INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Medications for Opioid Use Disorder***
-January 2024-

Background:

The recent emergence of high-potency synthetic opioids (HPSOs) in the illicit drug supply has resulted in increased overdose mortality rates for American Indian/Alaska Natives (AI/AN). The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) reviewed recent evidence for treatment of Opioid Use Disorder (OUD) following the latest review of Medications for Opioid Use Disorder (MOUD) in August 2021. Medication(s) listed on the IHS National Core Formulary relevant to OUD treatment include buprenorphine, buprenorphine-naloxone, and extended-release naltrexone. Following clinical review and analysis, the NPTC made **no modifications** to the National Core Formulary

Discussion:

Since 2021, there have been several major updates to support access to medications and improve outcomes for persons with OUD diagnosis. This brief will focus on these major updates.

Buprenorphine: In December of 2023, the Mainstreaming Addiction Treatment (MAT) Act was passed by U.S. Congress. The MAT Act removed (1) DATA Waiver requirements to prescribe buprenorphine and (2) provider restrictions for number of patients treated for OUD. Buprenorphine prescribing now only requires a standard DEA registration number. Additionally, in 2023, a new long-acting buprenorphine injectable product was approved for both weekly and monthly dosing to support additional patient management considerations. New research identified buprenorphine dose response and plasma concentration to effectively block respiratory depression from fentanyl.

Clinical Considerations: Fentanyl and HPSOs are highly lipophilic compounds demonstrating slow release from adipose tissue. These factors complicate opioid withdrawal management and may impact patient management and adherence and traditional buprenorphine induction dosing may not be effective.

The American Society of Addiction Medicine (ASAM) Clinical Considerations: Buprenorphine Treatment of Opioid Use Disorder for Individuals Using High-Potency Synthetic Opioids (HPSO) was published in December 2023. These ASAM considerations can aide clinicians in supporting individualized strategies for buprenorphine initiation, stabilization, and long-term management for patients exposed to HPSO. This expert consensus was developed to address the emergent clinical questions that arose due to HPSO emergence and the paucity of research to provide clinical practice with strong evidence to support evidence-based guideline development. A PICOTS framework (below) was used to support analysis:

- *Population*: individuals with severe OUD chronically exposed to HPSO, and pregnant individuals with OUD chronically exposed to HPSO
- *Interventions*: buprenorphine initiation, buprenorphine stabilization, and 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 (e.g., nonfatal overdose, premature hospital discharge, infections), all-cause mortality, opioid-related mortality
- *Timing*: any
- *Setting*: all outpatient/ambulatory practice settings, emergency department (ED), and hospital-based practice[1]

ASAM provided clinical considerations for the following six questions:

1. What specific clinical situations favor use of low or high-dose buprenorphine initiation strategies?

   Based on observational studies, authors recommended that clinicians chose initiation strategies based on the healthcare setting and individual patient preferences. Also, authors cited evidence that Low Dose Buprenorphine – Opioid Continuation (LDB-OC) was well tolerated in the inpatient/hospital setting. Spreen et al. (2022) reported a 95.6% success rate for traditional initiation and a 96% success rate for LDB-OC in hospitalized patients in their systematic review of observational, feasibility, and case series studies. ASAM guidelines cite the inability to provide full opioid agonists in the ambulatory setting (with the underlying rationale of needing more evidence) before the optimal LDB-OC approach can be determined for use in outpatient settings.[2-4] With regard to High Dose Buprenorphine (HDB), authors found rapid dose escalation in the ED to be safe in patients with chronic exposure to HPSO.[5-6]

2. What strategies can address patient discomfort, including precipitated opioid withdrawal, if it occurs during buprenorphine initiation?

   In addition to higher doses of buprenorphine, authors recommended the use of available alpha$_2$ adrenergic agonists (i.e., clonidine or lofexidine) to improve patient comfort due to mild to moderate withdrawal symptoms during buprenorphine initiation[1]. For patients who have a high tolerance to opioids, authors recommended considering **doses >24mg on day 1** for patients in mild to moderate opioid withdrawal.

3. After buprenorphine initiation, what range of buprenorphine dosing and/or dosing strategies can be considered during stabilization and long-term treatment?
   Recommendations were made for clinicians to consider using buprenorphine doses >24 mg/day in patients with high opioid tolerance. Higher doses may be needed for stabilization in this patient population. The authors again, recommended clinicians to consider physiological pregnancy changes that may require buprenorphine dose and dosing interval adjustments.[23] For patients unable to stabilize, authors recommended clinicians consider dose and frequency adjustments, psychosocial supports, and higher level of care. Additionally, patients who remain on >24mg of buprenorphine long-term should be reassessed if the patient has no return to use.[25-30]
4. What are indications for injectable extended-release buprenorphine for OUD treatment vs. sublingual formulations?
   Based on current literature, the recommendation was made for clinicians to consider extended-release buprenorphine as soon as possible after buprenorphine initiation, particularly when patients are unable to stabilize on trans mucosal buprenorphine formulations, have had extensive HPSO exposure, are living in unsafe environments, and/or have had multiple opioid overdoses. Additionally, authors recommended considerations for additional transmucosal buprenorphine, even at steady state, particularly in pregnant patients.[24] These recommendations were made based on findings from studies showing long-acting buprenorphine has equivalent or higher plasma concentrations when compared to 24mg of transmucosal buprenorphine and decreased respiratory depression at higher plasma concentrations in the presence of fentanyl.[10-20]
5. How do other novel drug components affect buprenorphine initiation and stabilization?
   Authors recommended clinicians consider withdrawal from other substances when the opioid withdrawal symptoms do not respond as expected to ancillary medications and buprenorphine, and to consider utilizing a higher level of care as needed. Considering other etiologies or overdose from other substances (when an individual does not respond as expected to multiples doses of naloxone) and using comprehensive toxicology testing and drug checking to identify drug components were also advised.
6. What are OUD treatment alternatives after repeated unsuccessful attempts at buprenorphine treatment?
   Authors stated that all medications for OUD should be available to all patients including methadone and naltrexone. The 2022 National Drug Control Strategy and proposed legislative changes in the Modernizing Opioid Treatment Access Act recommend changes that would expand access to methadone for patients. Additionally, proposed legislation may also include provisions for telehealth visits and tele-prescribing.

Naltrexone: Three systematic reviews of naltrexone have been published since the last NPTC review on MOUD in 2021. Hockheimer et al. (2022) looked at three OUD medications and found that all were equally effective in treatment retention in all genders and ethnicities/races. Zangiabadian et al. (2022) found treatment retention was 63% higher with naltrexone-treated patients than those in the control group (Odds Ratio: 1.64, 95% confidence interval (CI) 0.78-3.44).[8] Lastly, Lim et al. (2022) reported methadone to be superior to buprenorphine for treatment retention (Risk Ratio 1.22, 95% CI=1.06-1.40) and buprenorphine superior to naltrexone (Risk Ratio 1.39, 95% CI=1.10-1.80).[9] The authors reported study limitations of their review due to the minimal number of high quality trials.[7-9]

Findings:

Management of OUD is a changing landscape due to HPSOs. Evidence from current available studies suggests individualized care planning is essential to support patient outcomes including novel initiation and stabilization strategies. Additionally, extended-release buprenorphine may improve symptom management and reduce overdoses.

Clinician Resources for Managing MOUD:

Substance Use Disorder ECHO Program	PCSS	www.ihs.gov/opioids	Substance Use Warmline

References:

1. Weimer M, Herring A, Kawasaki S, et al. (2023). ASAM Clinical Considerations: Buprenorphine Treatment of Opioid Use Disorder for Individuals Using High-potency Synthetic Opioids
2. Spreen L, Dittmar E, Quirk K, at al. Buprenorphine initiation strategies for opioid use disorder and pain management: A systematic review. Pharmacotherapy. 2022 May;42(5):411-427.
3. 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.
4. 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.
5. Herring A, Vosooghi A, Luftig J, et al. High-Dose Buprenorphine Induction in the Emergency Department for Treatment of Opioid Use Disorder. JAMA Netw Open. 2021 Jul 1;4(7):e2117128.
6. Snyder H, Chau B, Kalmin M, et al. High-Dose Buprenorphine Initiation in the Emergency Department Among Patients Using Fentanyl and Other Opioids. JAMA Netw Open. 2023 Mar 1;6(3):e231572.
7. Hochheimer M, Unick GJ. Systematic review and meta-analysis of retention in treatment using medications for opioid use disorder by medication, race/ethnicity, and gender in the United States. Addict Behav. 2022 Jan; 124:107113.
8. Zangiabadian M, Golmohammadi S, Nejadghaderi SA, et al. The effects of naltrexone on retention in treatment and being opioid-free in opioid-dependent people: A systematic review and meta-analysis. Front Psychiatry. 2022; 26;13:1003257.
9. Lim J, Farhat I, Douros A, et al. Relative effectiveness of medications for opioid-related disorders: A systematic review and network meta-analysis of randomized controlled trials. PLoS One. 2022 Mar 31;17(3):e0266142.

10. Sublocade [package insert]. North Chesterfield, VA: Indivior Inc, 2018.
11. Kennedy A, Wessel C, 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.
12. Di Petta G and 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.
13. 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.
14. 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.
15. Danilewitz M, McLean M. High-dose buprenorphine for treatment of high potency opioid use disorder. Drug Alcohol Rev. 2020;39(2):135–137.
16. 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.
17. 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.
18. Poliwoda S,NoorN, Jenkins JS, et al. Buprenorphine and its formulations: a comprehensive review. Health Psychol Res. 2022;10(3):37517.
19. 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. ClinPharmacokinet. 2021;60(4):527–540
20. 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 Jan 27;17(1):e0256752..
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. 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.
24. 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.