spreen LA, Dittmar EN, Quirk KC, Smith MA. Buprenorphine initiation strategies for opioid use disorder and pain management: A systematic review. Pharmacotherapy. 2022 May;42(5):411-427. doi: 10.1002/phar.2676. Epub 2022 Mar 25. PMID: 35302671; PMCID: PMC9310825. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9310825/

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# HIGH-DOSE BUPRENORPHINE STARTS

## Rapid high-dose buprenorphine (HDB) initiation after opioid discontinuation:

- After a period of opioid abstinence, HDB is initiated with ≥8mg sublingual (SL) buprenorphine once mild withdrawal symptoms have developed.
- 16-32 mg sublingual buprenorphine in 1-2 doses.
  - **No increased incidence of adverse events compared to standard initiation.**
  - HDB is commonly seen in emergency setting or urgent care centers.
  - For people with:
    - Undertreatment of opioid withdrawal symptoms.
    - Chronic use of high-potency synthetic opioids (HPSO).
    - Anticipated delay in outpatient access to care.

**Open-Access Articles:**

Herring, A. A. et al. (2021). High-Dose Buprenorphine Induction in the Emergency Department for Treatment of Opioid Use Disorder. JAMA network open, 4(7), e2117128. https://doi.org/10.1001/jamanetworkopen.2021.17128

Snyder, H. et al. (2023). High-Dose Buprenorphine Initiation in the Emergency Department Among Patients Using Fentanyl and Other Opioids. JAMA network open, 6(3), e231572. https://doi.org/10.1001/jamanetworkopen.2023.1572

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# BUPRENORPHINE TREATMENT OUTCOMES IN CONTEXT OF FENTANYL

| Buprenorphine Treatment Outcomes in Context of Fentanyl | | | | |
|---|---|---|---|---|
| **Location data collected** | **Start when** | **First dose** | **Toxicology conducted** | **Results** |
| California Emergency Departments | COWS 8 or higher and Objective withdrawal | 8mg buprenorphine | No 10% reported using fentanyl | Less than 2% of total group experienced worsening of withdrawal symptoms; of those who used fentanyl 5% reported worsening of withdrawal symptoms |
| US Emergency Departments | COWS 8 or higher | 8mg buprenorphine or extended-release buprenorphine | Yes 78% using fentanyl | Less than 1% reported worsening of withdrawal symptoms |

California Emergency Departments; US Emergency Departments
Clinical Opioid Withdrawal Scale (COWS)

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# WHAT STRATEGIES CAN ADDRESS PATIENT DISCOMFORT, INCLUDING PRECIPITATED OPIOID WITHDRAWAL, IF IT OCCURS DURING BUPRENORPHINE INITIATION?

- For mild to moderate OWS during buprenorphine initiation give 24-32mg SL on day 1, given the safety of buprenorphine and randomized controlled trials.
- For severe OWS: consider transfer “to emergency department additional buprenorphine to reach 24-32mg.”
  - Randomized controlled trial: 32 vs 64mg vs 96mg.
  - 64mg decreased carvings more than 32mg.
  - 96mg did not decrease symptoms beyond 64mg.

Source: Ahmadi, et al. (2018). Single high-dose buprenorphine for opioid craving during withdrawal. Trials, 19(1), 675. https://doi.org/10.1186/s13063-018-3055-z.

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# INTRACTABLE PRECIPITATED OPIOID WITHDRAWAL KETAMINE HAS BEEN TRIED, MORE RESEARCH IS NEEDED

**Double blind placebo-controlled trial of ketamine vs saline in anesthesia facilitated antagonist induction; did NOT report intent to treat analysis (Jovaisa, 2006).**

- Significantly lower cardiovascular, respiratory and neuroendocrine responses and withdrawal scores in the ketamine group compared to saline infusion group.
- **0.5mg bolus, followed by .5mg/kg/h** (unclear how many hours).

**Case reports and case series:**

- 2 cases of opioid withdrawal ketamine 5mg IV bolus, repeated once; both given buprenorphine (Omoigui, 2011).
- Patient presented with buprenorphine precipitated opioid withdrawal and was given .6mg/kg IV ketamine over 1 h + 16mg buprenorphine and discharged from ED 4 hour later (Hailozian, 2022).
- Retrospective case series of 10 patients treated in ED 2021-2022 with precipitated withdrawal .3mg/kg IV over 15 min, followed by .3mg/kg IV over 1 hour + buprenorphine (Henney, 2022).

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# After buprenorphine initiation, what range of buprenorphine dosing and/or dosing strategies can be considered during stabilization and long-term treatment?

- **Buprenorphine Stabilization:** “refers to the treatment period when individuals do not experience opioid withdrawal symptoms and have minimal to no opioid cravings” according to SAMHSA TIP 63.
- ASAM NPG recommends titrating dose to “alleviate symptoms” and “discontinue illicit opioid use.”
  - Buprenorphine doses should be individualized.
  - Psychosocial factors, including social determinants of health (SDOH) should be considered when determining dosage and levels of care of treatment.
  - No high-quality data to inform the most effective dose of buprenorphine for individuals using HPSOs compared to other opioids.



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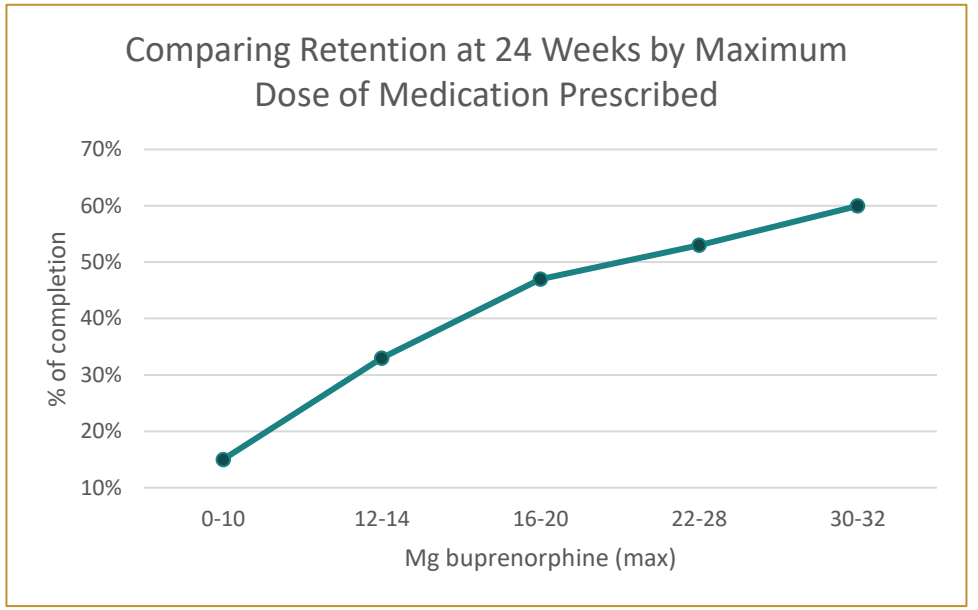
# WHAT RANGE OF BUPRENORPHINE DOSING SHOULD BE CONSIDERED FOR LONG-TERM TREATMENT?

- Randomized open label trial of 1267 patients in OTPs in the US.
- Linear increase in retention in treatment with buprenorphine dose with 60% still in treatment at 24 weeks with 30-32mg buprenorphine.
- Linear decrease in opioid use for every mg buprenorphine increase.




Sources: 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.

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# WHAT RANGE OF BUPRENORPHINE DOSING SHOULD BE CONSIDERED FOR LONG-TERM TREATMENT?

- 650 patients in an observational study outside the US.
- Linear decrease in opioid and other drug use with increased doses.

**Table 2. Urinalysis for patients receiving different doses of buprenorphine**

| Buprenorphine dose | Positive urinalysis |
|---|---|
| 24-32 mg | 2% positive for opiates<br>10% positive for cocaine<br>10% positive per benzodiazepines<br>30% positive for cannabinoids |
| 32-40 mg | 100% negative for opiates★<br>5% positive for cocaine<br>20% positive for cannabinoids |
| 40-56 mg | 100% negative for all urinary metabolites★ |

Source: 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.

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# DOSE STABILIZATION AND LONG-TERM TREATMENT

Some patients may require buprenorphine higher than 24mg/ day during stabilization.

- When this occurs, weigh pros and cons and document medical reasoning and shared decision making.

Consider reassessment of doses higher than 24mg/day once patient enter long- term treatment without ongoing opioid use.

Physiologic changes during pregnancy are known to necessitate adjustment to buprenorphine dosing and dose interval.

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# WHAT ARE INDICATIONS FOR INJECTABLE EXTENDED-RELEASE BUPRENORPHINE FOR OUD TREATMENT COMPARED WITH SUBLINGUAL FORMULATIONS?

## Buprenorphine Extended-Release (XR) Injection

### Sublocade®

- Decreased opioid use compared to placebo.
- Limited data on single day buprenorphine dosing followed by extended-release.
- Buprenorphine is mixed with a compound that is teratogenic in animals.

### Brixadi®

- Decreased opioid use compared to up to 24mg/day SL buprenorphine.
- Extensive data using single dose of SL buprenorphine followed by extended-release.
- Buprenorphine is not mixed with teratogenic compound.
  - May consider this for pregnant females.

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# WHAT ARE INDICATIONS FOR INJECTABLE EXTENDED-RELEASE (XR) BUPRENORPHINE FOR OUD TREATMENT COMPARED WITH SUBLINGUAL FORMULATIONS?

- Consider XR buprenorphine formulations for individuals:
  - Unable to stabilize on SL buprenorphine formulations.
  - High opioid tolerance.
  - High stimulant co-use.
- Same day XR buprenorphine administration may be considered.
- Consider the risks and benefits of additional SL buprenorphine:
  - Particularly with pregnant persons.
- Complex patients can be stabilized on Sublocade®:
  - 65% discontinued opioid use.
  - 55% of patients required supplemental SL buprenorphine.

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# HOW DO OTHER NOVEL DRUG COMPONENTS AFFECT BUPRENORPHINE INITIATION?

**Novel Drug Components:** "…substances added to the expected drug to enhance or mimic the intended effects."

Limited data but the following was recommended

1. If an individual does not respond to multiple doses of naloxone, consider that the overdose may be complicated by other substances.
2. Consider utilizing comprehensive toxicology testing to identify various drug components.

Polysubstance use and overdose is the norm.

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# HOW DO OTHER NOVEL DRUG COMPONENTS AFFECT BUPRENORPHINE INITIATION AND STABILIZATION?

- When opioid withdrawal symptoms do not respond as expected, consider that withdrawal may be complicated by other substances and may require a higher level of care.

**Example:**
**Xylazine: an alpha-adrenergic agent added to fentanyl**

- Overdose will not respond to naloxone or another opioid antagonist.
- Withdrawal symptoms will not respond to buprenorphine or methadone.
- Suggest treating with alpha adrenergic agents such as clonidine, or other agents such as gabapentin or benzodiazepines.

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# WHAT ARE OUD TREATMENT ALTERNATIVES AFTER REPEATED UNSUCCESSFUL ATTEMPTS AT BUPRENORPHINE TREATMENT?

1

## Buprenorphine

- If outpatient initiation is unsuccessful, then consider referral to ED or medically managed inpatient care.
- Buprenorphine initiation in supportive environments can improve treatment retention.
  - Hospitalization and criminal justice setting  improved retention compared to those started in the community.

2

## Methadone

- The first recommended alternative medication to buprenorphine.
- Those with high potency synthetic opioid (HPSO) use may need faster up titration.

3

## Naltrexone Extended-Release Injectable (Vivitrol®)

- This is considered a second-line treatment for OUD.
- If someone has recently been using HPSO and they want XR naltrexone, this should be done in a hospital.
- Individuals who tested positive for fentanyl were 11x less likely to initiate XR naltrexone than buprenorphine or methadone.

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**Source:** Kennedy et al. Factors Associated with Long-Term Retention in Buprenorphine-Based Addiction Treatment Programs: a Systematic Review. J Gen Intern Med. 2022 Feb;37(2):332-340.

# WHAT ARE OUD TREATMENT ALTERNATIVES AFTER REPEATED UNSUCCESSFUL ATTEMPTS AT BUPRENORPHINE TREATMENT?

"…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**."

- ASAM National Practice Guidelines

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# ARTICLE KEY TAKEAWAYS

**1. Precipitated withdrawal is < 5%.**

**2. Treatment on Day 1 (and for long term) may be >24mg.**

- The need for doses up to 32 mg per day for some patients has been recognized since 2004.
- Single doses of up to 64mg have been reported.

**3. Day 1 use of extended-release injection may be considered.**

**4. Low-dose buprenorphine similar success but no consensus on dosing.**

**5. Polysubstance use is the norm and should be addressed.**

Sources: https://journals.lww.com/journaladdictionmedicine/fulltext/2023/11000/asam_clinical_considerations__buprenorphine.2.aspx

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# DISCUSSION

# POLLING QUESTIONS

1. Overall, today's webinar was:
   A. Very useful
   B. Somewhat useful
   C. Not very useful
   D. Not useful at all

2. The material presented today was:
   A. At the right level
   B. Too basic
   C. Too detailed

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# CONTACT US

## FOR ANY QUESTIONS OR COMMENTS

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# THANK YOU!

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