Medication Assisted Treatment in Bureau of Prisons & SUBLOCADE®

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Objectives

- Impact of the Opioid Epidemic
- Understand why to treat OUD in Prison
- Evolution of Medication Assisted Treatment in the BOP
- Review Basics of Medication Assisted Treatment
- Comprehensive review of SUBLOCADE®

Opioid Epidemic

- Opioid Epidemic: [2, 6, 8]
  - 2017: HHS declared opioid crisis a public health emergency
    - Overdose deaths involving opioids increased 519.38% from 1999-2019
    - 72% -- Opioids are a factor in at least 7 out of 10 overdose deaths
    - 136 deaths per day and climbing – Almost 50K people every year from opioid overdose
  - 2021: National Center for Health Statistics: More than 104,000 Americans died of overdose in a 12-month period ending September 2021 [10]
- Opioid Use Disorder (OUD): A chronic, relapsing disease with significant economic, personal, and public health consequences
  - In 2018, 2.1 million people in the U.S. had OUD [3,10]
  - In 2020, 2.7 million people qualified as having an OUD [7]

Opioid Epidemic and Incarceration

- The Who:
  - Studies show that up to 65% of incarcerated individuals meet criteria for a substance use disorder and up to 25% have OUD [3,10]
- The What & When:
  - The First Step Act was signed into law by President Trump in December 2018
- The Why: *Why* treat OUD in prison?
  - OUD impacts transition back to our communities
  - Individuals with OUD have a much higher risk of death from drug overdose in the first two weeks after release from prison compared to the general population [1,10]
  - Reduce mortality rates, reduce recidivism, improve public health effects, improve family systems [1, 11]

Evolution of MAT in the BOP

- Collaboration between Health Services Division, Reentry Services Division and Community Treatment Services
- 2018: The BOP initially offered long-acting naltrexone (Vivitrol®) to qualified inmates within 12 months of transfer to Residential Reentry Centers (RRCs) in Massachusetts.
- December 2018: The First Step Act (FSA) was signed into law, requiring the BOP to provide MAT services nationwide.
- May 2019: The initiative expanded to include all three FDA-approved medications (methadone, buprenorphine, naltrexone) for qualified inmates within 12 months of transfer to community placement.
- Currently MAT screening is available to all inmates in the BOP
  - Any inmate who self-refers, is referred by staff, has an OUD diagnosis or arrives on a MAT medication at intake
  - Screening does not guarantee treatment – this is a clinical decision

Basics of Treatment

- Medication Assisted Treatment (MAT): an evidence-based treatment for OUD that combines medication and behavioral therapy
- FDA-Approved Medications for treatment of OUD
  - Methadone
  - Buprenorphine
  - Naltrexone
- Medication Treatment Goals [3]
  - Minimize harm associated with illicit opioid use
  - Abstinence from other illicit substances
  - Reduce cravings for illicit opioids
  - Engagement in recovery-oriented services

Buprenorphine Mechanism of Action & Metabolism[3,10]

- Buprenorphine: partial agonist with high-affinity at mu receptors
  - Allows the analgesic effect to plateau at higher doses
- Buprenorphine is broken down by the cytochrome CYP 3A4 enzymes to an active metabolite (norbuprenorphine) with weak intrinsic activity.
  - Sublingual administration is the preferred route of administration because it avoids the first-pass effect
  - Slow onset of action, peak effect occurring 3-4 hours after administration
  - The average half-life of buprenorphine is about 38 hours (25 to 70 hours) following sublingual administration.
- Several possible methods of administration (ie, buccal film, sublingual film, sublingual tablet, transdermal patch, transdermal implant)

Buprenorphine ER (SUBLOCADE®)[9]

- Designed to deliver continuous buprenorphine plasma levels over a period of a month
  - It is injected subcutaneously by a healthcare professional as a liquid and once inside the body it turns into a solid, called a depot.
  - The depot gradually releases buprenorphine at a controlled rate all month
  - Buprenorphine levels peak at 24 hours following injection and then decrease to a level that is stable for the month

Risk Evaluation and Mitigation Strategy (REMS)[9]

- Serious harm or death could result if extended-release injection is administered intravenously.
  - The injection forms a solid mass upon contact with body fluids and may cause occlusion, local tissue damage, and thromboembolic events, including life-threatening pulmonary emboli if administered intravenously.
- Because of the risk of serious harm or death that could result from intravenous self-administration, buprenorphine extended-release injection is only available through a restricted program called the SUBLOCADE® REMS Program.
  - Healthcare settings and pharmacies that order and dispense buprenorphine extended-release injection must be certified in this program and comply with the REMS requirements.

SUBLOCADE® REMS[9]

What are the SUBLOCADE® REMS program requirements?

- All healthcare settings and pharmacies that dispense SUBLOCADE must be certified in the SUBLOCADE REMS program
- Healthcare providers, healthcare settings, and pharmacies must obtain SUBLOCADE through a restricted distribution program
- **SUBLOCADE ® should never be dispensed directly to a patient.**

Which healthcare settings MUST BE certified in the SUBLOCADE ® REMS program?

- All healthcare settings and pharmacies that dispense SUBLOCADE® must be certified. Examples of healthcare settings include: group practice, independent practice, institution, Department of Defense (DoD) facility, outpatient clinic, hospital, Veterans Administration (VA) facility, opioid treatment program (OTP), closed healthcare system, other healthcare setting.

REMS Program | SUBLOCADE® (buprenorphine extended-release) injection, for subcutaneous use (CIII) (sublocaderems.com)

Buprenorphine ER: Dosing [9]

- Patients should first undergo induction and stabilization by initiating a buprenorphine-containing product, delivering the equivalent of 8-24 mg/day of transmucosal buprenorphine (Subutex/Suboxone) for a minimum of 7 days
  - Initial: 300 mg monthly for the first 2 months *after treatment/stabilization on 8-24 mg of transmucosal buprenorphine*
    - Clinical Pearl: The 300-300-100 mg dosing is roughly equivalent to 16-24 mg transmucosal; SUBLOCADE® may not be suitable for patients stable on lower than 8 mg transmucosal *see next slide
  - Maintenance: 100 mg monthly
    - Maintenance 300 mg doses should be considered for those patients who had previously stabilized on high dose Sublingual Buprenorphine (e.g. 24 to 32mg daily), or continue to experience cravings, withdrawal or unsanctioned opioid use during the first 2 month period of SUBLOCADE® dosing or with 100mg SUBLOCADE® doses
  - **Note**: Recommend dosing every 28 days

Table 1 Transition of Patients Established on Long-term Treatment with Transmucosal Buprenorphine Whose Disease Symptoms are Controlled [9]

Transmucosal Buprenorphine Doses	SUBLOCADE		
	Injection #1	Injection #2	Maintenance Dose
8 – 18 mg/day	300 mg	100 mg*	100 mg
20 – 24 mg/day	300 mg	300 mg	100 mg

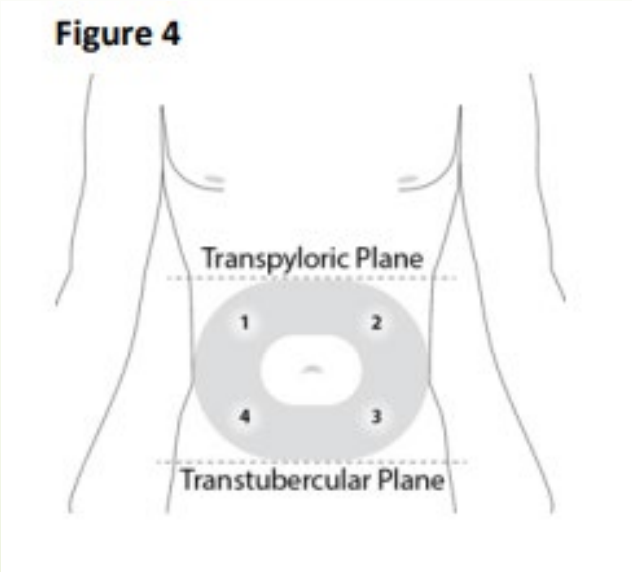
*For patients still experiencing craving or withdrawal symptoms after the initial 300-mg dose, consider giving 300 mg as the second dose

Buprenorphine ER: Administration[9]

- Remove SUBLOCADE® from refrigerator at least 15 minutes prior to administration to allow it to come to room temperature (59 – 86°F)
  - Do not open the foil pouch until the patient has arrived for their injection
  - Keep refrigerated at 35.6 - 46.4°F when not in use
  - Discard if left at room temperature over 7 days
- When ready to administer, remove from foil and inspect liquid (SUBLOCADE® ranges from colorless to amber colored) and *attach the safety needle supplied*
- Prepare the abdominal injection site (an area free of nodules, lesions, excessive pigmentation) by cleaning it with alcohol wipe (recommended for patient to be in supine position)
- Remove excess air from the syringe by holding the syringe upright for several seconds to allow air bubbles to rise.

Buprenorphine ER: Administration[9]

- Pinch the skin around the injection site to ensure you have enough adipose tissue to accommodate the needle size and life adipose away from underlying muscle
- Inject between the transpyloric and transtubercular planes in an area with adequate SUBQ tissue that is free of skin conditions (eg, nodules, lesions, excessive pigment).



Buprenorphine ER: Administration[9]

- Remove the needle at the same angle used for insertion and release pinched skin
- DO NOT rub injection site after
  - Patient education: The patient may have a lump for several weeks that will decrease over time; *advise not to rub or massage* the injection site.
- There may be some blood that can be wiped with gauze before applying a bandage with minimal pressure
- Rotate the injection site between injections
- In the event the depot from an ER injection must be removed, it can be surgically excised under local anesthesia within 14 days of injection. See prescribing information for details.

Adverse Effects[9]

- **Most common:** Sedated state (<66%), Constipated (8-9%), Vertigo (5-10%), Nausea (5-10%), Drowsiness (2-5%), fatigue (4-6%); Injection site: pruritis (6-10%), Pain (5-6%), erythema (3-4%)
- **Side effects: 1-10%:** Increase in liver enzymes: AST (3-5%), ALT (1-5%), GGT (3-4%), Increased Creatinine phosphokinase (3-5%), Hypotension (1-5%), Dizziness (2-10%), Vomiting (1-9%), Headache (1-9%), Diaphoresis (1-5%), Miosis (1-5%), Hypoventilation (1-5%)
- **Patient Education:** ***"Contact your provider if you have…***
  - Trouble breathing
  - Sleepiness, dizziness, and problems with coordination
  - Liver problems: educate about signs/symptoms (Ie, jaundice, dark urine, light color stool, etc.)
  - Allergic reaction: Rash, Hives, swelling of your face, wheezing, etc
  - Opioid withdrawal: Flu-like symptoms

Monitoring[9]

- **Hepatic Impairment**– Before & monthly during early treatment; hepatitis has been reported (transient, asymptomatic transaminase elevations to hepatic failure, most with pre-existing hepatic impairment)
  - Because buprenorphine levels cannot be rapidly decreased, SUBLOCADE® is not recommended for patients with pre-existing moderate to severe hepatic impairment.
  - If moderate or severe impairment develops during treatment with the ER injection, continue with caution and monitor for toxicity for several months.
- **QTc Prolongation** – Buprenorphine has been observed to cause QTc prolongation
  - Avoid using in patients with a personal or family history of long QT syndrome or in patients taking concurrent class IA or III antiarrhythmics or other medications that prolong the QT interval.
  - Use with caution in patients with hypokalemia, hypomagnesemia, or clinically unstable cardiac disease, including unstable heart failure, unstable atrial fibrillation, symptomatic bradycardia, or active MI.
- **Respiratory Depression-** Monitor closely for respiratory depression especially during initiation & dose escalation
  - Concomitant use of buprenorphine and benzodiazepines (or other CNS depressants, including alcohol) may result in coma or death
  - If the ER injection is discontinued due to respiratory depression, monitor the patient for ongoing respiratory depression for several months due to its ER characteristics.
  - Use with caution in patients with compromised respiratory function (eg, chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression)

This is not a complete list of potential adverse events. Please see the full Prescribing Information for a complete list.

Interactions[9]

- CYP 3A4 Inducers – Typically LOWER Buprenorphine levels
  - Strong -- Carbamazepine, Phenobarbital, Phenytoin, Rifampin
  - Moderate- Estradiol
- CYP 3A4 Inhibitors – Typically RAISE Buprenorphine levels
  - Strong - Clarithromycin, Indinavir, Itraconazole, Ketoconazole, Nefazodone
  - Moderate -- Amiodarone, cyclosporine, diltiazem, fluconazole, grapefruit juice, verapamil
- CYP 3A4 Substrates- Typically RAISE Buprenorphine levels
  - Buspirone, Lovastatin, Tacrolimus, Vardenafil, Sildenafil, Tadalafil, Lurasidone, Quetiapine
- Serotonergic Drugs (risk of Serotonin Syndrome)
  - SSRIs, SNRIs, TCAs, Triptans, 5-HT3 antagonists, Linezolid

Benefits of SUBLOCADE®

- Low risk for diversion
- Reduced pill line burden and staff monitoring – compared to daily dosing in an observed pill line
- Stable blood levels
- It has all the benefits of buprenorphine products – partial opioid agonist, ceiling effect, etc

Disadvantages of SUBLCOADE®

- It can only be started in patients that have already initiated treatment with a transmucosal buprenorphine containing product for a minimum of 7 days and has been stabilized on an oral dose of buprenorphine of 8 mg daily or higher
- Boxed warning noting serious harm or death could result if this medication was given intravenously (REMS)
- Constrictions with dosing to address any ongoing symptoms
- Challenges with continuing medication with transition to community (ie, insurance coverage, pricing, not as readily used in community setting)

Naloxone[3]

- Discuss availability of naloxone for the emergency treatment of opioid overdose
- Strongly consider prescribing naloxone at the time of release or transfer because patients being treated for opioid use disorder have the potential for relapse, putting them at risk for opioid overdose
- Educate patients on how to recognize respiratory depression and, if naloxone is prescribed, how to treat with naloxone
- Encourage patients to educate family about symptoms of overdose and how to use naloxone as it will not be self-administered
- Higher than usual doses may be needed for reversal due to buprenorphine's high affinity binding and long duration of action

FAQs

- What should I do if I need to give a dose early?
  - Doses should be given no less than 26 days apart. Delays in dosing up to 2 weeks are not expected to have a clinically significant impact on treatment effect. [9]
- I have a patient that went to 100 mg dosing and patient is complaining about withdrawal symptoms. When can I increase back to 300 mg?
  - The maintenance dose may be increased to 300 mg monthly for patients who do not demonstrate a satisfactory clinical response, as evidenced by self-reported illicit opioid use or urine drug screen positive for illicit opioid use. It can be considered for patients in which the benefits outweigh the risks. The patient will feel different as their body adjusts to the new dose and should be educated about this prior to receiving first injection. [9]
  - A reasonable trial, as perceived by the prescribing clinician, on 100 mg should be completed and if the above indications continue, then an increase to 300 mg can be considered. As a clinical PEARL, steady state is not achieved for 4-6 months.
- I have a patient with a diagnosis of Opioid Use Disorder, Severe. They have never been on a buprenorphine product. Is SUBLOCADE® a reasonable first choice?
  - Initiating treatment with SUBLOCADE as the first buprenorphine product has not been studied. Initiate SUBLOCADE treatment only following induction and dose-adjustment with a transmucosal buprenorphine-containing product [9]

FAQs continued

- My patient had improvement with supplemental sublingual supplementation after complaints of withdrawal with SUBLOCADE® 300 mg. What is the difference between oral buprenorphine-containing product and SUBLOCADE®?
  - Under-treatment of withdrawal is unlikely after administration of the 300 mg dose of the LAI, particularly in combination with 8mg of supplemental sublingual. The patient's stable dose of sublingual buprenorphine at 8mg per day prior to initiation of the LAI formulation produced an inadequate amount of opioid tolerance for the transition to the 300 mg LAI.
  - The patient's report of improvement with sublingual supplementation is likely an artifact of the formulation change. Patients are often more sensitive to both physical and emotional symptoms when changing formulations and maybe could benefit from being specially asked about symptoms during this process.
- My patient received a second dose of SUBLCOADE® 300 mg. They are complaining of itchiness, nausea and sedation. What are the signs of overdose?
  - Common opioid side effects can be pruritis, sweating and vomiting. The emergence of these symptoms may be due to the patient adjusting to the increased buprenorphine levels associated with the loading dose.
  - The manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression, and death.

FAQs Continued

- I discontinued SUBLOCADE® for a patient 2 months ago. The patient is reporting withdrawal symptoms now. What do I do?
  - If SUBLOCADE is discontinued, its extended-release characteristics should be considered, and the patient should be monitored for several months for signs and symptoms of withdrawal and treated appropriately. After steady-state has been achieved (4-6 months), patients discontinuing SUBLOCADE® may have detectable plasma and urine levels of buprenorphine for twelve months or longer [9]
  - Monitor and quantify symptom severity with Clinical Opiate Withdrawal Scale (COWS) & Provide symptomatic treatment for withdrawal- the goal is at reducing the signs & symptoms of withdrawal to reduce self-medicating and return to illicit use: ie, buprenorphine product, anti-diarrheal, clonidine, anti-emetics, non-steroidal anti-inflammatory agents, buspirone, benzodiazepines. [3]
  - Patients stabilized on higher doses in the 24-32 mg/day range prior to the initiation of the LAI may require supplementation for the first 2-3 months only if the patient is experiencing excessive craving and at high risk of relapse. This approach has not been systematically studied and should not be used in conditions where the risk of diversion is high such as in penal institutions.

FAQs Continued

- A patient complained about withdrawal symptoms after inconsistent dosing times of oral buprenorphine-containing product. Is this common?
  - Buprenorphine has a long half-life (24-42 hr) and high binding affinity for mu opioid receptors in the brain therefore the time of administration is not clinically relevant in a stabilized patient.
- A patient is relatively new into MAT treatment with oral buprenorphine and appears to be seeking different doctors for dose increases due to complaints about cravings. How should I address?
  - Opioid use disorder and addiction in general are characterized by loss of control over drug consumption and dysfunctional coping strategies. Often in early treatment with medications such as buprenorphine the physical symptoms of withdrawal have been addressed but the poor impulse control and difficulty coping with stress and anxiety remain in place. Combined, it is not unexpected the patient continues to seek medications or even continues to use opioids to pacify discomfort while new coping strategies are being developed with ongoing treatment.

How to get involved in MAT

- Educate, Educate, Educate – Provide education to your colleagues about medications, treatment benefits, review literature, diversion control techniques
- Get involved – ie, BOP staff can work with their institution MAT Point-of-Contact (POC) to participate in multi-disciplinary team meetings to provide valuable input about pharmacology
- STOP stigmatizing language - be aware of personal biases & respectfully correct peers (“addicts,” “dirty urine,” “give them their drugs,” “replacement therapy”)

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Further Questions?

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