Substance Use Disorder ECHO

RUTGERS

Project ECHO®

State of New Jersey
DHS Department of Human Services

MEDICATION-ASSISTED TREATMENT CENTERS OF EXCELLENCE

Rowan Medicine

RUTGERS New Jersey Medical School

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Our Goal

- Combat the substance use crisis through education on best preactices in a safe space for peer-to-peer learning
- Engage healthcare providers in the primary care setting to increase skills to safely and compassionately manage, treat, and support their clients with a substance use disorder
- Recognize the importance of reducing stigma to advance equity and improve access to care for patients with substance use disorders

Financial Disclosures

- The following sessions leader(s) have no relevant Financial relationships with ineligible companies to disclose:
  - Mohammad Addar
  - James Bailey
  - Clement Chen

Long-Acting Injectable Medications for Opioid Use Disorder (MOUD) and Future Innovations: Implications in the Age of Fentanyl

Jun 9, 2023

Presented by:
Clement Chen, PharmD, BCPS
Clinical Pharmacist/Academic Detailer
Northern NJ MAT Center of Excellence
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Learning Objectives

- Distinguish the key pharmacological properties between the injectable and sublingual buprenorphine formulations
- Identify the potential role of injectable buprenorphine in the era of highly potent synthetic opioids
- Describe clinical experiences with the use of injectable buprenorphine
- Discuss the newly FDA-approved formulation of injectable buprenorphine

Pre-Poll Questions

- 1) I currently use Sublocade, or work with patients, on Sublocade.
  - Yes
  - No
  - N/A
- 2) I feel confident in the use of or working with patients on Sublocade.
  - Yes
  - No
  - N/A
- 3) On a scale of 1-5, I understand the rationale for the use of extended-release injectable vs. transmucosal buprenorphine. (1=Low, 5=High)
- 4) I am aware of the newly FDA-approved extended-release injectable buprenorphine formulation, Brixadi.
  - Yes
  - No

Notice for Presentation

- For the purpose of this presentation, both the trade-names Sublocade® and Brixadi® will be used to distinguish the different formulations of extended-release injectable buprenorphine

Age of Fentanyl – Pharmacology

MOR Signaling

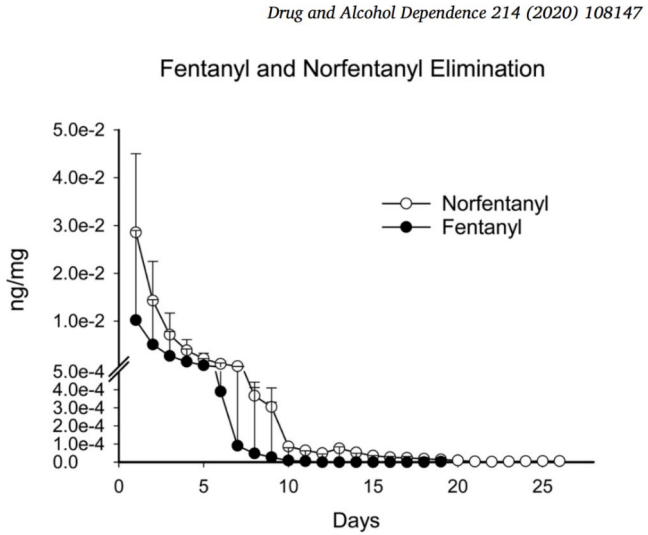
G-Protein Pathway (Analgesia) ← Morphine | Fentanyl → B-Arrestin Pathway (Resp. Depression)

"Desensitized" from G-protein pathway"

Morphine	Fentanyl
Less lipophilic	More lipophilic
Slow CNS entry	Rapid CNS entry

Fentanyl and analogs account for >70% of opioid overdose deaths

Illicit fentanyl is illegally synthesized, forming many different analogs



Comer SD, et al. *Neurosci Biobehav Rev.* 2019 Nov;106:49-57.
Huhn AS, et al. *Drug Alcohol Depend.* 2020 Sep 1;214:108147.

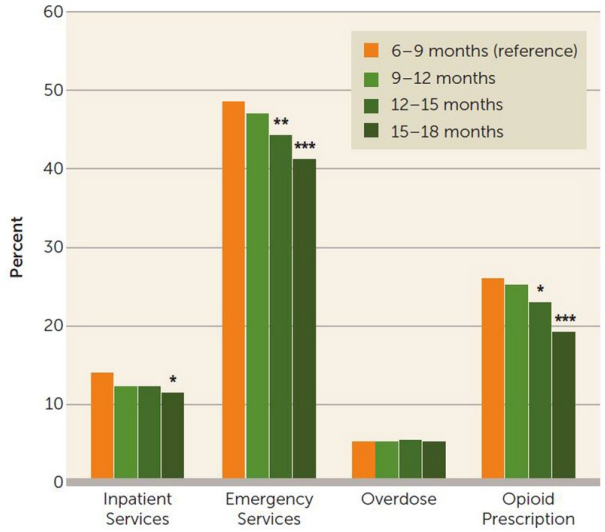
Long-Term Buprenorphine Use

60-day lead in (buprenorphine free)

Index buprenorphine (day 0)

180+ days of continuous buprenorphine:
6-9 months
9-12 months
12-15 months
15-18 months

All were subsequently followed for 6-months after discontinuation



Williams AR, et al. *Am J Psychiatry.* 2020 Feb 1;177(2):117-24.

Sublocade

Sublocade Overview

- An FDA-approved injectable formulation for the treatment of OUD
- Monthly subQ injection every 26-30 days
  - After 7-day stabilization?

Package Insert Specifics

- Available in:
  - 300 mg/1.5 mL
  - 100 mg/0.5 mL
- Dosed with “two monthly initial doses of 300 mg followed by 100 mg monthly maintenance doses” after 7-day stabilization on transmucosal buprenorphine
- “Increasing the maintenance dose to 300mg monthly may be considered for patients in which the benefits outweigh the risks”

Good Candidates for Sublocade

- Patients with moderate-severe OUD
- Those who are stable on buprenorphine for at least 7 days and on 8-24mg buprenorphine (package insert recommendation)
- Benefit from stability of monthly injections
  - Lifestyle
  - Non-adherence
- Contraindications
  - Absolute: Allergy to buprenorphine or components of the delivery system
  - Relative: On full opioid agonists

Haight BR, et al. *Lancet.* 2019 Feb 23;393(10173):778-90.

Advantages

- Are unstable/frequently miss visits
  - Real-world experience
- Have buprenorphine access challenges
  - Transportation
- Have concerns about safe storage (eg children, diversion/stolen medications)
- Can't reliably get to clinic
- Don't want to take daily medication
  - Less polypharmacy
- Are concerned about stigma related to daily buprenorphine

Haight BR, et al. *Lancet.* 2019 Feb 23;393(10173):778-90.

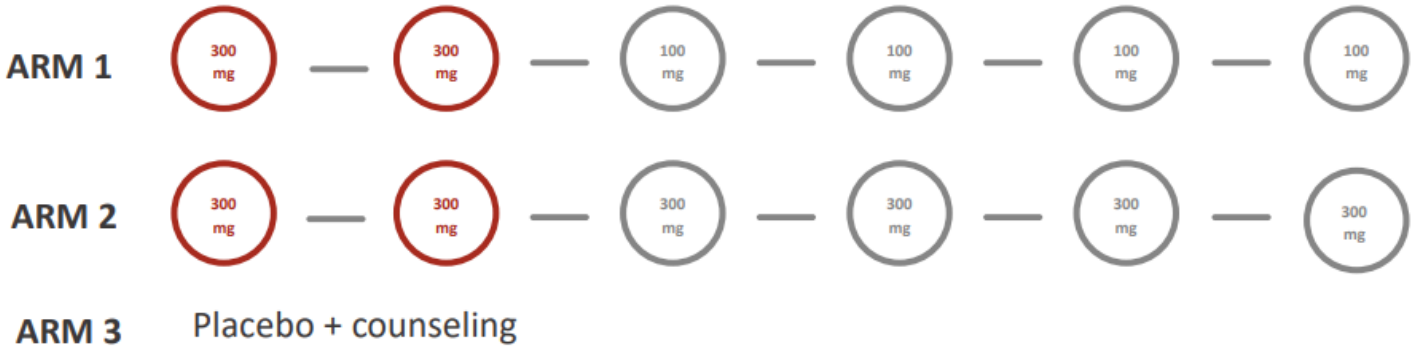
Pharmacology – Plasma Concentrations of Sublocade vs. SL Buprenorphine

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)

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

Pivotal Trial

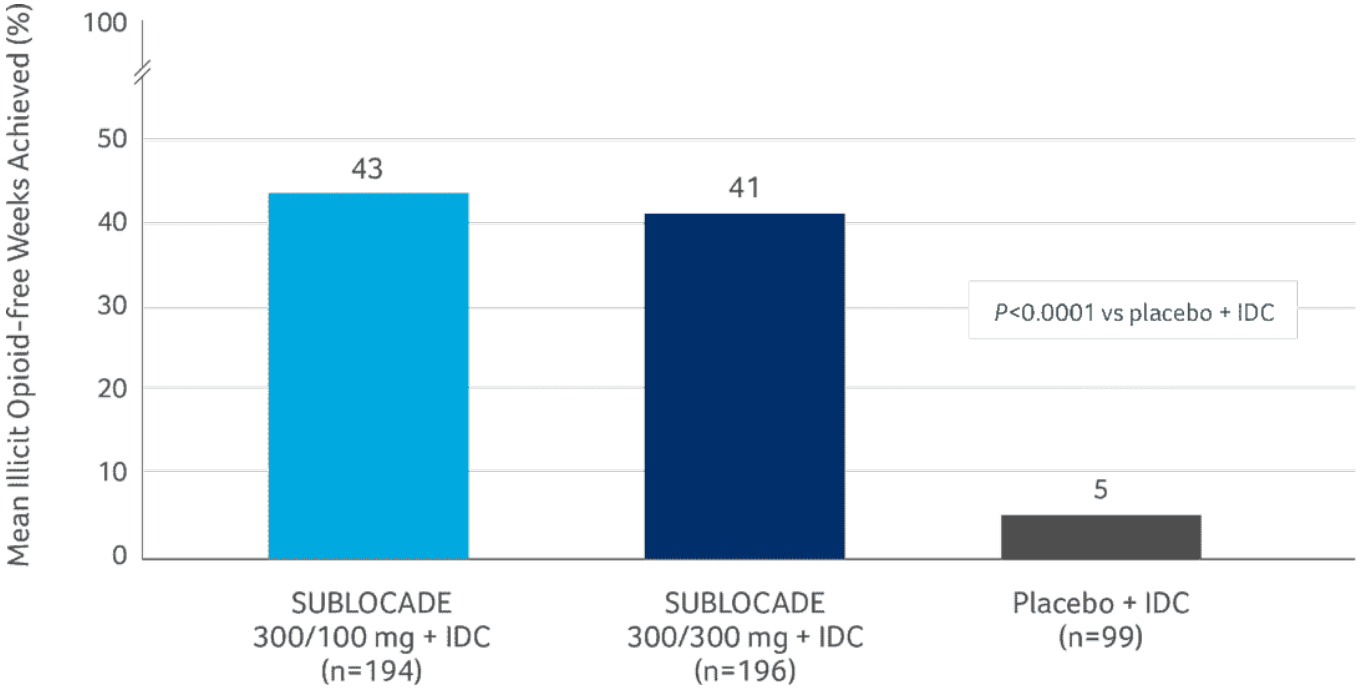


Primary outcome (% opioid abstinence at 6 months):

- 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)

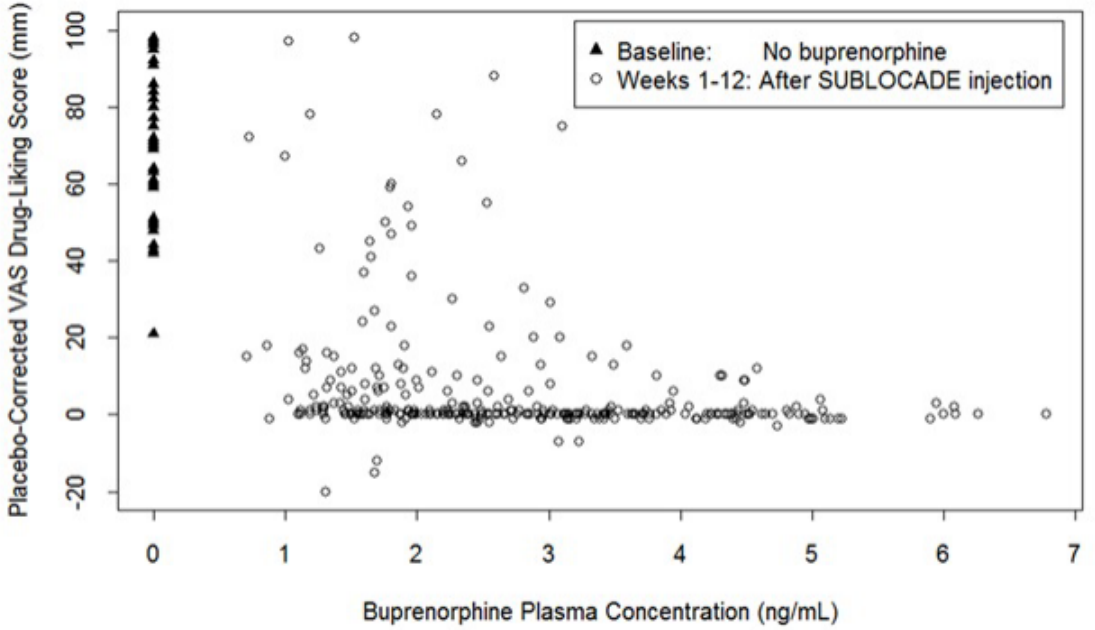
Pivotal Clinical Trial

Mean Patients' Percentage Illicit Opioid-Free Weeks (Week 5 Through 24)[1,2]



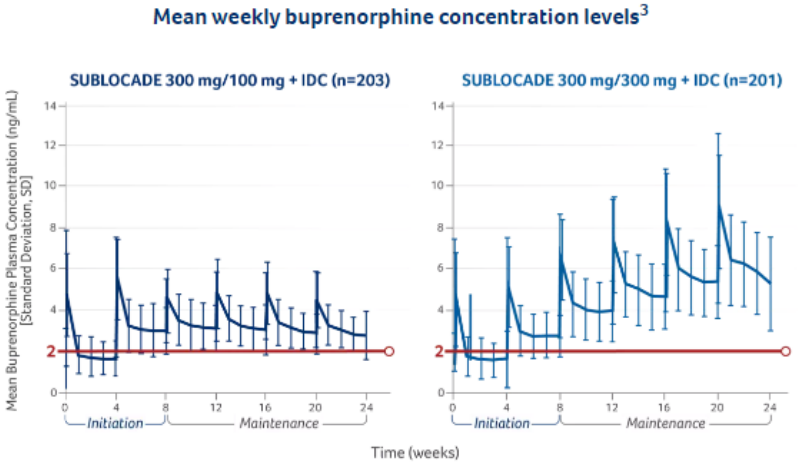
Drug-Liking VAS vs. Plasma Buprenorphine Concentration After 18mg Hydromorphone Challenges

Figure 10 Drug Liking VAS vs. Plasma Buprenorphine Concentration Following 18 mg Hydromorphone Challenges



Indivior, Sublocade Prescribing Information

Sublocade Steady State Levels



See full image description -

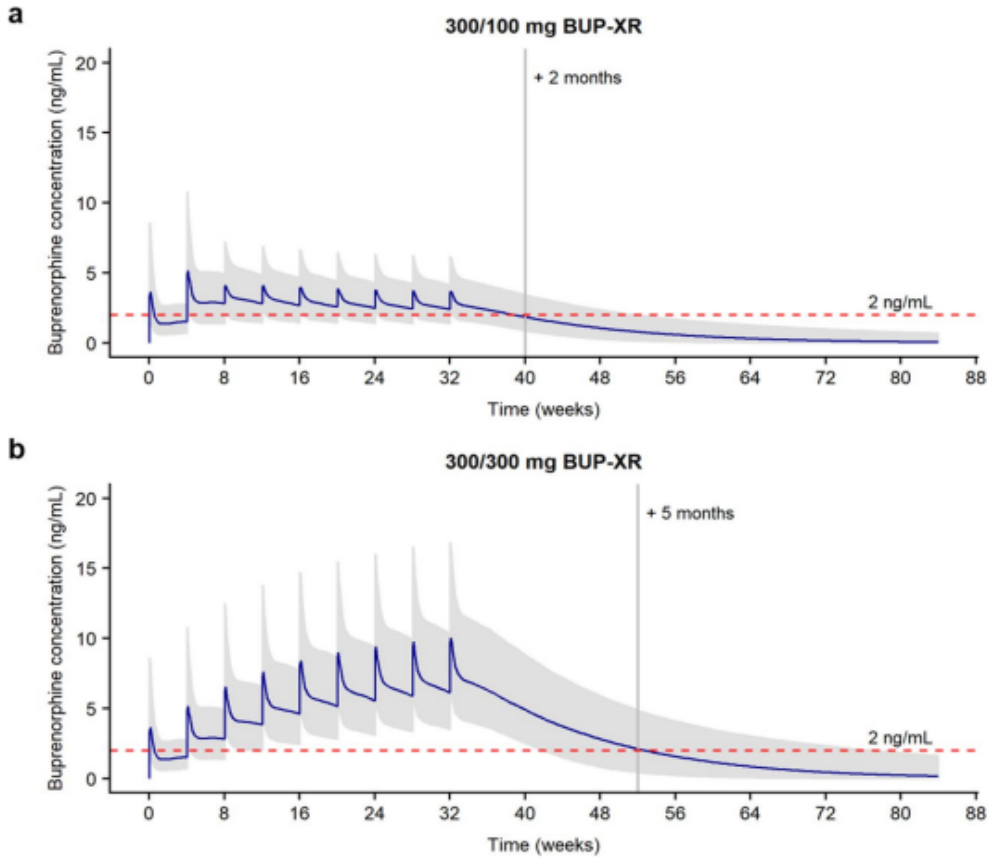
The first graph depicts the results for the SUBLOCADE 300 mg/100 mg + IDC group (n=203). After Week 4 (during the initiation period of 8 weeks), mean weekly buprenorphine levels are maintained above 2ng/mL up to Week 24.

The second graph depicts the results for the SUBLOCADE 300 mg/300 mg + IDC group (n=201). After Week 4 (during the initiation period of 8 weeks), mean weekly buprenorphine levels see a steady incline above 2ng/mL up to Week 24.

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

Indivior, Sublocade Prescribing Information

Fig. 6 Predicted decrease in buprenorphine plasma concentrations for BUP-XR dosing regimens following treatment interruption. **a** 300/100-mg dosing regimen 2; **b** 300/300-mg dosing regimen. Blue solid lines: median of the simulated data; gray shaded areas: 90% prediction intervals of simulated data. A total of nine subcutaneous injections were simulated in 5000 subjects. The horizontal red dashed line indicates the 2-ng/mL minimum concentration required for opioid blockade, as established from modeling and simulation and confirmed by clinical data (Nasser et al. [18])



Jones AK, et al. *Clin Pharmacokinet.* 2020 Nov 2.

Disadvantages

Insurance and logistical barriers/cost

Time from ordering to administration

Provider confidence

Management challenges

Dose adjustments

Initiation – supplemental SL buprenorphine needed?

Adverse reactions

- Pain (during injection)
- Thrombosis (Black Box Warning of serious harm if injected into vein)
- Orthostasis

Administration

- Inject **subQ** as a **slow**, steady push
- Strategies to minimize pain/discomfort
  - Minimum of 15 mins at room temperature before injection
  - Lidocaine injection 10–15 minutes before Sublocade
  - Use ice pack before injection
- Counsel patients on lump (depot) that will be present for several weeks and decrease over time

Figure 4

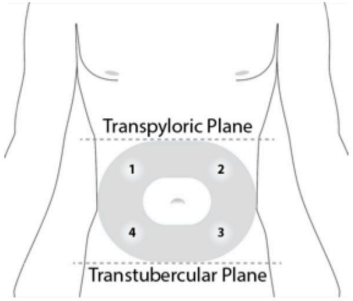
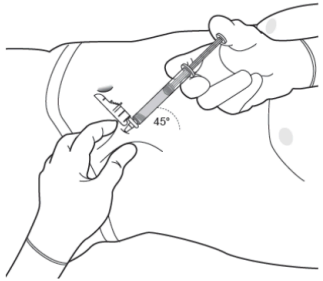


Figure 7



Aftercare

- Do not massage or rub on area
- No belts/waistbands on the area
- Use ice packs to limit pain *Should decrease over 24 hours
- Mild redness, itching, tenderness normal for a few days
- Call your doctor if signs of persistent redness, swelling, fever, or chills
- Avoid alcohol, benzodiazepines and other central nervous system depressants
- Tell all healthcare providers you are on XR-BUP (pain issues)

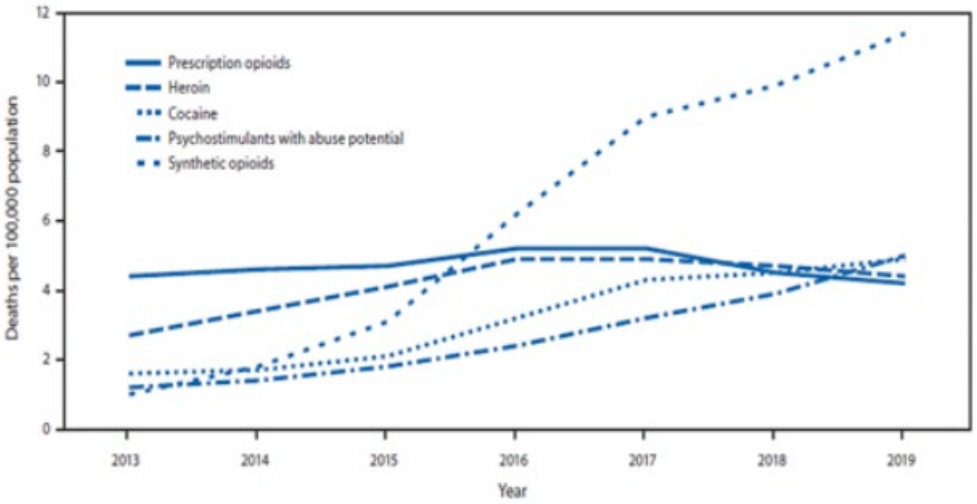
Using Sublocade in Practice

- Are patients asking about injectable buprenorphine?
- Do your patients prefer to be on injectable buprenorphine?

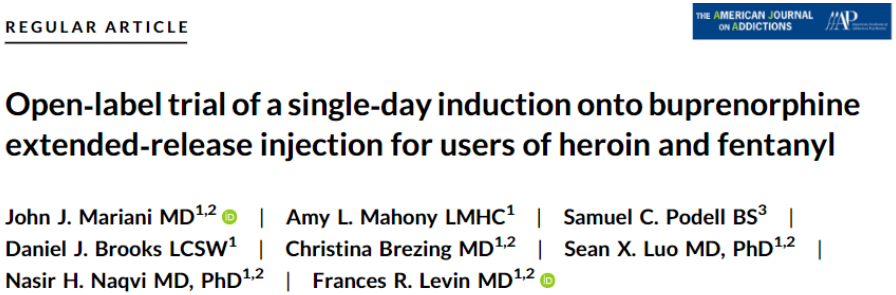
- What tips do you have for administering XR-BUP?

Sublocade 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 16-24mg followed by XR-BUP
  - Withdrawal symptoms well-controlled after 24 hours – corresponding to spike in XR-BUP levels



Real World Induction in the Literature



REGULAR ARTICLE

THE AMERICAN JOURNAL ON ADDICTIONS

Open-label trial of a single-day induction onto buprenorphine extended-release injection for users of heroin and fentanyl

John J. Mariani MD[1,2] | Amy L. Mahony LMHC[1] | Samuel C. Podell BS[3] | Daniel J. Brooks LCSW[1] | Christina Brezing MD[1,2] | Sean X. Luo MD, PhD[1,2] | Nasir H. Naqvi MD, PhD[1,2] | Frances R. Levin MD[1,2]

- Open-label, uncontrolled 12-week outpatient clinical trial of a single-day induction onto XR-BUP for five adults using heroin-containing fentanyl
- All 5 received XR-BUP 300mg injection on the first day of induction after receiving 24mg of SL bupe
- COWS score ranged from 0-15 on Day 1, and 0-7 on Days 2-4

Mariani JJ, et al. *Am J Addict.* 2021 Sep;30(5):470-76.

Real World Induction in the Literature

Retrospective case series in a low-barrier bridge clinic from 2/1/2019 – 7/31/2019 of 40 patients

- 78% were unstably housed, mostly male (68%), and non-Hispanic white (98%)

10 (25%) received SL bupe for fewer than the 7 recommended days

XR-BUP at 300mg monthly was administered to 25%, and 55% treated with supplemental SL bup from 4-24mg, daily or as needed

65% remained on XR-BUP at the end of data collection

Peckham AM, et al. *J Subst Abuse Treat.* Jul;126:108316.

Real World Experiences in the Literature

- Retrospective analysis of 200 patients prescribed XR-BUP between 12/1/2018-12/31/2020
- Results: **88% primarily used heroin/fentanyl**; 2/3 reported IV use
  - 63% male identified as non-Hispanic white, 92% insured by Medicaid
  - Average number of injections received during 6-month period was 3.8.
  - 6 patients were on SL buprenorphine for <7 days
  - **Average lag time between XR-BUP prescribing and receipt of first dose was 35 days (SD 25.3)**
  - **Average SL dose of bupe was 20mg prior to XR-BUP and 60% required supplemental SL bupe**
  - **70% remained on maintenance dose of 300mg**

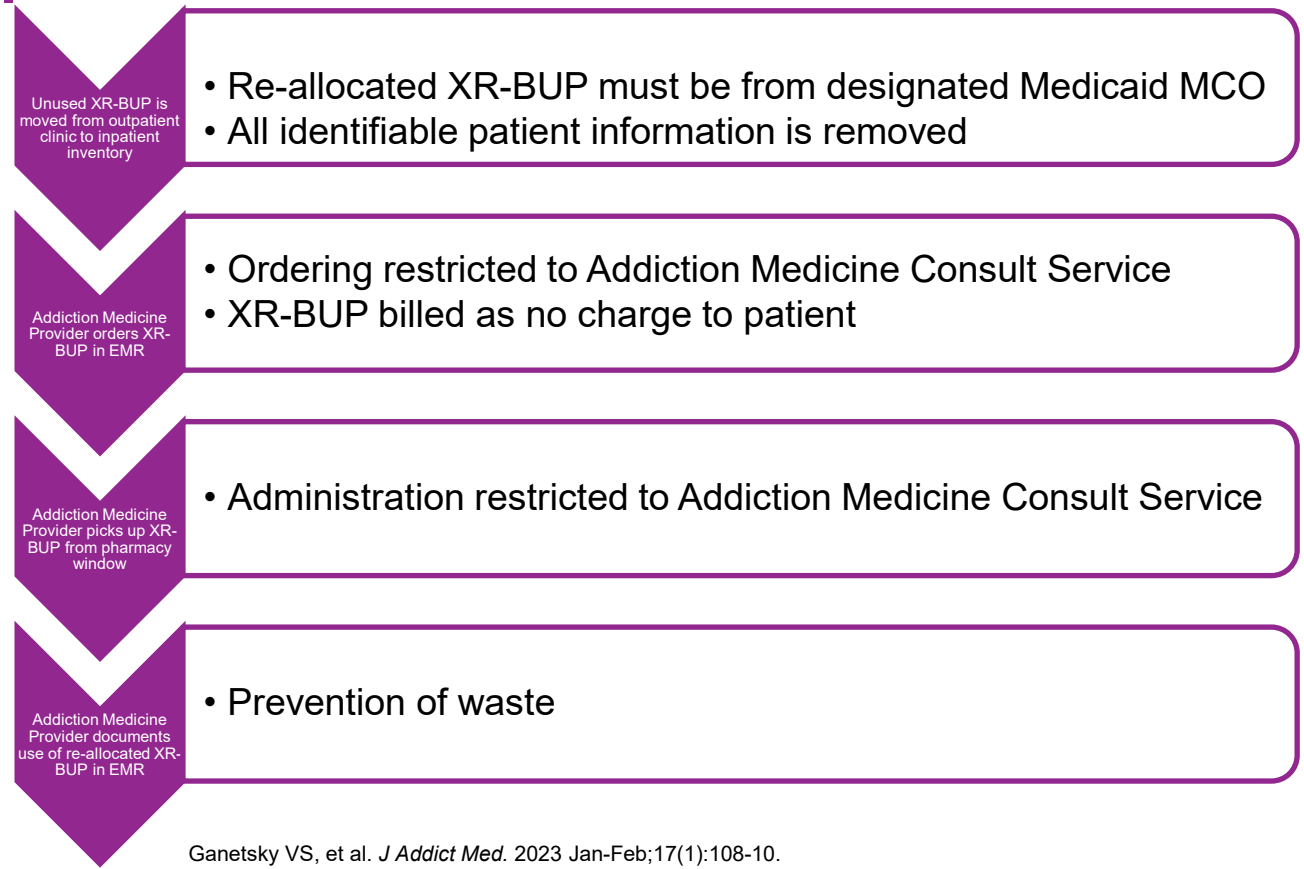
Heil J, et al. Poster: Real-world evaluation of an injectable extended-release buprenorphine program. ASAM 2022; Hollywood, FL.

Real World Experiences in the Literature

- XR-BUP 12-month patient-centered outcomes of 412 patients
- Quality of life stable or improved
- Employment rates increased by 7%
- High patient satisfaction with XR-BUP (>88%)
- 80% of patients were on 300mg maintenance dose
- Limitations
  - Open-label study (non-blinded), no control group
  - 50% of patients dropped out (loss to follow-up, withdrawal of consent)

Ling W, et al. *J Subst Abuse Treat.* 2020 Mar;110:1-8.

Using Extended-Release Injectable Buprenorphine In the Hospital



Ganetsky VS, et al. *J Addict Med.* 2023 Jan-Feb;17(1):108-10.

Clinical Scenarios with Sublocade

- Persistent withdrawal symptoms during first few weeks of injection
- Persistent withdrawal symptoms towards end of dosing interval
- Drowsiness throughout month
- Off-label dosing
- Missed doses
- Using XR-BUP for taper

XR-BUP and Pregnancy

- **In published animal reproduction studies with NMP**, an excipient in SUBLOCADE, preimplantation losses, delayed ossification, reduced fetal weight, developmental delays and reduced cognitive function were reported at doses equivalent to the doses of NMP via SUBLOCADE.

- **Based on animal data, advise pregnant women of the potential risk to a fetus.**

Brixadi

Brixadi

- FDA-approved (available in 9/2023) for the treatment of moderate-severe opioid use disorder for patients who are already stable on buprenorphine OR have started treatment with a dose of a transmucosal buprenorphine formulation

Image: www.brixadi.com

Brixadi vs. Sublocade

- Available as weekly and monthly dosing
- Uses “FluidCrystal” Injection Depot Technology Lipid-based
  - Thin needle (23-g vs. 19-g)
  - No refrigeration
  - Multiple SC sites beyond the abdomen
    - Buttock
    - Thigh
    - Abdomen
    - Upper Arm
- Must rotate injection sites for weekly injectable (8 weeks apart)

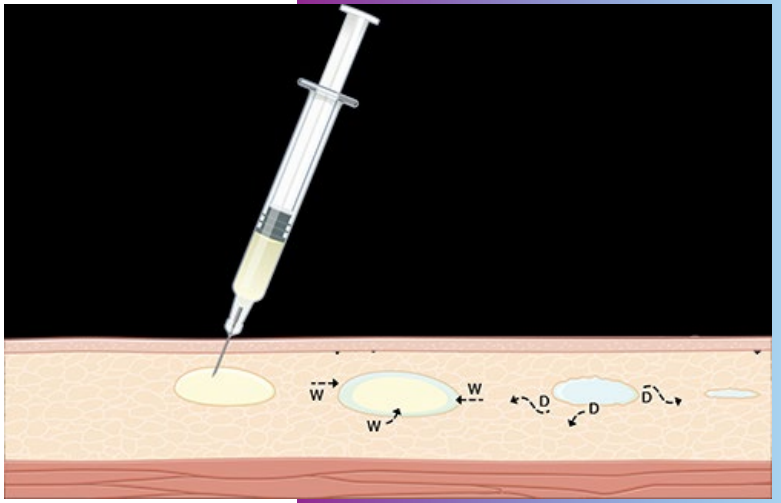


Image: https://product.statnano.com/product/10675/cam2038

Weekly/Monthly Injectable Buprenorphine vs. SL Buprenorphine (n=428)

"The trial enrolled patients representative of the real-world population, including patients that injected opioids (52%), patients that primarily used heroin (71%), patients with evidence of fentanyl use (26%) and patients using nonopioid substances at screening (71%)."

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%)

Lofwall MR, et al. *JAMA Intern Med.* 2018;178(6):764-73.

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??)

Dosing Information

- Weekly Formulation
- Administer in 7-day intervals (+/- 2 days)
  - 8mg/0.16mL, 16mg/0.32mL, 24mg/0.48mL, 32mg/0.64mL
- Monthly Formulation
- Administer in 28-day interval (+/- 1 week)
  - 64mg/0.18mL, 96mg/0.27mL, 128mg/0.36mL

SL Bupe Daily 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

Concentrations

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

Sample Dosing Titration with Weekly Injectable and Monthly Conversion

- If buprenorphine-naïve, titrate to weekly 24mg dose of Brixadi®.
- If the patient is already stable on buprenorphine (tolerated), administer the first dose of Brixadi (weekly formulation), 16mg
  - Otherwise, start with 4mg transmucosal test dose
- Administer an additional dose of 8mg Brixadi (weekly formulation) within 3 days of the first dose to achieve 24mg
  - Can further up-titrate another 8mg dose to 32mg (wait at least 24 hours)

Brixadi (Weekly)	Brixadi (Monthly)
16 mg	64 mg
24 mg	96 mg
32 mg	128 mg

Special Considerations

Steady-state	• Weekly: 4 weeks → can remain in plasma for 4 weeks when discontinued • Monthly: 4 months → can remain in plasma for 4 months when discontinued
Not recommended to be surgically removed	• Liquid crystalline gel so may not be feasible
No concern of NMP excipient	• However, weigh benefits >>> risks

Extended-Release Naltrexone

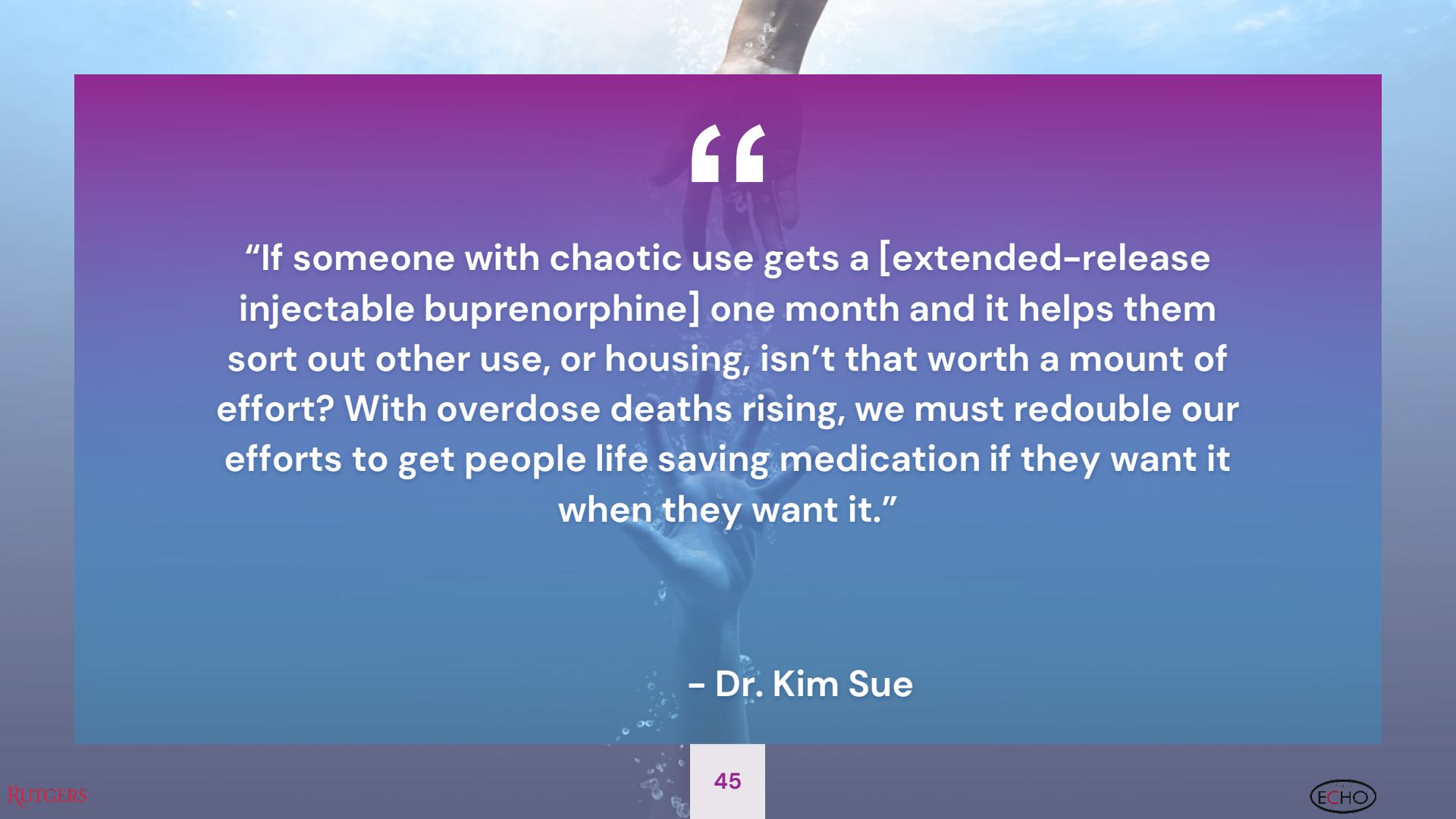
- **Advantages**
  - Monthly injection → adherence
  - Access: More providers may be comfortable as it is not an opioid
  - Patient desire for no physical opioid dependence

- **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/shorter intervals → concern in HPSO era

Lee JD, et al. *Lancet*. 2018 Jan 27;391(10118):309-18.

Implications for Treatment

- Are extended-release injectable formulations the future of OUD treatment?
  - Improves treatment adherence
  - No risk for diversion
  - Persistent concentration of buprenorphine in the plasma
  - Improved overdose mortality prevention?
    - Consider that pivotal trials were non-inferior and the primary outcomes of the study



“If someone with chaotic use gets a [extended-release injectable buprenorphine] one month and it helps them sort out other use, or housing, isn’t that worth a mount of effort? With overdose deaths rising, we must redouble our efforts to get people life saving medication if they want it when they want it.”

– Dr. Kim Sue

Conclusions

Injectable formulations for OUD has many benefits for treatment especially in the age of fentanyl

Understanding the most up-to-date evidence-based information is crucial in educating patients on the best options for them to improve their health outcomes

References

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Thank you!

Any questions?