MOUD: Medications for Opioid Use Disorder

Maine Substance Use Disorders Learning Community

1/23/25

Your Speaker

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Objectives

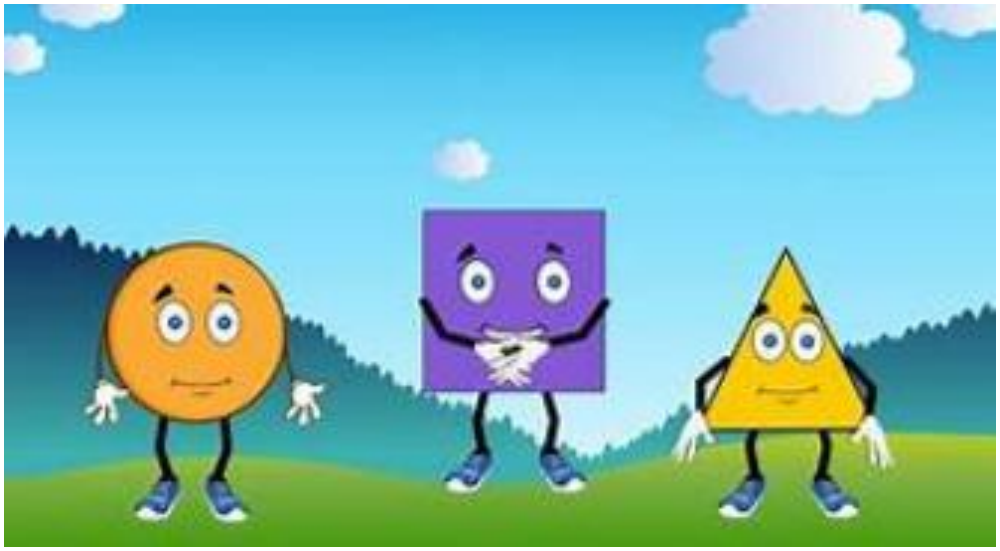
1. Participants will be able to name the THREE primary medications indicated for opioid use disorder, as well as considerations for different formulations of each medication.
2. Participants will be able to name at least one MAJOR difference between methadone, buprenorphine, and naltrexone.
3. Participants will be able to identify at least ONE factor to be considered for patient selection for methadone, buprenorphine, or naltrexone for the treatment of OUD.

Preamble

- As with any other medical treatment, we must be aware of and in pursuit of the goals of care.
- The use of MOUD is to stop or reduce the use of illicit opioid.
- OUD is a condition with high mortality and although the use of any opioid runs the risk of adverse effects (even death) the benefits of using these medications outweigh the risks.

Three Medication Classes

- Agonist
- Antagonist
- Partial Agonist



The Agonist

- The chemical "on switch" for our receptors on the cells
- You get maximum desired effects and maximum side effects
- We have natural agonists and medications that are agonists

Methadone is a Mu Agonist

- Activation of the MU receptor leads to:
  - Pain modulation
  - Euphoria
  - Respiratory depression
  - Slowed gut motility
  - And more
- MU receptors are located:
  - Central nervous system (brain and gut)
  - Peripheral nervous system
  - Regions of the brain associated with reward

Mayse, et al. (1997). Electron microscopic distribution of mu opioid receptors on noradrenergic neurons of the locus coeruleus. *Eutorpean journal of neuroscience,* 9(1), 128-39.

Other Mu Agonists

- Morphine
- Oxycodone
- Hydrocodone
- Hydromorphone
- Fentanyl
- Heroin
- Others…

Methadone as MOUD

Pros	Cons
• Easy transition from other mu agonists • Dosing can be robust enough to compete with high potency street drug supply • Generally provided in clinics in conjunction with mental health counseling	• Medication offered in clinics • Usually daily dosing to start • Clinics often located in higher populated areas • Does not blunt "high" feelings • Common side effects: lightheadedness, sedation, nausea/vomiting, sweating, constipation

Methadone Serious Adverse Effects

- Respiratory depression
- QT prolongation
- Serotonin syndrome
- Adrenal insufficiency
- Severe hypotension
- Seizures
- Hypoglycemia

Methadone Package Labelling

Liquid vs Tablet Methadone

- Methadone clinics only offer liquid formulation
- Ease of precise dosing
- Decreased risk of diversion

- Tablets can be used outside of a clinic but ONLY FOR PAIN
- It is illegal to prescribe tablets for addiction

Federal Regulation code, Title 42, Section 8.
ASAM

Patient Considerations for Methadone

Pros	Cons
• Can start this medication without concern for recent opioid use • Usually no long waits to get into a clinic • Tighter control over dosing and patients initially have witnessed dosing • Long half life	• High burden of care with daily visits to the clinic • Difficult to earn take-homes • Consider cardiac health and risk of QT prolongation (look at other medications) • Long half life

The Antagonist

- The chemical "off switch" for our receptors on our cells
- Effect is gained by STOPPING activation of the receptor
- The Mu receptors are blocked and will blunt any effect of an opioid if taken
- It also blocks the effects of endogenous opioids and reduces compulsive behavior associated with addiction

Tablets	Monthly Long acting injection
• 50 mg tablets, dose is usually 50 mg daily (can dose 100 mg every other day or 150 mg every 3rd day per ASAM) • Common side effects include nausea, vomiting, insomnia and watch those liver enzymes • Lower starting doses and titrating up can decrease side effects	• 380 mg once monthly IM injection (gluteal) • Approved in 2010 • Patient must be 100% opioid free as naltrexone can induce opiate withdrawal.

Naltrexone is an Antagonist

Patient Considerations for Naltrexone

Pros	Cons
• Non-opioid, not a controlled medication • Can be prescribed by a primary care provider • Can stay on tablets or may choose to get monthly injections • Helps with alcohol use disorder too • Efficacy equal to other MOUD • Well covered by insurance (both tablet and injection)	• Must be 100% opioid free or will precipitate withdrawal • Many view this as a lesser treatment (stigma) • Monthly injection is $$$$ • Training needed to administer the monthly injection • Will most likely need a PA for injection

Partial Agonist

- This type of medication is still an "on switch"
- But has less of an effect, more like a dimmer switch
- Partial agonists will compete for the receptor sites as well and reduce effects of full agonists

Buprenorphine Risks

- Misuse
- Respiratory Depression (particularly when used in conjunction with benzodiazepine or alcohol)
- Adrenal insufficiency
- Hepatic events
- Orthostatic hypotension
- Precipitated withdrawal

Buprenorphine Formulations for Opioid Use Disorder

- Sublingual
  - Buprenorphine-Naloxone (films and tablets)
  - Buprenorphine (tablets)
- Buccal
  - Buprenorphine-Naloxone (buccal film)
- Injectable
  - Buprenorphine extended release with Atrigel, brand name ***Sublocade***
  - Buprenorphine extended release with either anhydrous ethanol (weekly) or N-methyl pyrrolidine (monthly), brand name ***Brixadi***

Sublingual Buprenorphine with or without Naloxone

- Naloxone is an opioid blocker
- It is known as the name brand ***Narcan*** that is used to treat opioid overdoses
- Won't naloxone reverse buprenorphine?
- Naloxone is not well-absorbed when taken SL
- It is well-absorbed if injected
- The Naloxone is there as a deterrent for injecting

A Word on That…

- It seems that there are patients who either inject their buprenorphine or do not inject their buprenorphine.
- In speaking with patients who have injected buprenorphine/naloxone, I am told that there is a very brief period of withdrawal that quickly goes away.
- However, insurance companies have a preference for the combination product

The risk of precipitated withdrawal

- If buprenorphine is given too close to the last dose of agonist opioid, there is a risk it will precipitate withdrawal
- This has NOTHING to do with the naloxone and EVERYTHING to do with buprenorphine's affinity for the mu receptor
- Buprenorphine simply out competes heroin, fentanyl, oxycodone, morphine, etc.

Buccal Buprenorphine

- This is brand name Zubsolv
- It is put inside the cheek and not under the tongue
- It has a little better absorption than SL medication and a little less bitter tasting
- 6 strengths (0.7, 1.4, 2.9, 5.7, 8.6, and 11.4)
- Some insurances have a preference for this product, but it's no worse or better than SL formulations

Buprenorphine Long Acting Injectables

At Last

- Monthly or weekly SC injections
- 2 products that are FDA approved
  - Brand name Sublocade
    - Indivior
    - FDA approved in the US on 11/30/2017
  - Brand name Brixadi
    - Braeburn
    - FDA approved in the US on 5/23/2023

Goals

- Decreased/no risk of diversion, exploitation, sharing, over use, under use, misuse
  - These medications are never in the hands of the patients
  - They are stored and administered at a health care office or pharmacy
- Prolong life
- "Steady state"

Prolong life

- It is well established that there is a reduced risk of overdose death in people who are treated with any form of buprenorphine.

Vakkalanka, et al. (2021). Association between buprenorphine for opioid use disorder and mortality risk. *American Journal for Preventative Medicine, 61* (3), 418-427.

Prolong life

- But, here is the exciting part about long acting injectables

RESULTS

Buprenorphine produced mild respiratory depression, while high doses of fentanyl caused pronounced respiratory depression and apnea in both populations. When combined with fentanyl, buprenorphine produced a receptor binding–dependent reduction of fentanyl-induced respiratory depression in both populations. In individuals with chronic opioid use, at buprenorphine plasma concentrations of 2 ng/mL or higher, a protective effect against high-dose fentanyl was observed.

JCI Insight. 2022 May 9;7(9):e156973. doi: 10.1172/jci.insight.156973

Modeling buprenorphine reduction of fentanyl-induced respiratory depression

Erik Olofsen [1], Marijke Hyke Algera [1], Laurence Moss [2], Robert L Dobbins [3], Geert J Groeneveld [1,2], Monique van Velzen [1], Marieke Niesters [1], Albert Dahan [1,✉], Celine M Laffont [3]

Steady state - Sublocade

After the first injection of SUBLOCADE, patients showed a peak in buprenorphine plasma levels at ~24 hours, then decreased slowly and stabilized around 2 ng/mL[1,2]

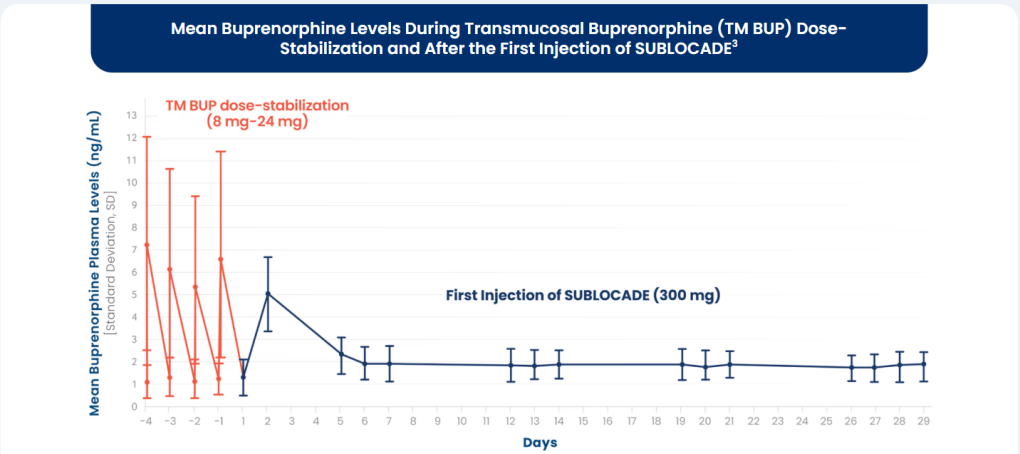


Table 7 Comparison of Steady-state Buprenorphine Plasma Exposure Between Daily Transmucosal Buprenorphine and Once Monthly SUBLOCADE at Trough (C_{trough}), Average (C_{avg}) and Peak (C_{max}) Levels (Geometric Mean (CV%))

Pharmacokinetic parameters	Transmucosal Buprenorphine				SUBLOCADE	
	8 mg	12 mg	16 mg	24 mg	100 mg	300 mg
$C_{avg,ss}$ (ng/mL)	1.37 (40)	1.79 (40)	2.16 (40)	2.84 (40)	2.87 (32)	6.32 (32)
$C_{max,ss}$ (ng/mL)	4.27 (45)	5.60 (45)	6.77 (45)	8.86 (45)	5.10 (33)	11.81 (35)
$C_{trough,ss}$ (ng/mL)	0.66 (63)	0.87 (63)	1.04 (61)	1.37 (62)	2.46 (40)	5.47 (39)

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Manufactured by Curia Global Inc. Albany, NY 12203
For more information, go to www.SUBLOCADE.com or call 1-877-782-6966.

Steady state Brixadi

Drug product dose			C_{av} (ng/mL)			C_{max} (ng/mL)			C_{trough}[a] (ng/mL)		
SL BPN •	Brixadi (weekly)	Brixadi (monthly)	SL BPN •	Brixadi (weekly)	Brixadi (monthly)	SL BPN •	Brixadi (weekly)	Brixadi (monthly)	SL BPN •	Brixadi (weekly)	Brixadi (monthly)
8 mg	16 mg	64 mg	1.2	2.1	2.0 $	4.7	4.3	4.0 $	0.7	0.8	1.3 $
16 mg	24 mg	96 mg	1.8	2.9 $	2.9 $	6.5	5.5 $	6.0 $	1.0	1.4 $	2.0 $
24 mg	32 mg	128 mg	2.5	4.2	3.9	8.2	6.9	11.1	1.4	2.6	2.1

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BRX-PI-002

Comparisons

- Dosing
- Administration
- Adverse events
- Storage
- Cost
- Insurance coverage

Dosing

Sublocade

- Comes in a 300 mg dose and a 100 mg dose
- First 1-2 injections are "loading doses" of 300 mg
- Maintenance dose is 100 mg
- A patient is allowed to maintain on 300 mg if needed for cravings or feeling under medicated
- Patient should be comfortable on at least 8 mg daily SL dose for 7 days prior to initiation

Brixadi

- Weekly dosing of 8, 16, 24, or 32 mg
- Monthly dosing of 64, 96, 128 mg
- Patient only needs to tolerate 4 mg once in office to initiate 8 mg weekly dose

Daily Sublingual Buprenorphine Dose*	BRIXADI Weekly	BRIXADI Monthly
≤6 mg	8 mg	-
8-10 mg	16 mg	64 mg
12-16 mg	24 mg	96 mg
18-24 mg	32 mg	128 mg

Brixadi dosing table

Daily Sublingual Buprenorphine Dose*	BRIXADI Weekly	BRIXADI Monthly
≤6 mg	8 mg	-
8-10 mg	16 mg	64 mg
12-16 mg	24 mg	96 mg
18-24 mg	32 mg	128 mg

braeburn

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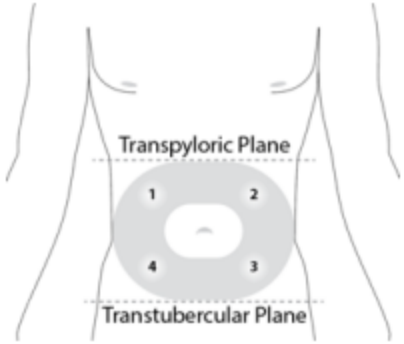
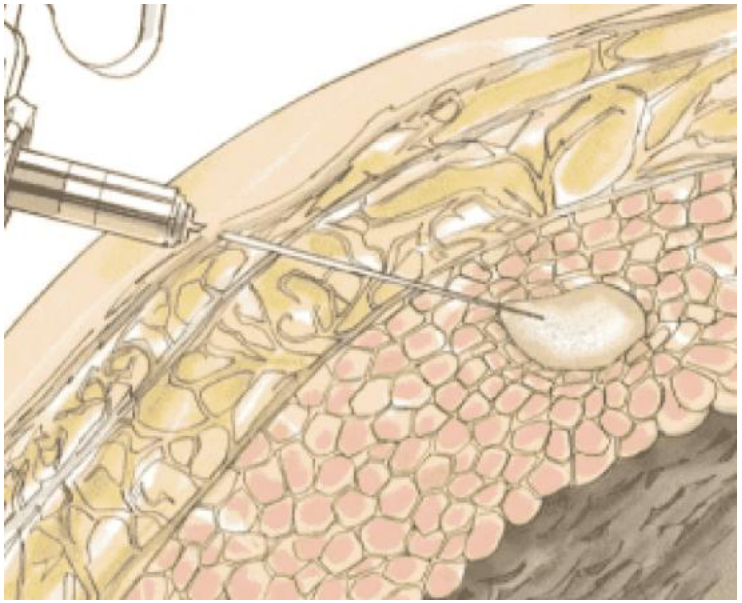
Administration Sublocade

- 300 mg is 1.5 mL
- 100 mg is 0.5 mL
- 19 gauge 5/8 inch needle
- SQ injection given at a 45 degree angle in the abdominal region only

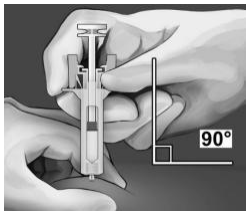


Sublocade Injection Site Adverse Events



Administration Brixadi

- 23 gauge ½ inch needle
- SQ injection given at a 90 degree angle



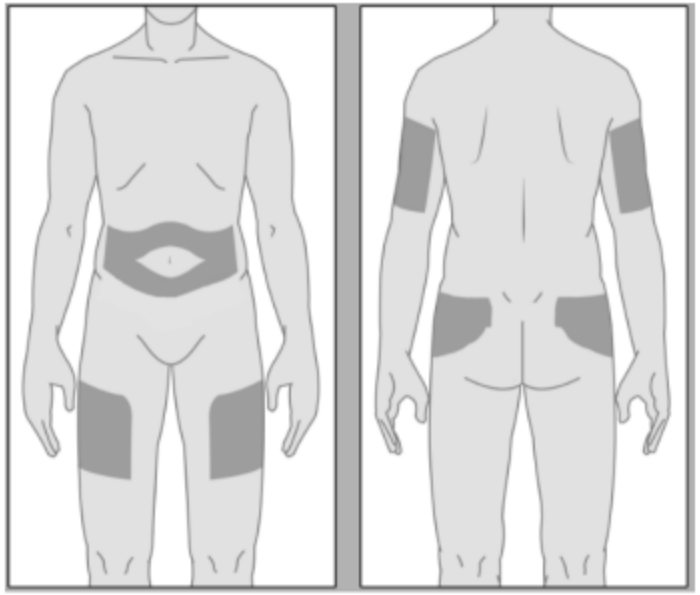


Table 3: BRIXADI (weekly) Strengths

BRIXADI (weekly) 50 mg/mL buprenorphine	
Dosage Strength	**Dosage Volume**
8 mg	0.16 mL
16 mg	0.32 mL
24 mg	0.48 mL
32 mg	0.64 mL

Table 4: BRIXADI (monthly) Strengths

BRIXADI (monthly) 356 mg/mL buprenorphine	
Dosage Strength	**Dosage Volume**
64 mg	0.18 mL
96 mg	0.27 mL
128 mg	0.36 mL

Brixadi Injection Site Adverse Events

- I have only personally seen redness or itching at the site
- I could not find any evidence of wounds, but time will tell

Storage

Sublocade	Brixadi
• Must be refrigerated (35.6 – 46.4 degrees F) • Once out of refrigeration, can be stored at room temperature (59-86 degrees F) for up to 12 weeks prior to administration	• Store at room temperature between 68-77 degrees F • "Excursions permitted" between 59-86 degrees F

Cost

Sublocade	Brixadi
• The cost of the drug is a little north of $2000 regardless of dose • This does not include the cost of administration	• $400-500 for weekly injections • $1800-2000 for monthly injections • This does not include the cost of administration

Insurance Coverage

- Generally, is good, especially for Medicaid
- However, Medicare and private insurances all vary and can be A TON of work to get approved
- Buy and bill
  - The organization buys the medication and bills insurance once it's administered
  - Tough to break even
  - Billed through MEDICAL benefits
- White bag
  - The medication is prescribed and sent to a specialty pharmacy
  - PA will be needed through PHARMACY benefits
  - Once approved and paid for, the pharmacy will deliver to the practice

Some DEA and Regulatory Considerations

- The prescriber AND the location must have a DEA number
- The medication needs a very tight chain of custody
- Staff members are not legally allowed to transport the medication from one office location to another

So, which one?

- Where is the patient starting?
  - Are they on higher dose buprenorphine and still not comfortable?
  - Are they on lower dose buprenorphine and feeling properly medicated?
- What is the patient's body habitus?
  - Brixadi is my personal preference for patients with less sub-Q tissue
- What will the patient's insurance cover?
  - Just be careful with your sales pitches

Thank you!

For your interest in this topic and for your work with people who use drugs