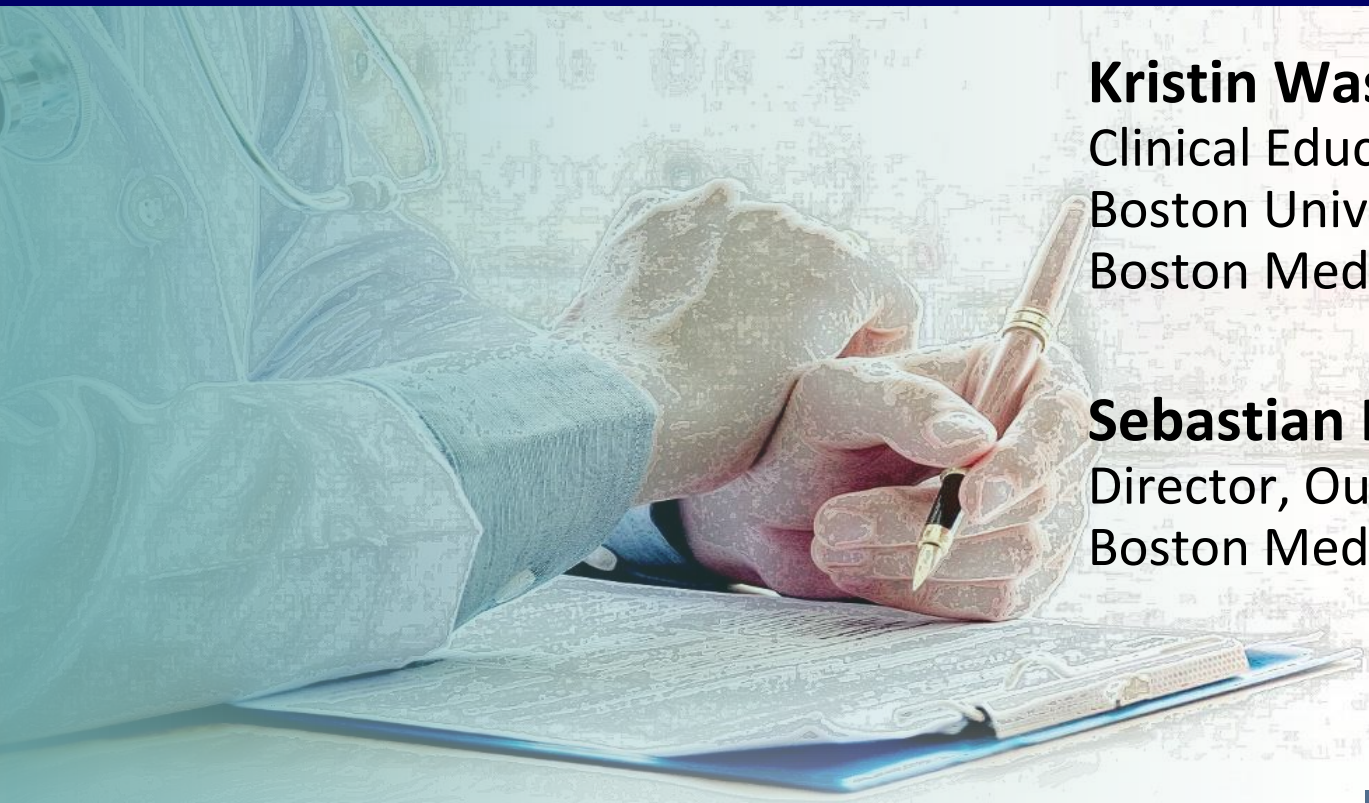
Module 4

Incorporating Long-Acting MOUD Formulations Into Clinical Practice



Kristin Wason, MSN, NP-C, CARN
Clinical Educator, Massachusetts OBAT TTA
Boston University Chobanian & Avedisian School of Medicine
Boston Medical Center

Sebastian Hamilton, BSP, MBA, PharmD, RPh
Director, Outpatient Pharmacy Services
Boston Medical Center

CARE

Grayken Center for Addiction
Boston Medical Center

BU Chobanian & Avedisian School of Medicine

Objectives

- Discuss strategies to overcome the challenges of utilizing long-acting buprenorphine and naltrexone for treating opioid use disorder (OUD) in office-based practices

- Address clinical and operational issues involved in developing an integrated multidisciplinary approach, including existing primary care models for treating OUD

Injectable Buprenorphine

Injectable Buprenorphine

Subcutaneously injected long-acting buprenorphine

- Indication: Treatment of moderate to severe OUD in patients who have previously initiated treatment with transmucosal buprenorphine
- DEA schedule: CIII
- FDA Risk Evaluation and Mitigation Strategy (REMS) requirement: Yes

REMS: Risk Evaluation and Mitigation Strategy

Injectable Buprenorphine: Formulations

Sublocade

- FDA approved 2017
- For patients who tolerate 8-24mg buprenorphine for one week
- Monthly subcutaneous injection into abdomen
- Two dosing options, requires two loading doses

Brixadi

- Tentative FDA approval 2019; not yet available
- For patients who tolerate a single dose of a transmucosal buprenorphine
- Weekly and monthly injection with multiple possible injection sites
- Range of weekly and monthly dosing options, no loading doses

Injectable Buprenorphine: Safety

- Safety profiles similar to transmucosal buprenorphine with exception of anticipated injection site reactions
- Liquid medications that form a semi-solid when coming into contact with body fluids
- Patients must never handle injectable formulations
- Medications only to be administered by healthcare professionals

Injectable Buprenorphine: How It Works

Buprenorphine + gel delivery in a preloaded syringe

- Two targeted release phases: rapid achievement of therapeutic levels that are sustained over monthly dosing interval
- Opioid blockade occurs at 70-80% mu opioid receptor occupancy which correlates to about 2-3 ng/mL buprenorphine plasma concentration
- Sublocade reaches this threshold on day one for the first injection and maintains the plasma level with little to no peak or trough

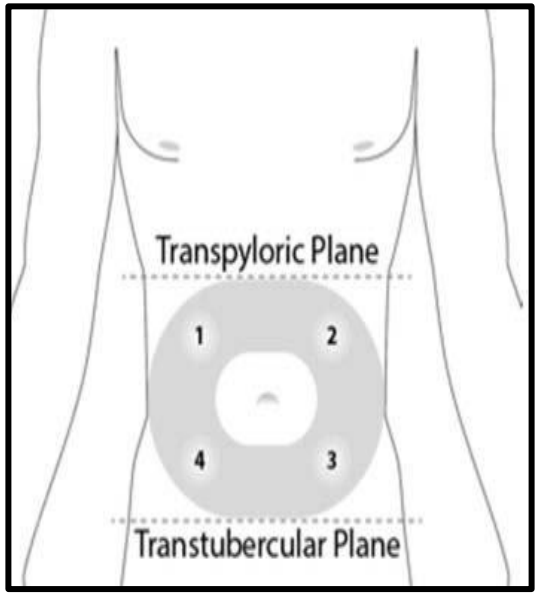
Greenwald MK, et al. *Drug Alc Depend.* 2014;144:1-11. Nasser AF, et al. *Clin Pharmacokinetics* 2014;53:813-24. Bickel WK, Amass L. *Exp Clin Psychopharmacol.* 1995;3:477-89. Comer SD, et al. *Psychopharmacol.* 2005;181:664-75.

Starting Injectable Buprenorphine

- Obtain signed Patient Informed Consent
  - Example consent form available at www.bmcobat.org
- Ensure that insurance is in place, and medication is ordered and stored appropriately until the patient's appointment
- Continue patient on transmucosal formulation until day prior to injection
- Inform patient that injectable buprenorphine liquid can appear as clear, yellow or amber color
- Advise patient that a lump will persist for weeks, and reduce in size over time; avoid rubbing, touching, and tight clothing

Starting Injectable Buprenorphine

- Bring prefilled syringe to room temperature prior to administration (at least 15 min)
- With patient supine, administer subcutaneous injection into abdominal site free of skin conditions
  - Note: medication may stings during administration
  - Administer loading doses into lower abdomen
- Record location of injection, rotate injection sites



Instructions for Use. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209819s000lbl.pdf

Injectable Buprenorphine: Dosing Schedule

- First two months at 300 mg (1.5 mL)
- Following injections at 100 mg (0.5mL)
- Consider continuing at 300 mg doses for patients who:
  - Experience withdrawal symptoms
  - Have significant chronic pain
  - Continue to struggle with opioid use
- A small subset of patients may benefit from supplemental doses of transmucosal buprenorphine during the first 2 months of treatment
- Toxicology screens may test positive for buprenorphine up to 12 months after last injection

Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209819s000lbl.pdf

Injectable Buprenorphine: Pros and Cons

Pros

- Rapid and sustained therapeutic buprenorphine levels
- Enhanced adherence
  - Reduced diversion
  - Reduced risk of accidental poisoning in children
  - Reduces transportation issues
  - Avoids risk of lost or stolen medication
  - Avoids ritual of drug taking with transmucosal formulations

Cons

- Cost may be prohibitive
- No “carrot effect”
- Loading dose required
- Some patients may require supplemental transmucosal buprenorphine initially
- Injection stings
- Unstudied in pregnancy
- Cosmetic appearance of the depot site is distressing for some
- More logistics with in–office storage and dispensing

Tkacz J, et al. *Am J Addict* 2011;21:55-62.

Injectable Naltrexone

Injectable Naltrexone

Naltrexone is an opioid receptor antagonist with very high receptor affinity. Vivitrol is the only commercially available injectable naltrexone product in the United States

- Indication: Prevention of relapse to opioid use, following full opioid detoxification. Treatment of alcohol use disorder
- DEA Schedule: VI
- Prescriber criteria: No DEA license or DATA 2000 “X” waiver needed
- FDA REMS program: No

Efficacy of Injectable Naltrexone

Injectable naltrexone vs transmucosal buprenorphine/naloxone,

- 24-week, RCT with 570 participants recruited following inpatient opioid detox
- Randomized to either transmucosal buprenorphine, 8-24 mg/day or injectable naltrexone, 380 mg/month
  - Significantly more patients were successfully initiated onto buprenorphine
  - Of participants initiated onto medication, both groups had similar outcomes including treatment retention, negative urine screens, days of opioid abstinence, and reduced cravings
  - Adverse events did not differ, with the exception of injection site reactions among the injectable naltrexone group

Lee JD, et al. *Lancet*. 2018;391(10118):309-18.

Safety of Injectable Naltrexone

- Generally a safe and well tolerated medication
- Most common adverse effects include: injection site pain, injection site reactions, hepatic enzyme abnormalities, insomnia, and anorexia
- Caution in persons with moderate to severe renal or liver impairment, thrombocytopenia, or any coagulation disorder
- When withdrawal is precipitated, the resulting withdrawal syndrome can be severe
- **Life-threatening opioid intoxication is possible if a patient returns to opioid use**

Starting Naltrexone

- One dose, 380 mg (4mL), delivered intramuscularly into gluteal muscle every 4 weeks
- Patients must be fully withdrawn from opioids prior naltrexone initiation. Washout period of 7-10 days recommended
- Recommended to start treatment with oral naltrexone to ensure tolerability and then advance to extended-release injectable formulation

Naltrexone/Naloxone Challenge

A naltrexone or naloxone challenge test should be performed whenever there is a risk of precipitating opioid withdrawal

- **Naltrexone challenge**
  - Naltrexone 25-50mg orally x one dose
  - Observe patient for withdrawal for minimum of 45 minutes

- **Naloxone challenge**
  - Inject 0.8-1.2 ml of naloxone
  - Observe patient for withdrawal for minimum of 15 minutes

Administering Injectable Naltrexone

- Medication at room temperature prior to administration
- Reconstitute medication after patient arrives for visit and is determined to be appropriate for injectable naltrexone
- There will be 2 needle sizes 1.5” and 2” choose needle that will ensure medication goes into muscle. Do not substitute manufacturer components
- Once mixed, give injection quickly so that the medication does not solidify
- Document location of injection.
- Alternate sites

Injectable Naltrexone vs Oral Naltrexone: Pros and Cons

Pros

- Enhanced adherence
- Avoids drug taking ritual of daily oral formulation

Cons

- Cost may be prohibitive
- Injection site pain and reactions
- Pain management can be complex for patients experiencing emergent medical situations
- Logistics with ordering and storing of medication

Storage and Handling Injectable Formulations

Naltrexone

- Store at 2-8°C (35.6-46.4°F).
- Unrefrigerated, store at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration
- Do not expose the product to temperatures above 25°C (77°F)
- Should not be frozen

Buprenorphine

- Store at 2-8°C (35.6-46.4°F)
- Unrefrigerated, store in original packaging at room temperature, 15-30°C (59-86°F), for up to 7 days prior to administration
- Discard if left at room temperature for longer than 7 days

Specialty Pharmacy Process:
Injectable Buprenorphine and Naltrexone

- Make sure pharmacy benefit coverage is accepted at pharmacy
- Understand coverage limitations and co-pay implications
  - Specialty pharmacy can work with the manufacturer's patient assistance program and other resources to eliminate barriers
- Send prescription (e.g., e-prescribe, fax, mail) to pharmacy
- Have a process to accept the prescription sent/mailed from specialty pharmacy
  - **Prescription is <u>never</u> to be provided directly to the patient by pharmacy**
- Follow process for the safe handling, storage, and security of controlled prescriptions (i.e., buprenorphine)
- Be able to store prescription under refrigeration until administration

Medications for Treating Opioid Use Disorder

Module 1: Overview

Module 2: Challenging Cases

Module 3: Patient & Provider Perspectives

Module 4: Incorporating MOUDs into Practice

CARE

Grayken Center for Addiction
Boston Medical Center

BU Chobanian & Avedisian School of Medicine