Clinical Updates on the Use of Injectable Medications for Opioid Use Disorder (MOUD)

Valerie S. Ganetsky, PharmD, MSc
Cooper University Health Care
Center for Healing, Division of Addiction Medicine
Camden, New Jersey

05/07/2021

Financial disclosure

- No financial disclosures

Learning objectives

- State the currently available extended-release injectable medications for opioid use disorder (MOUD) and describe their advantages, induction and maintenance strategies, and clinical and patient-centered outcomes.
- Describe the potential role of extended-release injectable MOUD in the high-potency synthetic opioid (HPSO) era.
- Describe an extended-release injectable buprenorphine program within a specialty addiction medicine outpatient practice.

Availability of injectable MOUD over the years

Extended-release naltrexone (XR-NTX, **Vivitrol)** approved as monthly intramuscular injection for prevention of return to opioid dependence

Brixadi *tentatively* approved as once-weekly or once-monthly subQ buprenorphine injection

Sublocade approved as monthly subcutaneous (subQ) buprenorphine injection

SAHMSA. TIP 63. 2018

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Extended-release buprenorphine (XR-BUP) have several advantages for patients who...

- Are unstable/frequently miss visits
- Have buprenorphine access challenges (e.g., incarceration, entering residential treatment programs not allowing MOUD)
- Have concerns about safe storage (e.g., children, stolen medications)
- Can't reliably get to clinic
- Don't want to take daily medication
- Are concerned about stigma related to daily buprenorphine

Neale, et al. Harm Reduction Journal. 2019.

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Sublocade - general overview

- Monthly subQ injection only by a healthcare provider
- Repeat injections every 26-30 days
- Labeling states that occasional delays in dosing up to 2 weeks are not clinically significant
- Stored in refrigerator

SUBLOCADE [prescribing information]. Indivior Inc.; 2018

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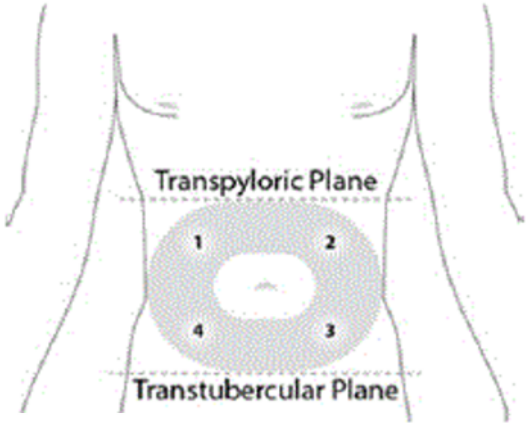
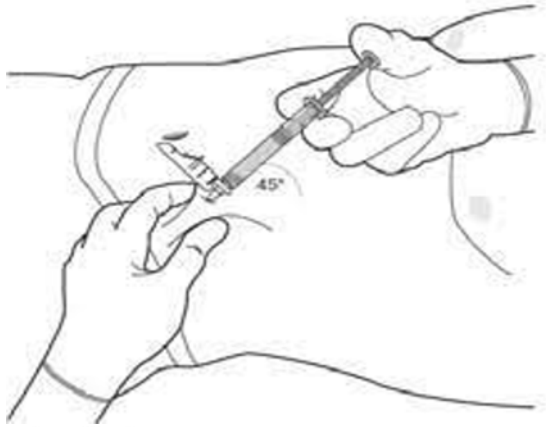
Sublocade injection strategies

- Injected subQ as a slow, steady push
- Strategies to minimize pain/discomfort
  - Minimum of 15 min at room temperature before injection
  - Lidocaine injection 10-15 minutes before Sublocade
- Counsel patients on lump at injection site that will be present for several weeks and decrease over time





SUBLOCADE [prescribing information]. Indivior Inc.; 2018

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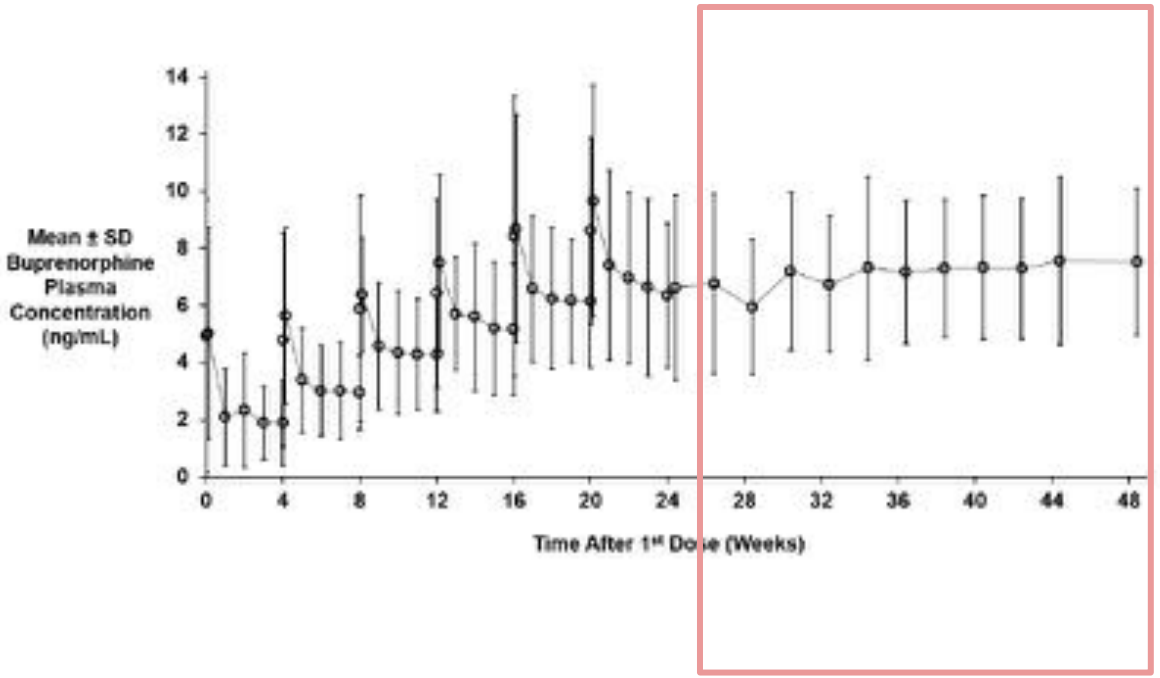
Sublocade steady state levels



- Steady state achieved at 4-6 months
- Levels may be detectable for 1+ year after stopping (once at steady state)

SUBLOCADE [prescribing information]. Indivior Inc.; 2018; RBP-6000 FDA Briefing Document. https://www.fda.gov/media/108382/download

Sublocade concentrations compared to sublingual (SL) buprenorphine

Mean	300 mg* (first injection)	100 mg† (ss)	300 mg† (ss)
$C_{avg,ss}$ (ng/mL)	2.19	3.21	6.54

Average concentration of SL buprenorphine 24 mg = 2.91

- Both 100 mg and 300 mg doses should suppress opioid withdrawal and cravings
- Average steady state concentration of 100 mg slightly higher than 24 mg SL buprenorphine
- Average concentration of 300 mg at steady state is even higher

Levels of 2-3 ng/ml are required to occupy ≥70% of mu-opioid receptors and reduce illicit opioid use

SUBLOCADE [prescribing information]. Indivior Inc.; 2018

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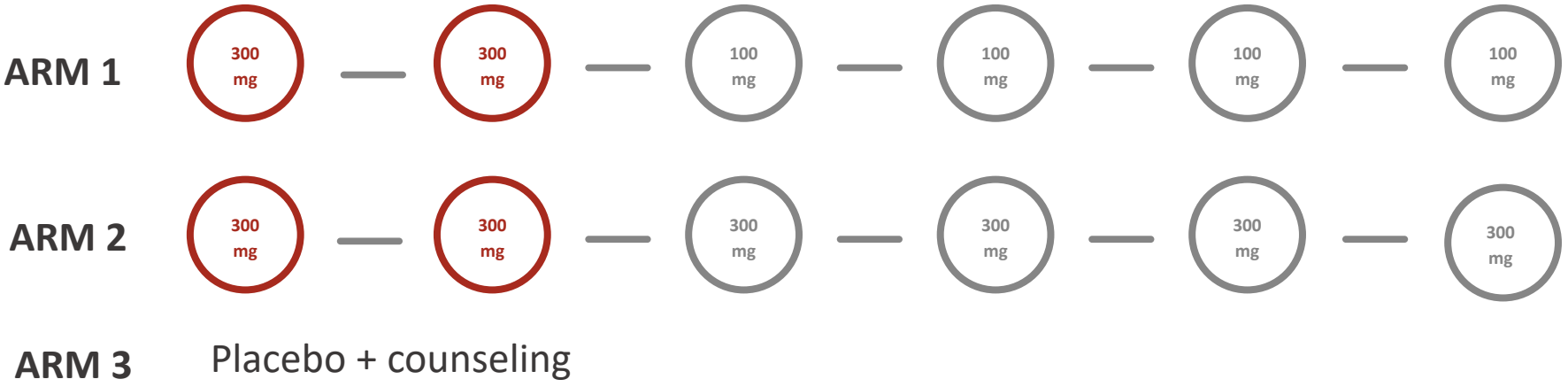
Sublocade pivotal trial (n=504)



Primary outcome (% opioid abstinence at 6 months):

- Higher in both Sublocade 100 mg and 300 mg maintenance groups compared to placebo (~40% vs. 5%)
- No significant differences between dosage groups
- Similar side effect profile to SL buprenorphine except for injection-site reactions (5-10% of patients)

Haight, et al. Lancet. 2019.

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Sublocade 12-month patient-centered outcomes

- Quality of life stable or improved
- Employment rates increased by 7%
- High patient satisfaction with Sublocade (88%)
- 80% of patients were on 300 mg maintenance dose
- Limitations
  - Open-label study (non-blinded), no control group
  - 50% of patients dropped out (loss to follow-up, withdrawal of consent)

Ling, et al. JSAT. 2020.

Sublocade induction strategies

- Product labeling recommends stabilization on SL buprenorphine 8-24 mg for ≥7 days before starting
- Goal of SL buprenorphine stabilization: establish tolerability/safety

SUBLOCADE [prescribing information]. Indivior Inc.; 2018

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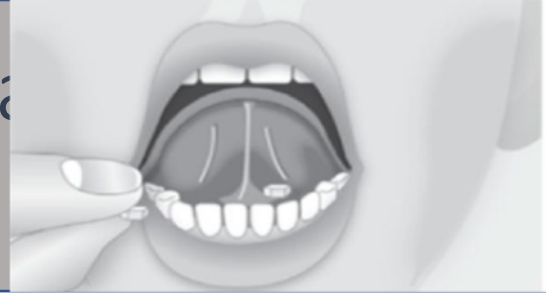
Sublocade induction strategies - rapid induction

- Several case series added to literature on safety of Sublocade initiation after being on SL buprenorphine for <7 days:
    - Mariani, et al (2020): 5 patients transitioned to Sublocade after 2-3 days of SL buprenorphine (average dose = 16 mg)
    - Peckham, et al (2021): rapid initiation in 25% of patients started on Sublocade
- Our institution has started Sublocade during hospital admissions in patients stabilized on SL buprenorphine for <7 days

Mariani et al. Am J Addict. 2020; Peckham, et al. JSAT. 2021.

Sublocade induction strategies - use of supplementa buprenorphine



- No supplemental SL buprenorphine was allowed in the Sublocade randomized study
- Over 50% of patients required 4-24 mg SL buprenorphine (daily or as needed) after starting Sublocade for varying time periods in recent “real-world” case series
- Reasonable to use in patients who have continued opioid withdrawal and/or cravings after starting Sublocade

Peckham, et al. JSAT. 2021.

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Sublocade 100 mg vs. 300 mg maintenance dose

Sublocade package labeling:

"The maintenance dose may be increaased to 300 mg monthly for patients who tolerate the 100 mg dose but do not demonstrate a satisfactory clinical response"

- 300 mg has greater average plasma buprenorphine concentrations vs. 100 mg
  - Benefit in the HPSO era
- May benefit persons who inject drugs (PWID)
  - Unpublished study found that PWID had 15% higher opioid abstinence rates in 300 mg vs. 100 mg maintenance group
- Majority of patients in our Sublocade program are on 300 mg maintenance dose

Wiest, et al. Poster: Abstinence Response to 300mg vs. 100mg RBP-6000 Among Opioid Injection Users. ASAM 2019. Orlando, FL

Sublocade access

Option 1: Specialty pharmacy delivers to the office for administration to individual patients

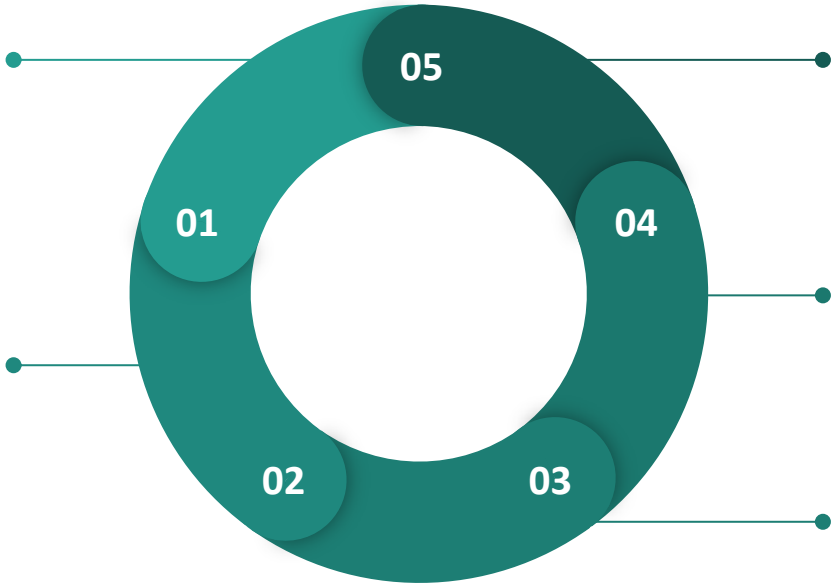
a. Prescriptions sent directly to specialty pharmacy
b. Indivior website has list of specialty pharmacies that carry Sublocade:https://www.sublocaderems.com/Content/pdf/certified-pharmacies.pdf

Option 2: Office purchases directly from a distributor ("buy-and-bill")

a. Healthcare setting must become REMS certified

SUBLOCADE [prescribing information]. Indivior Inc.; 2018

Our process for obtaining Sublocade for individual patients (Option 1)



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Cooper University Health Care Sublocade program

250
patients prescribed Sublocade since 2018

130
currently active Sublocade patients

Health coach initially assisted in establishing Sublocade program

Program assistant became “Sublocade champion”, ~50% of time spent on Sublocade

Three licensed practical nurses spend ~50% of their time on Sublocade

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Cooper University Health Care Sublocade program

Process-related challenges

- Staff time
- Medication storage and logging in/out
- Patient consent to ship
- Insurance barriers

Script date	Expires in	Script Notes	Status	Follow up
10/06	27 days	300-- 1 refill	1. Script Sent	10/15/20
09/28	19 days	300--2 refills on 9/28	2. Processing	10/09/20
09/22	13 days	300--5refills	2. Processing	10/09/20
09/28	19 days	300mg-- 1 refill on 9/28	3. Needs Consent	10/09/20
09/25	16 days	300--1 refill on 9/25	3. Needs Consent	10/12/20
08/12	(-28)	300-1 Rrefill on 8/12	3. Needs Consent	10/13/20
08/26	(-14)	300- 1 Refill on 8/26	3. Needs Consent	10/13/20
09/04	(-5)	100--5 refill on 9/4/20	3. Needs Consent	10/08/20
09/28	19 days	300--1 refill on 9/28	3. Needs Consent	10/12/20
09/18	9 days	300 -- 1 Refill on 9/18	3. Needs Consent	10/09/20
09/15	6 days	300- 1 Refill on 9/15	3. Needs Consent	10/13/20
07/01	(-70)	300-1 Refill on 7/1/20	3. Needs Consent	10/13/20
07/16	(-55)	300--1 refill on 7/16	3. Needs Consent	10/08/20
08/27	(-13)	300- 1 Refill on 8/27	3. Needs Consent	10/13/20
07/06	(-65)	300-1 refill on 7/7	4. Delivery Scheduled	10/09/20
09/29	20 days	100 -- 5 Refills on 9/29	4. Delivery Scheduled	10/14/20
09/24	15 days	300--2 refills on 9/24	4. Delivery Scheduled	elivery sched-10/9/2020
09/25	16 days	300--1 refill on 9/25	4. Delivery Scheduled	10/12/20
09/18	9 days	300--5 refill on 9/18	5. Delivered	10/09/20
09/26	17 days	300-5 Refill on 9/26	5. Delivered	10/15/20

Patient-related challenges

- Administrative burden for unstable patients
- Visits no longer tied to medications
- Injection-site pain/reactions
  - Patients with low subQ fat -- more pain, less effective (??)

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Lessons learned from our Sublocade program

- Dedicated individual to learn the process and become “Sublocade champion” to teach others
- Find out most commonly used insurance plans in your practice and develop a process -- gets easier with more practice!
- Figure out where to store injections and who will log them in/out
- >10 patients is approximately when the workload ramps up

Brixadi: weekly/monthly injectable buprenorphine vs. SL buprenorphine (n=428)

Pivotal Study

PHASE 1 Weekly injection x 12 weeks vs. SL buprenorphine

PHASE 2 Monthly injection x 12 weeks vs. SL buprenorphine

First Day of Study
All patients started with SL buprenorphine 4mg, patients randomized to weekly Brixadi were given 16 mg subQ on same day

Primary outcome (responder rate at pre-defined study timepoints): Brixadi "non-inferior" to SL buprenorphine

Secondary outcome (% urine samples negative for opioids): Brixadi superior to SL buprenorphine (35% vs. 28%)

Brixadi is still awaiting final FDA approval

Lofwall, et al. JAMA Intern Med. 2018.

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Brixadi vs. Sublocade

Dosing flexibility

- Brixadi >> Sublocade
  - Weekly - 8, 16, 24, 32 mg
  - Monthly - 64, 96, 128, 160 mg
  - Sublocade: 100 & 300 mg monthly only
  - Advantage of weekly dosing?

Storage

- Brixadi does not need to be refrigerated

Injection sites

- Sublocade: abdomen
- Brixadi: abdomen, buttock, thigh, upper arm

Comparison to standard of care

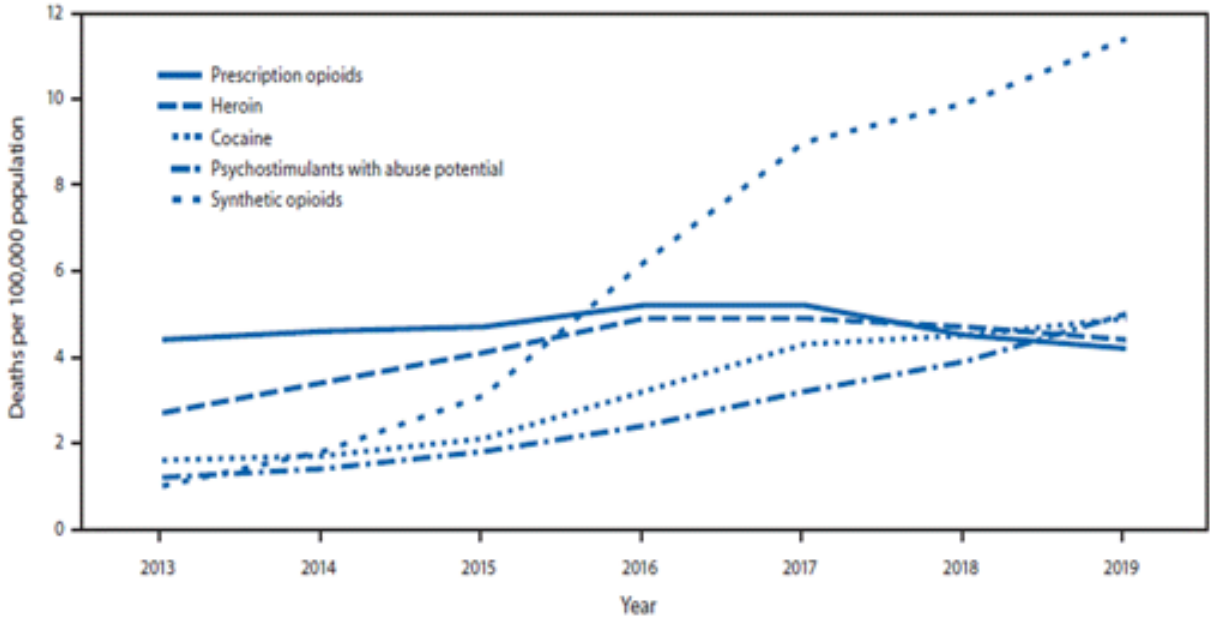
- Brixadi was compared to SL buprenorphine
- Sublocade compared to placebo (SL buprenorphine comparison studies ongoing)

Treatment induction

- Sublocade was studied with 2 week SL buprenorphine run-in phase
- Brixadi started on Day 1 (for weekly formulation, monthly formulation??)

XR-BUP in the HPSO era

- Higher serum buprenorphine concentrations vs. SL buprenorphine
- Ensures adherence x 4-6 weeks
- Case series of XR-BUP rapid induction for HPSO-positive patients
  - 2-3 days of SL buprenorphine 16-24 mg followed by XR-BUP
  - Withdrawal symptoms well-controlled after 24 hours - corresponding to spike in XR-BUP levels



Mattson, et al. MMWR Morbid Mortal Wkly Rep. 2021; Mariani et al. Am J Addict. 2020

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XR-NTX (Vivitrol)

- **Advantages**
  - Monthly injection → adherence
  - Access: more providers may be comfortable, can obtain from community pharmacies
  - Patient desire for no physical opioid dependence

- **Disadvantages**
  - Period of opioid abstinence makes induction difficult (Lee, et al. 2017: 72% XR-NTX vs. 94% SL buprenorphine)
  - Lowering of tolerance increases risk of opioid overdose after discontinuation/missed doses
  - Possible to override blockade with high opioid doses → concern in HPSO era

Lee, et al. Lancet. 2017.

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Thank you!
Questions & Discussion

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