Place in Therapy for Extended-Release Injectable Buprenorphine (XR-BUP)

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Financial Disclosures

- The following session leader has no relevant financial relationships with ineligible companies to disclose:

    - Clement Chen, PharmD

Learning Objectives

- Distinguish the key pharmacological properties between the injectable and sublingual buprenorphine formulations
- Identify the potential role of XR-BUP in the era of highly potent synthetic opioids
- Describe clinical experiences with the use of XR-BUP

Poll Questions

1) I have experience prescribing or working with patients on extended-release injectable buprenorphine:
   a) Yes
   b) No
   c) None of my patients are on extended-release injectable buprenorphine

2) What is my greatest concern of extended-release injectable buprenorphine?
   1) Open-ended question

Patient Case

- RE is a 50 year old male with a **PMHx of opioid use disorder**, **alcohol use disorder, cocaine use disorder, tobacco use disorder, major depressive disorder** with **numerous hospitalizations** for **depressive symptoms** and **suicide attempts** in the context of **homelessness, depression, and drug use.** He has **also experienced trauma regarding a friend who got shot in front of him** although he thought the bullets were for him. He has **difficulty coping** with these thoughts and is having nightmares and re-living symptoms, using **heroin/fentanyl to cope**. He has **had overdoses in the past, some of which were intentional but does not want to go on like this**. The patient has **been intermittently on SL buprenorphine and has been switched to XR-BUP 10 months ago.**

XR-BUP Overview

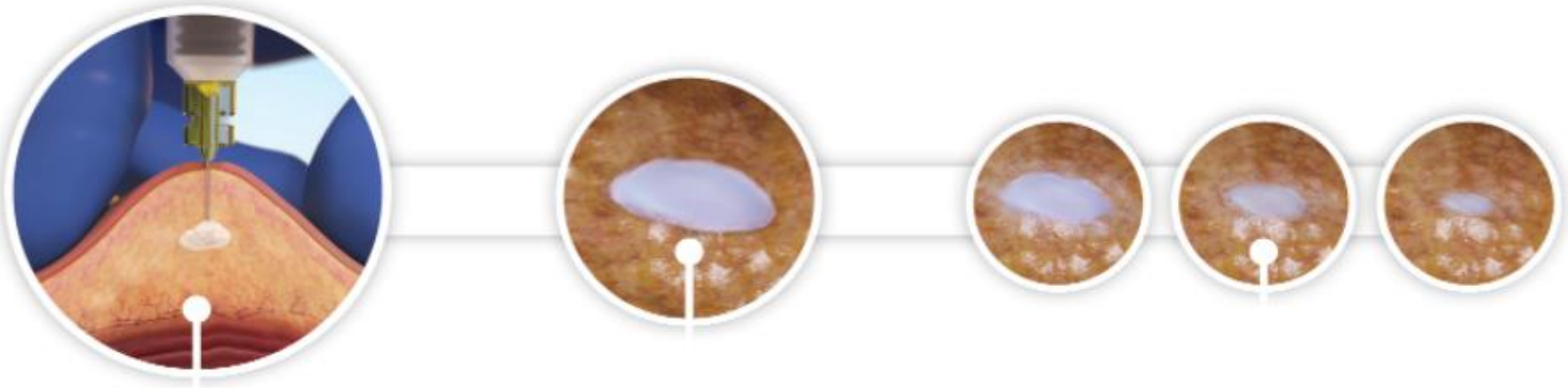
- Currently only 1 FDA-approved formulation for the treatment of OUD
- Monthly subQ injection every 26-30 days
  - After 7-day stabilization?

"Increasing the maintenance dose to 300mg monthly may be considered for patients in which the benefits outweigh the risks"

Indivior, XR-BUP Prescribing Information

How Does XR-BUP Work?

Inject at subq at 45 degree angle



Suspension

- Buprenorphine is injected into the subQ space

Rapidly Formed Solid

- Polymers respond to water by precipitating and trapping buprenorphine in a solid implant

Controlled Drug Release Over Time

- Biodegradable polymers degraded by hydrolysis, slow releasing buprenorphine

https://eligardhcp.com/atrigel-delivery

Good Candidates for XR-BUP

- 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

Pharmacology – Plasma Concentrations of XR-BUP 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)

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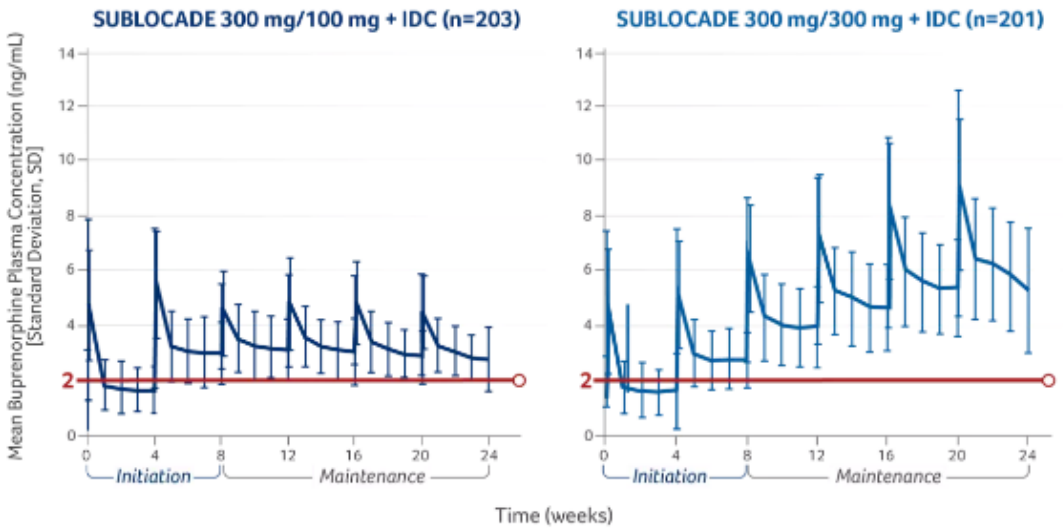
XR-BUP Steady State Levels

Mean weekly buprenorphine concentration levels[3]



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)

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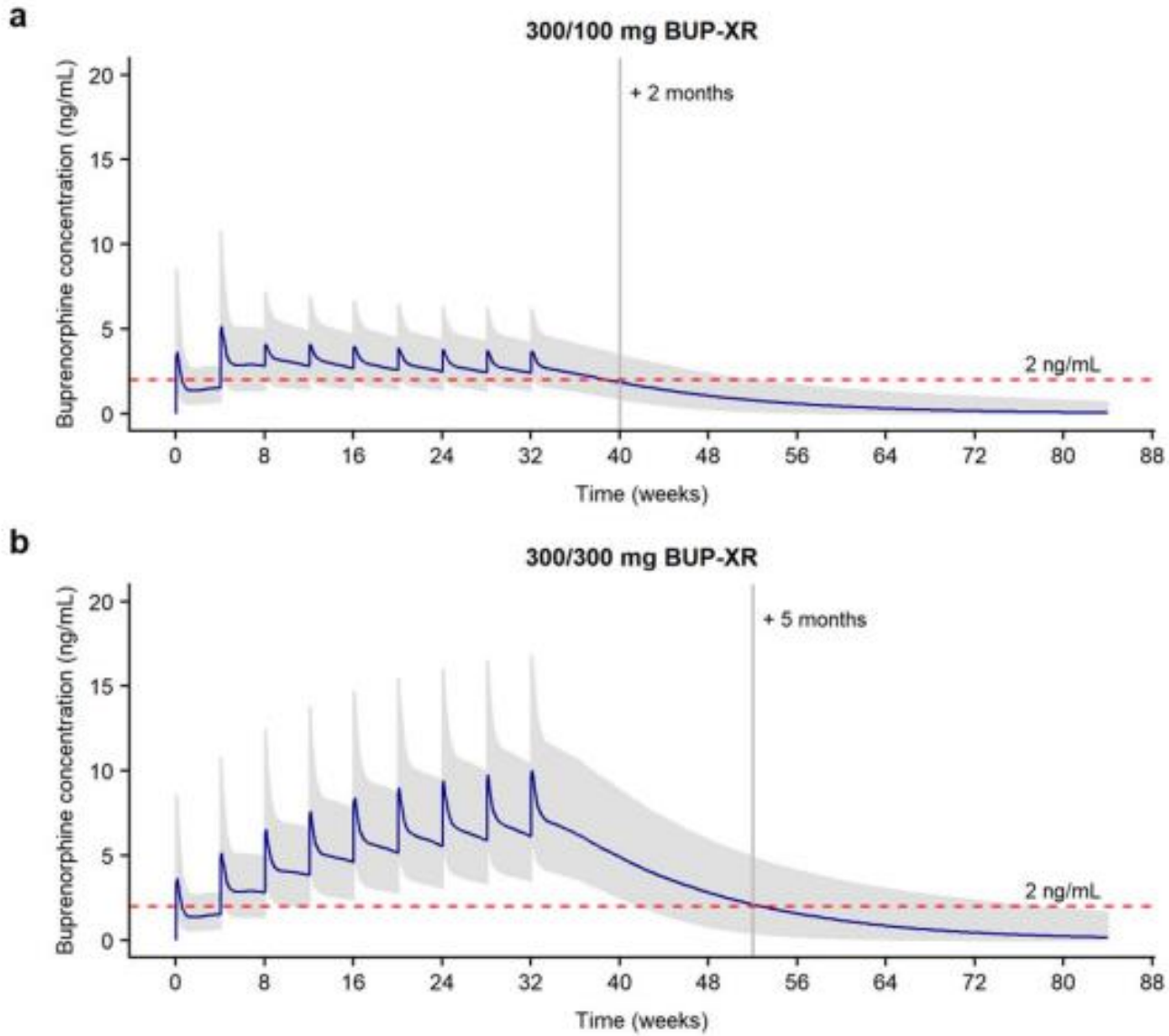


Fig. 6 Predicted decrease in buprenorphine plasma concentrations for BUP-XR dosing regimens following treatment interruption. **a** 300/100-mg dosing regimen 2; **b** 300/300-mg dosing regimen. Blue solid lines: median of the simulated data; gray shaded areas: 90% prediction intervals of simulated data. 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
  - Off-label dosing
  - Initiation
  - Adverse reactions
    - Ulcers
    - Thrombosis (Black Box Warning of serious harm if injected into vein)
    - Orthostasis
    - Pain (during injection)

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 XR-BUP
  - Use ice pack before injection
- Counsel patients on lump (depot) that will be present for several weeks and decrease over time

Figure 4

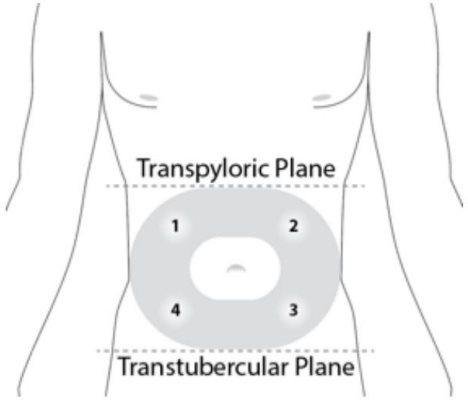
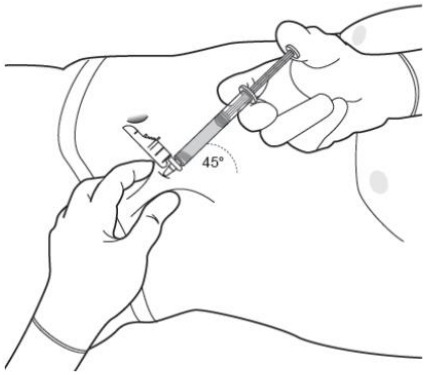


Figure 7



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Aftercare

- Do not massage or press on area (takes 4 hours to solidify)
- 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 if signs of redness after 3 days, swelling, fever, or chills
- Avoid alcohol, benzodiazepines and other sedatives
- Tell all healthcare providers you are on XR-BUP (pain issues)

Using XR-BUP in Practice

- How do you counsel patients about switching from SL buprenorphine to XR-BUP?
  - Are patients asking about XR-BUP prior to their appointment?
- What tips do you have for administering XR-BUP?

XR-BUP Induction Strategies

- Product labeling recommends stabilization on SL buprenorphine 8-24mg for at least 7 days before starting
  - “The recommended dose of XR-BUP is two monthly initial doses of 300mg followed by 100mg monthly maintenance doses”
  - “Increasing the maintenance dose to 300mg monthly may be considered for patients in which the benefits outweigh the risks”
- Peak effect is at 24 hours
- Goal of SL buprenorphine stabilization: establish tolerability/safety

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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.

Clinical Scenarios with XR-BUP

- Withdrawal symptoms persist first few weeks after injection
  - Steady state?
  - Persistent symptoms – overlapping buprenorphine?
- Withdrawal symptoms that develop late right before next injection
- Drowsiness throughout month
- Off-label dosing of 50mg? 200mg?
- Missed doses
- Using XR-BUP for taper

XR-BUP and Pregnancy

- **In published animal reproduction studies with NMP**, an excipient in XR-BUP, preimplantation losses, delayed ossification, reduced fetal weight, developmental delays and reduced cognitive function were reported at doses equivalent to the doses of NMP via XR-BUP. In animal reproduction studies with XR-BUP, XR-BUP administered subcutaneously to pregnant rats and rabbits during the period of organogenesis at a buprenorphine dose equivalent to 38 and 15 times, respectively, the maximum recommended human dose (MRHD) of 300 mg caused embryolethality, which appeared to be attributable primarily to the XR-BUP vehicle. In addition, reduced fetal body weights, increased visceral malformations and skeletal malformations were observed in rats and rabbits at a buprenorphine dose equivalent to 38 and 15 times, respectively, the MRHD. **Based on animal data, advise pregnant women of the potential risk to a fetus.**

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Back to the Patient Case

- **Substance Use:**
  - Multiple drug rehab stays for opioid use in the past but does not want to go to a homeless shelter or be on the streets, and previously attempted suicide by using 5 bags of fentanyl (3 bags IV and 2 bags IN), 10mg clonazepam, and causing physical injury to self.
- **Treatment:**
  - Prior to the pandemic, had been on buprenorphine 8/2mg BID-TID with continued drug use (would hold his buprenorphine when he uses to try to feel the effects of heroin/fentanyl)
  - Multiple rehab stays in various places and getting care from the CARE Center
  - Has had many issues with being denied treatment for various reasons
    - Positive UDS
    - Health coverage
- **Social history:**
  - No relationship with his parents although talks to his mother but he and his father do not talk
- **Urine Drug Screens:**
  - 7/23: +methadone, +fentanyl, +lorazepam (+BUP screen, -BUP and -NORBUP on confirmation)
  - 9/27: (mouth swab): +cocaine, +fentanyl, -BUP
  - 10/28: +BUP, +NORBUP
  - 2/8: +BUP, +NORBUP
  - 4/7: +BUP, +NORBUP
  - 5/5: +BUP, +NORBUP

Back to the Patient Case

- **Present Medications:**
  - Buprenorphine 8/2mg films – 1 film TID → XR-Bup 300mg monthly (first dose 10 months ago without cravings) with some anxiety of it wearing off so also given buprenorphine 8/2mg films 1 film daily PRN
  - Venlafaxine ER 187.5mg daily
  - Pregabalin 150mg BID
  - Quetiapine 50mg daily in AM, PM, and 100mg at bedtime
  - Melatonin 5mg daily
  - Gabapentin 800mg TID
  - Prazosin 1mg QHS
  - Pantoprazole 40mg daily

- **XR-Bup History:**
  - 8/2, 9/3, 9/30, 11/9, 12/7, 2/8 (feeling great and said “that’s what being drug-free will do to you” and actively participating in groups), 3/10 (still drug free), 4/7 (still drug free), 5/5 (127 days drug-free – stopped taking buprenorphine films as no longer having cravings although anxiety not well controlled)

Patient Story

- Started getting SL buprenorphine and was taking it inconsistently. The patient kept "relapsing" and **his lifestyle was erratic** – going into addiction in a vicious cycle.
  - He was **taking SL buprenorphine for a few days, stopping it, and going back to "heroin" use**. He did not take the heroin on top of the buprenorphine because he wanted the full effect of it.
  - Furthermore, he was taking the SL buprenorphine when he was unable to get "heroin" (no money). He is on SSI and he tried to manage that throughout the month when he was using. **When he had the money, he would use the heroin, and when he ran out of money, he would go back to taking SL buprenorphine.**
- It **wasn't until he go this XR-BUP that he began his path into recovery where he is now drug-free/sober** and living in a shelter facility, doing well other than persistent depression/anxiety.
  - No longer presenting to the hospital for suicidal ideations.
  - He decided to take XR-BUP because he was done with the vicious cycle above with the addiction and was committed to sobriety.
- Taking monthly XR-BUP 300mg

Patient Story

- Get a stable place so he could help other people with addiction, which has taken his whole life for 36 years
  - Focus on self?
- Get a job – he enjoyed working with animals as a manager of a doggie daycare and finds it therapeutic. Wants to get his life together before going back

Summary

- Real-world experiences with XR-BUP differ from those identified in the clinical trial setting
- XR-BUP is a great option for many patients, likely even for those who may not be stable on sublingual buprenorphine
  - Few contraindications
- XR-BUP may have a greater role in the age of highly potent synthetic opioids

Thank you!
Questions & Discussion