ECHO IDAHO

Opioids, Pain and Substance Use Disorders

Buprenorphine Basics

6/12/2025

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Project ECHO

Disclosures

- No financial disclosures

Learning Objectives

- Review the pharmacology and indications for the use of buprenorphine.
- Discuss the unique properties of buprenorphine that contribute to its efficacy and safety.
- Review the different formulations of buprenorphine.
- Discuss the nuances of treating Opioid Use Disorder with buprenorphine.

History of Buprenorphine
DATA ACT of 2000

- The Drug Addiction Treatment Act was passed in 2000 expanding treatment of OUD outside of traditional Opioid Treatment Programs (OTPs)
- Permitted physicians with specific qualifications to treat OUD with Schedule III, IV, or V medications with specific FDA approval
- Allowed for treatment in Office-based Opioid Treatment programs (OBOT)

History of Buprenorphine
FDA Approval of Buprenorphine for OUD

- In 2002, the FDA approved the use of sublingual buprenorphine for the treatment of OUD
- Three sublingual formulations were released:
  - Suboxone® (combo product of buprenorphine and naloxone)
  - Zubsolv® (buprenorphine and naloxone films)
  - Subutex® (monoproduct, buprenorphine alone)
- Physicians with an X-waiver now had an effective treatment for OUD that did not require daily OTP visits and could expand treatment outside of urban settings

History of Buprenorphine

Approval of Buprenorphine Formulations

- Probuphine®, the buprenorphine implant, was approved by the FDA in 2016. It was discontinued in 2020.
- Long-acting Injectable buprenorphine was first approved in 2017 with Sublocade® being released first and later Brixadi® in 2023.
- Other formulations of buprenorphine have been approved to treat pain and include IV buprenorphine, transdermal patch, and buccal film.

History of Buprenorphine

Changing Regulations

- The CARA Act (Comprehensive Addiction and Recovery Act) of 2016 allowed NPs to obtain X-waiver and prescribe buprenorphine products for the treatment of OUD.
- With the passing of the Consolidated Appropriations Act of 2023, Congress eliminated the X-waiver, making it possible for anyone with a DEA license to prescribe buprenorphine for the treatment of OUD.
- There are no limits or caps on the number of patients that a prescriber may treat.

Buprenorphine Pharmacology

What would the ideal Drug for MOUD do?

- Long half life
- Reduces cravings
- Eliminates withdrawal
- Blocks other drug use
- Low misuse potential
- Good safety profile
- Deterrent for misuse

Buprenorphine Pharmacology

Unique Pharmacology

- Long half life: 24-36 hours
- Reduces cravings: partial agonist effect
- Eliminates withdrawal: partial agonist effect
- Blocks other drug use: high affinity and slow dissociation
- Low misuse potential: partial agonist effect
- Good safety profile: partial agonist effect
- Deterrent for misuse: addition of naloxone

Buprenorphine Pharmacology

High Affinity for mu Opioid Receptor

Table 2

Drug	K_i (nM)	Drug	K_i (nM)	Drug	K_i (nM)
Tramadol	12,486	Hydrocodone	41.58	Butorphanol	0.7622
Codeine	734.2	Oxycodone	25.87	Levorphanol	0.4194
Meperidine	450.1	Diphenoxylate	12.37	Oxymorphone	0.4055
Propoxyphene	120.2	Alfentanil	7.391	Hydromorphone	0.3654
Pentazocine	117.8	Methadone	3.378	Buprenorphine	0.2157
		Nalbuphine	2.118	Sufentanil	0.1380
		Fentanyl	1.346		
		Morphine	1.168		

Buprenorphine Pharmacology

Unique Pharmacology

- Semi-synthetic analogue of thebaine
- Metabolized in the liver (CYP3A4), and has a less-active metabolite, norbuprenorphine
- Because of extensive first-pass metabolism and poor GI absorption, buprenorphine has low oral bioavailability when swallowed (<5%)
- Sublingual administration bypasses first-pass metabolism and allows bioavailability around 30%

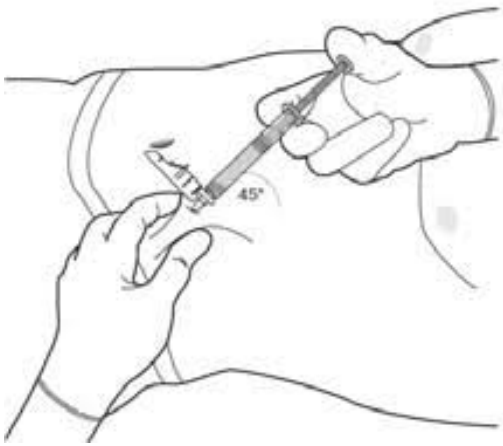
Buprenorphine

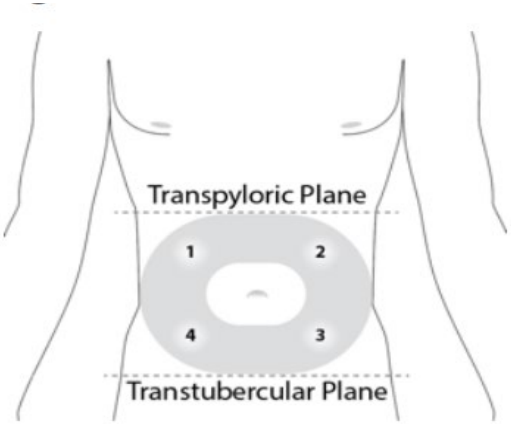
Long-acting Injectables

- Two formulations of long-acting injectable buprenorphine on the market: Sublocade® and Brixadi®
- Both form depot in subcutaneous tissue that is slowly released.
- Sublocade® is given in 300 mg or 100 mg doses and can be given monthly.
- Brixadi® can be given in weekly or monthly injections and dose ranges from 8 to 32 mg for weekly and 64 to 128 mg for monthly

Buprenorphine

Long-acting Injectables





Buprenorphine

Why Use Long-acting Injectable?

- Poor adherence
- Forgets to take doses
- Unable to safely store tablets (homeless, children at home, etc)
- Burden of taking oral medication
- Patient Preference
- Concerns for diversion
- Court ordered

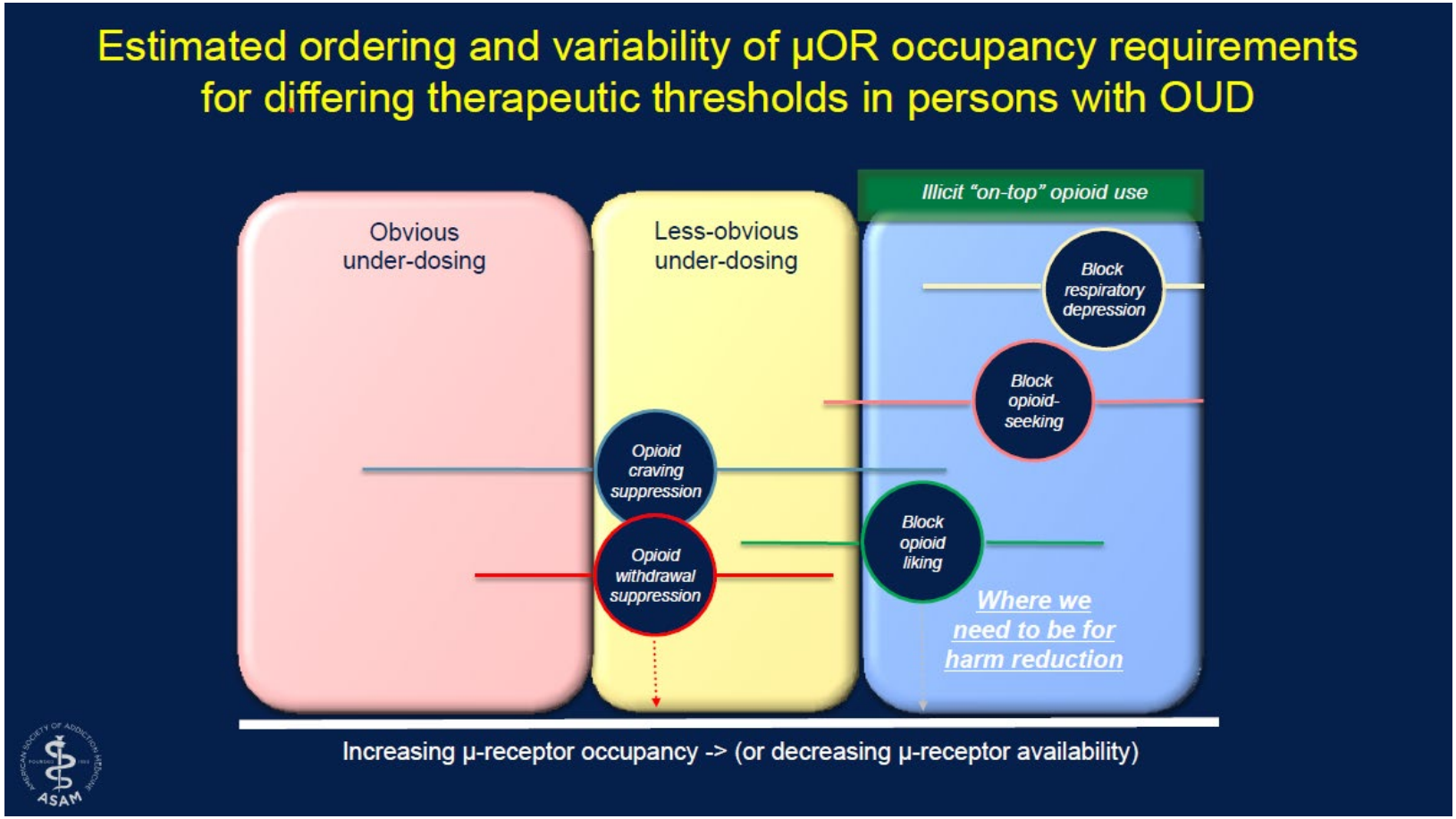
Buprenorphine

Treatment of Opioid Use Disorder

- Standard Induction involves dosing buprenorphine usually at 2 mg or 4 mg and monitoring for symptoms of withdrawal, then slow titration over days to weeks to dose ranges of 8 mg to 24 mg.
- Initial Office Based Treatment usually involved in office inductions, frequent visits, strict and frequent urine drug screening, mandatory concurrent psychotherapy, and withholding of medication for missed appointments or positive urine drug screens.
- Over time this has changed significantly to focus on harm reduction, safety, and goal of not interrupting treatment with buprenorphine.

Buprenorphine

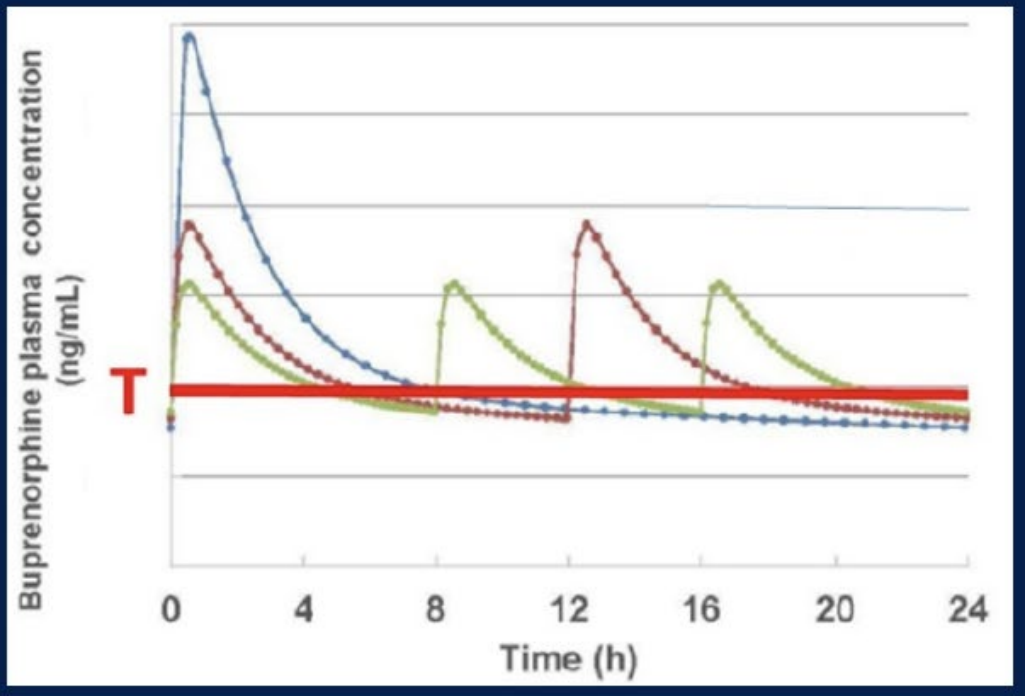
Higher Dosing Is Usually Better



Buprenorphine

Dosing Multiple Times a Day

- Simulated plasma concentrations of buprenorphine utilizing physiologically based pharmacokinetic modeling of nonpregnant subjects.
- Thick red line ("T") represents the threshold for clinically relevant opioid withdrawal symptoms.
  - Again, think C_{min}!
- Three times daily dosing (green line) results in a steadier plasma level and less time below withdrawal threshold compared to twice daily (red-purple) or once daily (blue) dosing (10.8, 14.4 and 16.3 hours, respectively).



Buprenorphine

Treatment of Pain

- Buprenorphine can be quite effective for treatment of pain.
- Perioperative management of pain in patients on OUD does not require stopping buprenorphine before or after surgery.
- Addition of full mu-agonist opioids for pain has good analgesic effect with mitigated euphoria and respiratory depression.

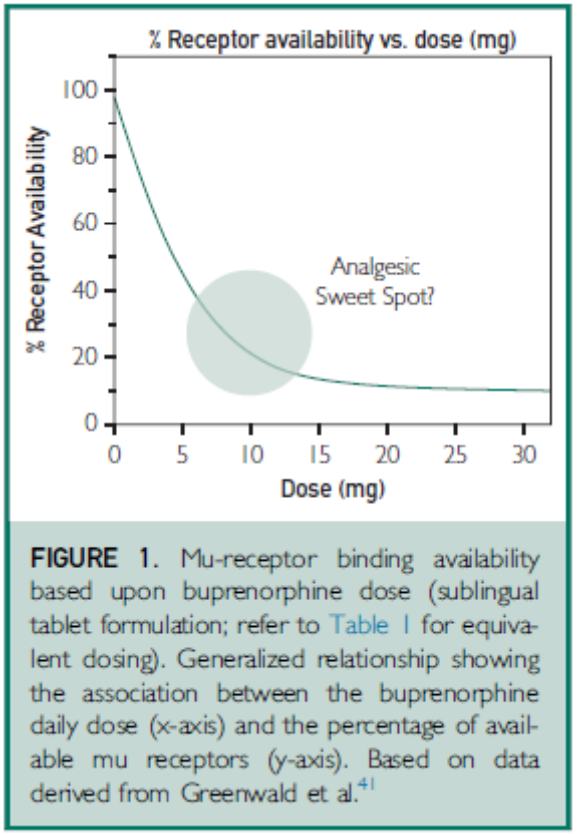


FIGURE 1. Mu-receptor binding availability based upon buprenorphine dose (sublingual tablet formulation; refer to Table I for equivalent dosing). Generalized relationship showing the association between the buprenorphine daily dose (x-axis) and the percentage of available mu receptors (y-axis). Based on data derived from Greenwald et al.[41]

Buprenorphine

What has Changed with Fentanyl?

- Fentanyl and its analogs (High Potency Synthetic Opioids) has overtaken heroin and prescription opioids as the most common opioid used for non-prescribed purposes.
- Use of fentanyl is much higher than doses used to treat pain, leading to deposition in adipose tissue and a long half-life that makes starting buprenorphine more difficult
- Starting buprenorphine using standard induction when patients are in minimal withdrawal can lead to precipitated withdrawal.

Buprenorphine

Fentanyl: Low-dose Inductions

- Low dose inductions typically involve using less than 2 mg buprenorphine and can be started while still using fentanyl or other long-acting opioid.
- Although off-label, various formulations have been used including IV, buccal films, and transdermal patches to avoid having to break 2 mg tabs/films into small pieces.
- Gradual titration of buprenorphine dose over 2-7 days (or longer in some cases) allows for avoidance of withdrawal.
- Concern for ongoing fentanyl use limits using LDI but may be only option patient will consider.

Buprenorphine

Fentanyl: High-dose Inductions

- High dose inductions involve giving significantly higher doses of buprenorphine (16 to 32 mg) with accelerated dosing for withdrawal symptoms.
- Typically would start at least 6 hours after last use of fentanyl but can be done 36-48 hours if patient tolerates abstinence for that long.
- Does not require expectation of complete opioid abstinence at the time of induction.
- Can be used after naloxone administration for overdose.
- Precipitated withdrawal is less common than expected and often resolves with repeat doses of buprenorphine. Adjunctive withdrawal medications can also be used.

Buprenorphine

Kratom Use

- Buprenorphine can be used to treat kratom (some use term Kratom Use Disorder vs Opioid Use Disorder).
- Depending on dose of kratom and formulation used, the opioid equivalent can be low or high.
- Standard induction is usually effective for kratom and patients can stabilize on lower doses of buprenorphine than is used in heroin, prescription opioids or fentanyl use.
- Many patients will still require higher doses of buprenorphine to stabilize.

Questions?