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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

EXTENDED-RELEASE BUPRENORPHINE

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project ECHO

SPEAKER DISCLOSURES

- ✓ No conflicts of interest

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Extended-Release Buprenorphine

- Thanks to Jamie Darnton and his NWAETC talk!

- References:

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  - Ling W, et al. J Addict Med. Nov/Dec 2019;13(6):442-449.
  - Lofwall MR et al. JAMA Intern Med. 2018 Jun 1;178(6):764-773.
  - Alyssa M, et al. J Subst Abuse Treat. 2021 Jul;126:108316.
  - Lintzeris N, et al. JAMA Netw Open. 2021 May 3;4(5):e219041.
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Case

- 49 year old with opioid use disorder on buprenorphine SL
  - Has remained engaged in treatment for 3 months
  - Struggled with buprenorphine adherence, intermittent use of fentanyl, and methamphetamine use
  - Most but not all his urine toxicology tests have had buprenorphine present – reported his medication was stolen
  - Due to this instability, he has continued to have weekly buprenorphine dispensing and he sometimes misses appointments and request refills the next day
- Could he benefit from extended-release buprenorphine?

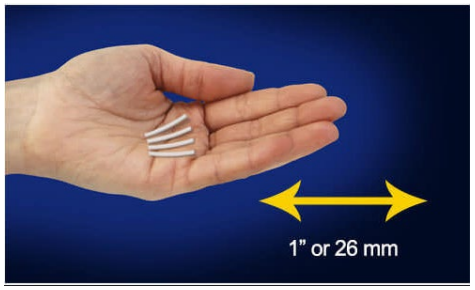
Background

- Buprenorphine is a partial opioid agonist with high receptor affinity that is effective for OUD treatment
- Limitations of SL buprenorphine/naloxone:
  - Treatment retention ~50% over 6-12 months
  - Requires daily medication adherence
  - Adherence interruptions are dangerous (e.g. jail)
  - Diversion concerns impede access, especially for polysubstance users
- Extended-release formulations may have advantages

Extended-Release Buprenorphine Products

Sublocade: FDA approved 2017

Brixadi: Not commercially available



Probuphine: Low uptake
Sales discontinued in 2020

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Potential Populations

- Adherence challenges (e.g. taste, sharing, using)
- Visit adherence challenges
- Difficulty safely storing buprenorphine
- Provider concerns about monitoring or diversion
- Leaving incarceration – pilot trial just published
- Initiating in the ED – trial ongoing

Sublocade®

- Monthly SQ injection turns solid, RN can administer
- Trial started with at least 1 week of BUP-SL
- Two doses: 300mg (1.5ml) and 100mg (0.5ml)
- FDA label: 300mg Q month x 2, then 100mg Q month
- SQ injection to abdomen only, can be painful
  - Pre-medicate with lidocaine or ice
- Secure storage required – IV use can cause thromboembolic events

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Risk Evaluation and Mitigation Strategy (REMS)

- FDA requirements to assure medication safety
- Restricts distribution to avoid IV misuse
- Sublocade cannot be dispensed directly to a patient
- Two options for providers to obtain Sublocade:
  - Through a certified pharmacy for a named patient
  - Have your organization become a certified distributor
- Certified distributors must assure that REMS requirements are followed (training, protocols)
- Other local pharmacy policies can complicate access

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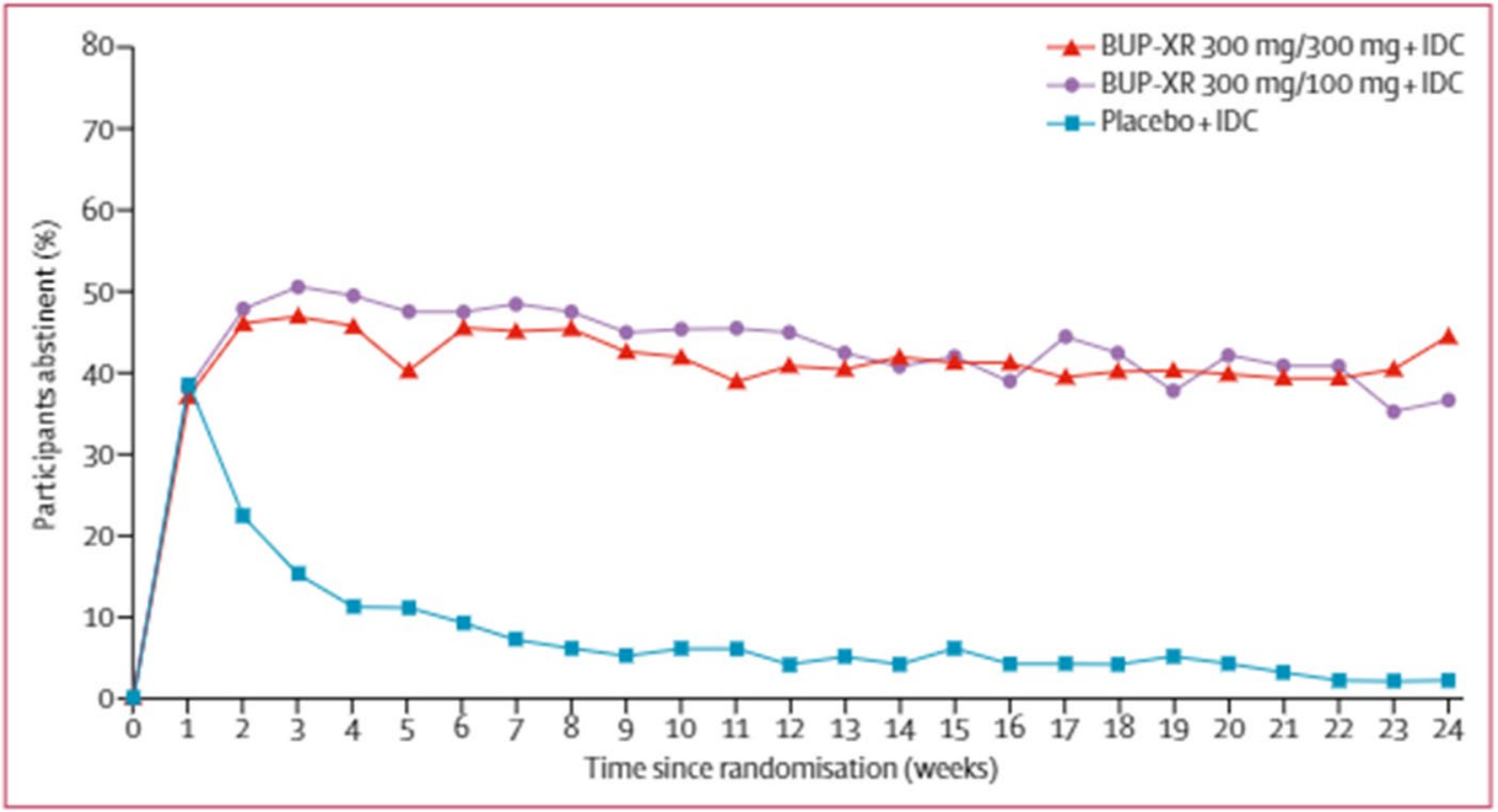
Evidence of Efficacy

Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

*Barbara R Haight, Susan M Learned, Celine M Laffont, Paul J Fudala, Yue Zhao, Amanda S Garofalo, Mark K Greenwald, Vijay R Nadipelli, Walter Ling, Christian Heidbreder, for the RB-US-13-0001 Study Investigators**

- 504 adults with moderate-severe OUD randomized to:
  - BUP-XR 300mg monthly
  - BUP-XR 300mg X 2 months, then 100mg monthly
  - Placebo injections
- Primary outcome: % weekly UDT/self-report negative for opioids
- Everyone received individual drug counseling

Results



Safety

	BUP-XR 300/300 mg plus individual drug counselling (n=201) (n=201)	BUP-XR 300/100 mg plus individual drug counselling (n=203) (n=203)	Placebo plus individual drug counselling (n=100)
Any treatment-emergent adverse event	134 (67%)	155 (76%)	56 (56%)
Any serious treatment-emergent adverse event	7 (3%)	4 (2%)	5 (5%)
Any severe treatment-emergent adverse event	13 (6%)	15 (7%)	4 (4%)
Any treatment-emergent adverse event leading to discontinuation	10 (5%)	7 (3%)	2 (2%)
Any treatment-emergent adverse event leading to death	1 (<1%)	0	0
Treatment-emergent adverse events, by preferred term*			
Headache	17 (8%)	19 (9%)	6 (6%)
Constipation	16 (8%)	19 (9%)	0
Nausea	16 (8%)	18 (9%)	5 (5%)
Injection-site pruritus	19 (9%)	13 (6%)	4 (4%)
Vomiting	11 (5%)	19 (9%)	4 (4%)
Insomnia	17 (8%)	13 (6%)	11 (11%)
Upper respiratory tract infection	12 (6%)	15 (7%)	1 (1%)
Injection-site pain	12 (6%)	10 (5%)	3 (3%)
Nasopharyngitis	10 (5%)	11 (5%)	1 (1%)
Fatigue	12 (6%)	8 (4%)	3 (3%)
Anxiety	8 (4%)	10 (5%)	5 (5%)
Drug withdrawal syndrome	7 (3%)	9 (4%)	6 (6%)
Blood creatine phosphokinase increase	5 (2%)	11 (5%)	1 (1%)
Diarrhoea	5 (2%)	5 (2%)	5 (5%)

*Reported in at least 5% of participants in any treatment group during the double-blind phase.

Table 4: **Treatment-emergent adverse events (safety analysis set)**

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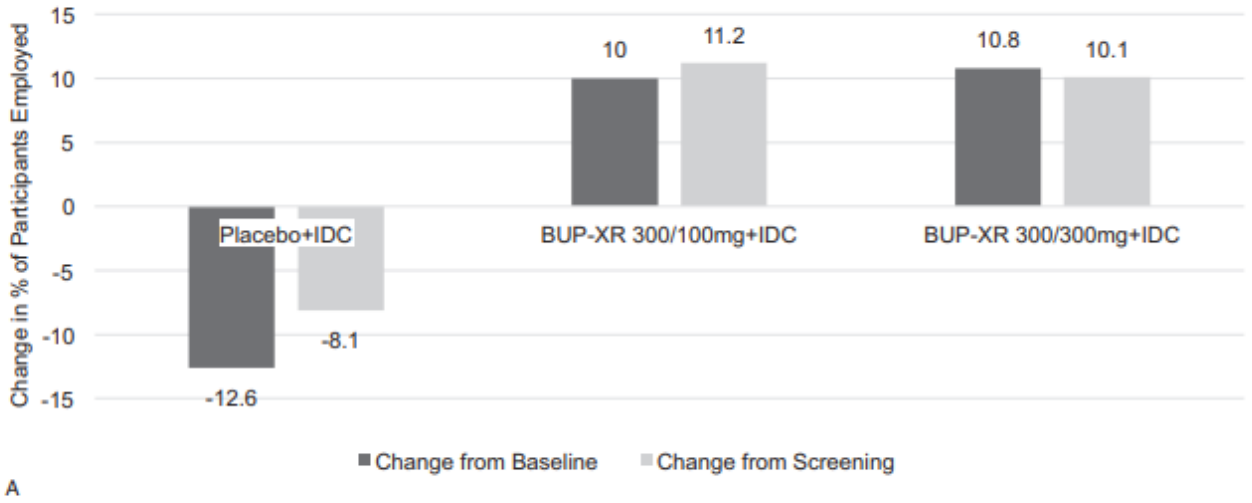
Trial Summary

- XR-BUP in two dosing schemes showed improved retention and abstinence vs placebo
- Not powered to detect difference between dosing regimens
- Safety similar to BUP-SL except for injection site reactions
- All aspects of the study were influenced by Indivior
- The comparison is to PLACEBO, not BUP-SL

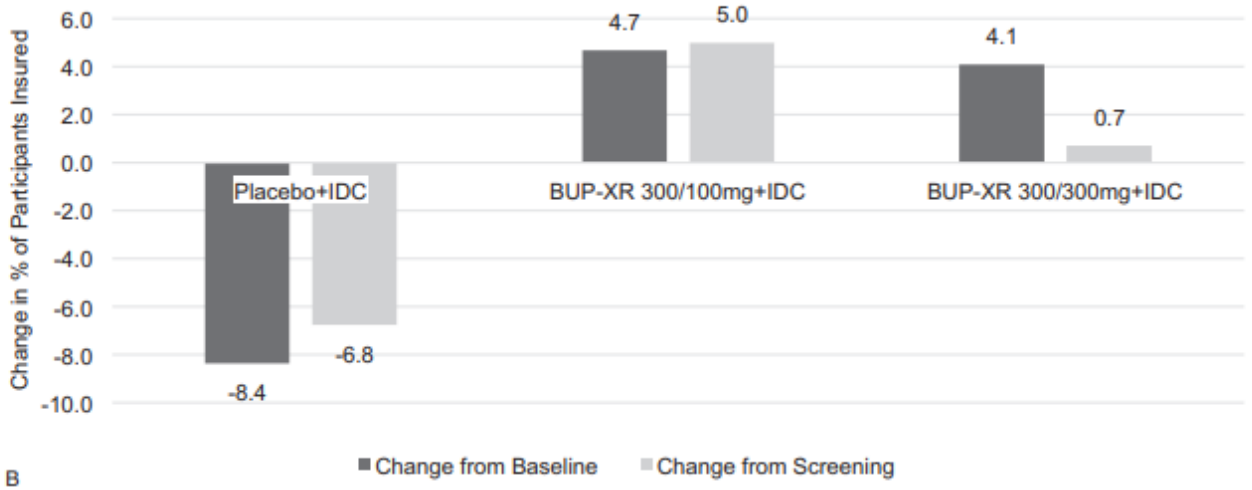
Additional Findings

% Employed



A

% Insured



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Brixadi® – Another BUP-XR Product

- Not currently FDA approved due to licensing issues
  - December 2021 FDA Response Letter cited only manufacturing issues
- Weekly and monthly doses tested
- Double dummy RTC showed Brixadi in 428 adults with OUD was non-inferior to BUP-SL for treatment retention and superior for opioid use
- Another RTC demonstrated improved patient-centered outcomes with weekly/monthly Brixadi vs BUP-SL dispensed at least weekly

Observational Study of BUP-XR in Practice

- 40 patients at MGH Bridge Clinic (78% unhoused)
- 27 retained on BUP-XR, 12 stopped (most commonly due to preference for BUP-SL), 1 LTFU
- 12 remained on 300mg BUP-XR monthly
- 22 used BUP-SL (4-24mg) after starting BUP-XR
- 12 started BUP-XR < 7days after starting BUP-SL
- Illicit opioid negative UDT 65%
- No precipitated withdrawal or overdoses

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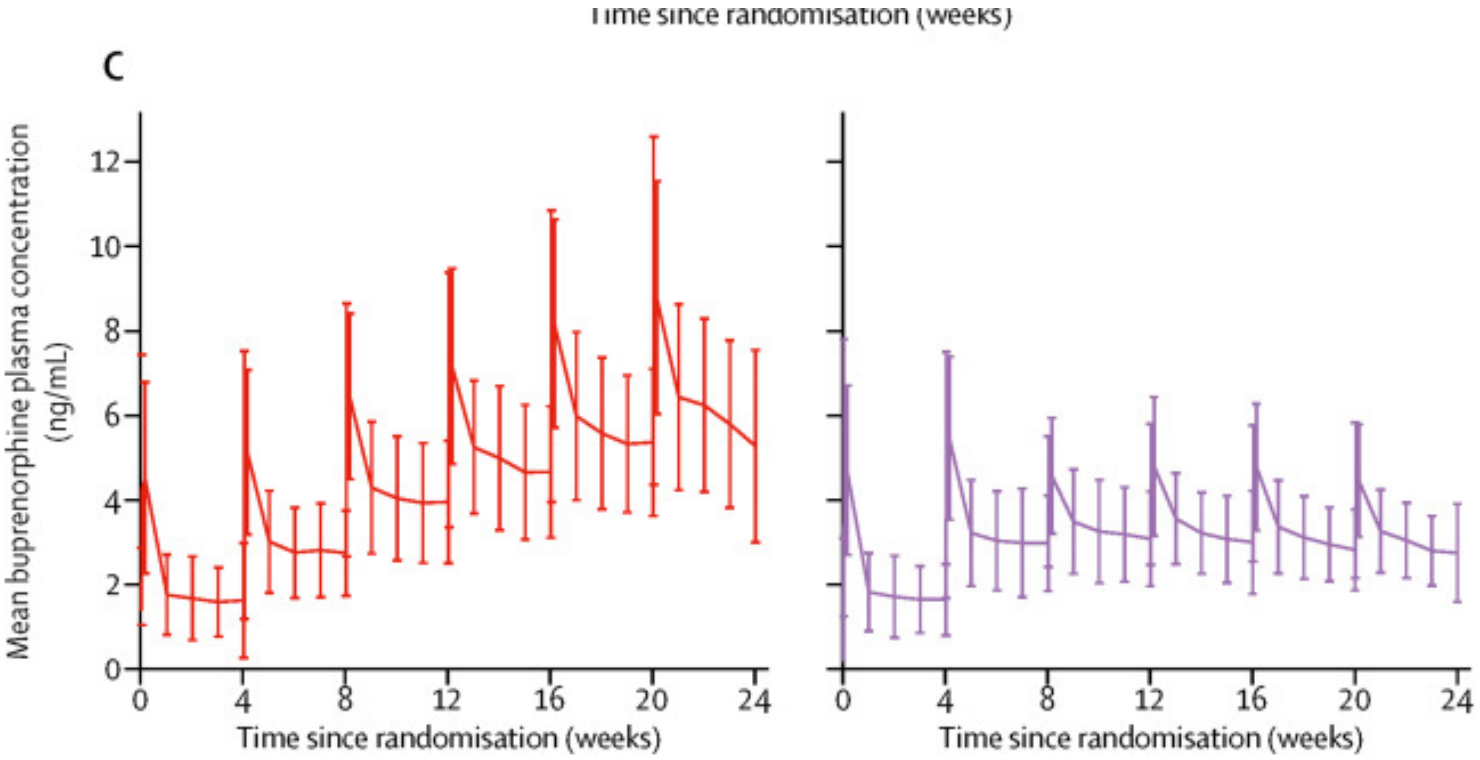
Pilot Trial at Time of Release from Jail

- Open-label randomized comparative effectiveness pilot trial (N=52) of BUP-XR vs BUP-SL at jail release
- Primary outcome was retention 8 weeks after release
- BUP-XR group had fewer jail medical visits
- Community treatment retention at 8 weeks was 69% for BUP-XR and 35% for BUP-SL
- Opioid negative urine tests were 55% for BUP-XR and 38% for BUP-SL

Serum Levels and Dosing

- Steady-state achieved in 2 months for 100mg group
- Steady-state achieved in 6 months for 300mg group



Dosing Considerations

- For folks who continue to use extra-medical opioids or experience cravings after their second injection of 300mg, it is reasonable to consider staying at 300mg
- For folks who experience increased instability or craving after reduction to 100mg, it is reasonable to consider increasing back to 300mg
- Supplemental SL dosing may be necessary for some patients who continue to experience craving or withdrawal after their first few injections

Troubleshooting

- In general, if a patient is late for an injection, they can be administered the dose within 2 weeks without compromising treatment or risking precipitated withdrawal
- Patients may test positive for buprenorphine months after last injection

Summary

- Injectable buprenorphine-XR may be a good option for patients with concerns around diversion, regular adherence, or regular attendance
- Favorable safety profile with adverse events similar to BUP-SL plus generally mild injection site reactions
- Few direct comparisons to buprenorphine-SL for the available formulation
- Some patients may need supplemental SL dosing
- Some may need to remain at 300mg monthly

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Discussion

- Is anyone using Sublocade?
- What are the barriers?
  - Outpatient
  - Inpatient
- Can we start BUP-XR without BUP-SL first?

Thank You!

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