How to Conduct a Buprenorphine Microinduction to Treat Opioid Use Disorder

Learning Objectives:

1) Understand the federal guidelines for prescribing buprenorphine
2) Identify candidates that may benefit from buprenorphine initiation compared to methadone for the treatment of opioid use disorder (OUD).
3) Understand the principles of buprenorphine microinduction and its significance in treating OUD.
4) Identify candidates that may benefit from buprenorphine microinduction compared to standard buprenorphine induction.
5) Recognize available microinduction protocols for initiating buprenorphine.

Step 1: Federal Guidelines on Buprenorphine Prescribing

- Per federal guidelines, a physician does NOT need to have a DEA license to prescribe buprenorphine for withdrawal management in the inpatient setting if a patient has been hospitalized for the management of another medical problem.
- Per the Medication Access and Training Expansion (MATE) Act, effective as of June 2023, physicians no longer require an X-waiver to prescribe buprenorphine in the outpatient setting or on hospital discharge. A DEA license is still required to prescribe buprenorphine outpatient.

Step 2: Buprenorphine vs. Methadone

- Methadone requires daily clinic visits to an Opioid Treatment Program (OTP) for dose administration, as federal regulations do not currently permit methadone to be dispensed to outpatient pharmacies when used for OUD treatment. Buprenorphine may be preferred when local methadone programs are unavailable or it is not feasible for a patient to visit a clinic daily.
- Because methadone is a full agonist and causes strong activation of the mu-opioid receptor, it has a higher risk for respiratory depression if dosed improperly. As a partial agonist, buprenorphine has a ceiling effect for receptor activation and is much less likely to result in fatal overdose in adults.
- Buprenorphine is less likely to result in QTc prolongation compared to methadone, which may make it preferable for patients with a history of arrhythmias or other cardiac comorbidities.
- Buprenorphine may be favorable for patients with chronic pain, as it has increased analgesic properties when dosed multiple times a day, while methadone is typically limited to daily dosing.

Step 3: Principles of Buprenorphine Microinductions

Buprenorphine, a partial agonist at the mu-opioid receptor, is FDA-approved for OUD treatment. Its use significantly reduces the risk of all-cause and opioid-related mortality, enhances engagement in outpatient treatment, and decreases illicit opioid use in patients with OUD. As a partial agonist, it occupies the opioid receptor with higher affinity but reduced activation compared to full agonists. Once a patient is stable on buprenorphine, it deters opioid use by blocking the euphoric effects of additional

opioids, such as heroin. However, this property poses a challenge when initiating buprenorphine. If introduced in the presence of a full opioid agonist, buprenorphine displaces the agonist, causing a relative reduction in receptor activation and resulting in withdrawal symptoms (termed “precipitated withdrawal”). Precipitated withdrawal is significantly more uncomfortable compared to natural withdrawal, potentially decreasing a patient’s future desire to use buprenorphine as a medication for opioid use disorder (MOUD).

Standard buprenorphine inductions avoid precipitated withdrawal by delaying buprenorphine administration until the patient has had a period of abstinence from all opioids (>12 hours for short-acting opioids, >3 days for long-acting opioids and fentanyl) and has started experiencing natural withdrawal. This method creates more barriers to treatment for patients who would otherwise be interested in MOUD (which is already a group of patients with historically limited and inequitable access to care), as it requires experiencing uncomfortable symptoms and may prolong hospital stays. However, a relatively new strategy for rapid microinduction of buprenorphine has emerged to minimize some of these barriers.

Microinduction allows for the safe and comfortable initiation of buprenorphine in patients who have recently used high-potency or long-acting full-agonist opioids (such as heroin, fentanyl) or are currently being treated for pain with full opioid agonists. It decreases the probability of precipitated withdrawal and eliminates the need for patients to be in withdrawal before starting MOUD. It also allows for the swift transition from methadone maintenance therapy to a less restrictive MOUD. Methadone as a MOUD mandates daily clinic visits for supervised medication administration at the start of treatment. This requirement is closely linked to the stigmatization of addiction treatment (as it does not exist for individuals being prescribed methadone for pain management) as well as its racialization. Black individuals are significantly less likely to be offered buprenorphine for MOUD compared to their white counterparts and are instead more likely to be referred to methadone programs. One of the goals for the retraction of the X-waiver, which loosened regulations around buprenorphine prescribing, was to minimize these disparities.

Microinduction involves introducing small (≤1 mg) and slowly increasing amounts of buprenorphine in the presence of full agonists, followed by tapering the full agonists after achieving a therapeutic maintenance dose of buprenorphine. This low-dose titration is theorized to avoid precipitated withdrawal because the number of full agonists displaced at any point in time by the "micro" doses of buprenorphine remains below the withdrawal threshold.

There are various methods available in the literature for successfully conducting microinduction. The initial published method, the "Bernese Method," was introduced in 2010 by German physicians, Dr. Hämmig and colleagues, using sublingual (SL) buprenorphine (Protocol A below). In the United States, the lowest available SL dose for management of OUD typically begins at 2 mg, making it challenging to initiate an oral microinduction as it would require cutting the 2 mg films/tablets into smaller pieces. This is generally prohibited in the inpatient setting because it is difficult to ensure accurate dosing. Thus, most hospital microinductions involve the administration of intravenous (IV) buprenorphine for the first several days before transitioning to the SL form (see example Protocols B and C, adapted from Dr. Thakrar and colleagues, 2022).

Table 1: When to Choose a Buprenorphine Microinduction
Recent use of high potency or long-acting opioids
Previous intolerance of opioid withdrawal and/or standard induction
Time-limited hospitalization
Currently being treated for pain with full agonists
Swift transition from methadone to buprenorphine is necessary (e.g., methadone is contraindicated)

Step 4: Choosing a microinduction protocol

Protocol A: 7-Day Outpatient Protocol (Bernese Method)

- Day 1: SL buprenorphine 0.5 mg once a day (1 dose)
- Day 2: SL buprenorphine 0.5 mg twice a day (2 doses)
- Day 3: SL buprenorphine 1 mg twice a day (2 doses)
- Day 4: SL buprenorphine 2 mg twice a day (2 doses)
- Day 5: SL buprenorphine 3 mg twice a day (2 doses)
- Day 6: SL buprenorphine 4 mg twice a day (2 doses)
- Day 7: SL buprenorphine 12mg once a day; **stop other opioids**

Protocol B: 5-Day Hospital Protocol

- Day 1: IV buprenorphine 0.15 mg q6hrs (4 doses)
- Day 2: IV buprenorphine 0.3 mg q6hrs (4 doses)
- Day 3: IV buprenorphine 0.6 mg q6hrs (4 doses); **begin full agonist taper (25% reduction/day)**
- Day 4: SL buprenorphine-naloxone 4-1 mg q6hrs (4 doses)
- Day 5: SL buprenorphine-naloxone 8-2 mg BID
- Day 6+: Can add SL buprenorphine-naloxone 2-0.5 mg as needed for cravings, restlessness, anxiety, myalgias, or pain. PRN doses should be added to the next day's scheduled dose for new scheduled dosing. **The maximum total daily dose is typically 24 mg.**

Protocol C: 3-Day Hospital Protocol

- Day 1: IV buprenorphine 0.15 mg q6hrs (2 doses), then IV buprenorphine 0.3 mg q6hrs (2 doses)
- Day 2: IV buprenorphine 0.6 mg q6hrs (2 doses) or SL buprenorphine-naloxone 2-0.5 mg q6hrs (2 doses), then SL buprenorphine-naloxone 4-1 mg q6hrs (2 doses)
- Day 3: SL buprenorphine-naloxone 8-2 mg BID; **begin full agonist taper (25% reduction/day)**
- Day 4+: Can add SL buprenorphine-naloxone 2-0.5 mg as needed for cravings, restlessness, anxiety, myalgias, or pain. PRN doses should be added to the next day's scheduled dose for new scheduled dosing. **The maximum total daily dose is typically 24 mg.**

Step 5: Other considerations in the use of buprenorphine

- Administration
  - If the combination buprenorphine-naloxone SL (Suboxone®) is unavailable, it is acceptable to substitute with buprenorphine SL. The combination formulation discourages medication misuse through intravenous injection. Naloxone, an opioid antagonist primarily used for opioid overdose reversal, has poor SL and oral bioavailability but will precipitate withdrawal if injected intravenously.
  - The relationship between IV and SL administration of buprenorphine is characterized by a linear correlation, where 0.15 mg of IV buprenorphine equates to approximately 0.5 mg of the SL form.
  - While both the 5-day (Protocol B) and 3-day (Protocol C) methods have similar efficacy, the risk of precipitated withdrawal is further decreased with a slower titration (Protocol B). Protocol selection should consider anticipated length of stay and patient preference.

- Side Effects and Precautions
  - The most common side effects include constipation, nausea, headaches, drowsiness, tooth decay (with the SL formulation), insomnia, palpitations, and precipitated withdrawal (if administered in the presence of full-opioid agonists).
  - Rare but serious adverse reactions include adrenal insufficiency, serotonin syndrome (when combined with other serotonergic medications), acute liver injury (most often associated with overdose or misuse in patients with comorbid hepatic dysfunction), and gastrointestinal obstruction.
  - Concurrent use of other central nervous system depressants, such as alcohol and benzodiazepines, with buprenorphine may result in respiratory depression.
  - Buprenorphine is a CYP3A4 substrate. Concurrent use with CYP3A4 inducers/inhibitors may affect dosing.

References

1. Ahmed, S., Bhivandkar, S., Lonergan, B. B., & Suzuki, J. (2021). Microinduction of buprenorphine/naloxone: a review of the literature. The American Journal on Addictions, 30(4), 305-315.
2. Anchersen, K., Clausen, T., Gossop, M., et al. (2009). Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. Addiction, 104, 993–999.
3. Chiang, C. N., & Hawks, R. L. (2003). Pharmacokinetics of the combination tablet of buprenorphine and naloxone. Drug and Alcohol Dependence, 70, S39–S47.
4. Connery, H. S. (2015). Medication-assisted treatment of opioid use disorder: Review of the evidence and future directions. Harvard Review of Psychiatry, 23(2), 63-75.
5. De Aquino, J. P., Parida, S., & Sofuoglu, M. (2021). The Pharmacology of Buprenorphine Microinduction for Opioid Use Disorder. Clinical Drug Investigation, 41(5), 425-436.
6. Dupouy, J., Palmaro, A., Fatséas, M., et al. (2017). Mortality associated with time in and out of buprenorphine treatment in French office-based general practice: a 7-year cohort study. Annals of Family Medicine, 15(4), 355–358.
7. Evans, E., Li, L., Min, J., et al. (2015). Mortality among individuals accessing pharmacological treatment for opioid dependence in California, 2006–10. Addiction, 110(6), 996–1005.
8. Funk, M. C., Nash, S., Smith, A., Barth, K., Suzuki, J., Rustad, J. K., Buonocore, S., Khandai, A. C., Smith, M. A., Jin, S., Drexler, K., & Renner, J. A., Jr (2023). Treatment of Opioid Use Disorder in the General Hospital. *The American journal of psychiatry*, *180*(8), 594–596.
9. Hämmig, R., Kemter, A., Strasser, J., von Bardeleben, U., Gugger, B., Walter, M., Dürsteler, K. M., & Vogel, M. (2016). Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: The Bernese method. Substance Abuse Rehabilitation, 7, 99-105.
10. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. (2012-). Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548196/.
11. MATE Act Training Requirements. (n.d.). U.S. Department of Justice. Drug Enforcement Administration. Diversion Control Division. https://www.deadiversion.usdoj.gov/faq/MATE_Act_faq.html (accessed November 13, 2023).
12. Mattick, R. P., Ali, R., White, J. M., O'Brien, S., Wolk, S., & Danz, C. (2003). Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. Addiction, 98, 441–452.
13. Netherland J, Hansen H. White opioids: Pharmaceutical race and the war on drugs that wasn't. Biosocieties. 2017 Jun;12(2):217-238. doi: 10.1057/biosoc.2015.46. Epub 2017 Jun 28. PMID: 28690668; PMCID: PMC5501419.
14. Randhawa, P. A., Brar, R., & Nolan, S. (2020). Buprenorphine-naloxone "microdosing": An alternative induction approach for the treatment of opioid use disorder in the wake of North America's increasingly potent illicit drug market. Canadian Medical Association Journal, 192(3), E73.
15. Substance Abuse and Mental Health Services Administration. (n.d.). What is Buprenorphine. https://www.samhsa.gov/medications-substance-use-disorders/medications-counseling-related-conditions/buprenorphine (Accessed November 13, 2023).
16. Sordo, L., Barrio, G., Bravo, M. J., et al. (2017). Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ, 357, j1550.
17. Thakrar, A. , Jablonski, L. , Ratner, J. & Rastegar, D. (2022). Micro-dosing Intravenous Buprenorphine to Rapidly Transition From Full Opioid Agonists. Journal of Addiction Medicine, 16 (1), 122-124.
18. Thomas, C. P., Fullerton, C. A., Kim, M., et al. (2014). Medication-assisted treatment with buprenorphine: assessing the evidence. Psychiatric Services, 65, 158–170.