Utilizing Low-threshold XRBUP to Address Stimulant-Fentanyl Overdose Risk in Rural Alaska

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ASAM 2023 Annual Conference

Disclosure Information

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April 2023 ASAM conference, DC

Sarah Spencer DO, FASAM

I have no financial conflicts of interest to disclose

I am currently employed by the Ninilchik Traditional Council

I work as an addiction treatment consultant for non-profit agencies including the Opioid Response Network and the Alaska Native Tribal Health Consortium

I am the volunteer medical director of Alaska's first rural SAP in Homer

Land Acknowledgment

I live and work on the ancestral lands of the Ninilchik tribe on the rural southern Kenai Peninsula. While stigma has prevented other tribes and clinics from offering MOUD to their patients, the Ninilchik traditional council has been instrumental in expanding access to addiction care and harm reduction services to all the tribes on the Kenai peninsula and to the general community.

Chin'an gheli (Thank You) to the Ninilchik Tribal Council.

https://www.ninilchiktribe-nsn.gov/about-the-tribe/#history

Learning Objectives

- Examine the epidemiology of comorbid stimulant and opioid use disorders and related overdose risk, especially in NA/AI populations, and explore barriers patients with severe SUDs face in accessing MOUD and harm reduction services in rural areas
- Summarize the pharmacology of XRBUP and its utility in increasing access to care and reducing risk of fentanyl induced respiratory depression and explore off-label, harm-reduction based approaches to utilizing XRBUP
- Understand the components of low-threshold care and how it can reduce barriers to access and increase treatment retention for patients with co-morbid stimulant and opioid use disorders
- Review case presentations to improve clinical skills in triaging and problem-solving complex patient presentations when treating co-morbid stimulant and opioid use disorders

Abbreviations

- OBOT: Office Based Opioid Treatment
- OTP: Opioid Treatment Program (methadone clinic)
- MOUD: medication for opioid use disorder
- SLBUP: sublingual buprenorphine
- XRBUP: monthly injectable extended-release buprenorphine
- CHAP: Community Health Aide Practitioner
- OD: Overdose
- WD: Withdrawal
- PW: Precipitated withdrawal

Over 200 Alaska Native tribes/villages

Spread over 660,000 mi²

Most off the road system

550 Community Health Aides/Practitioners (CHAPs) in 170 tribal clinics

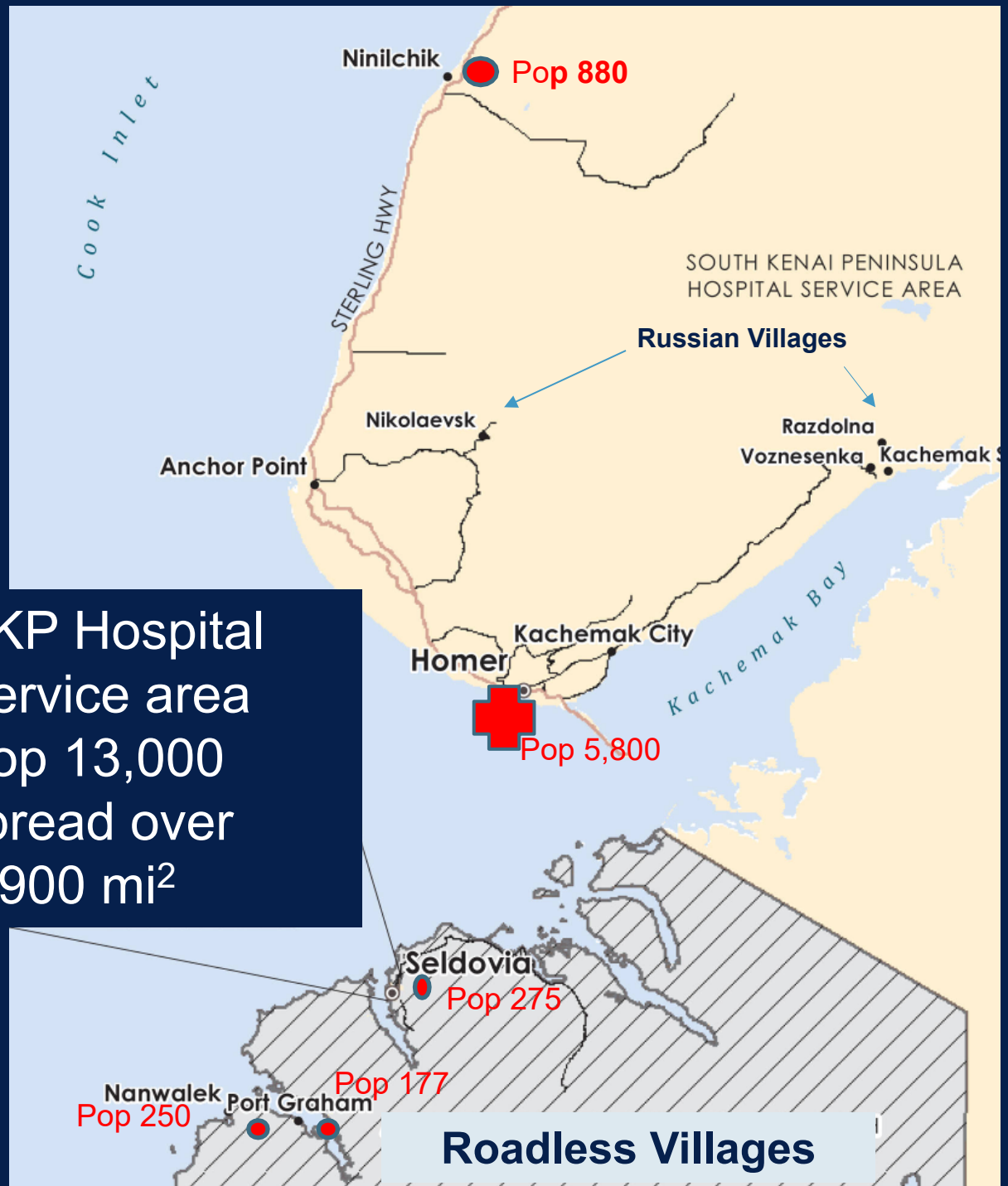
- Currently MOUD offered by 2/3 of the regional healthcare hubs

Southern Kenai Peninsula of Alaska

Tribal Entities

- Ninilchik Traditional Council
- Seldovia Village Tribe
- Chugachmiut

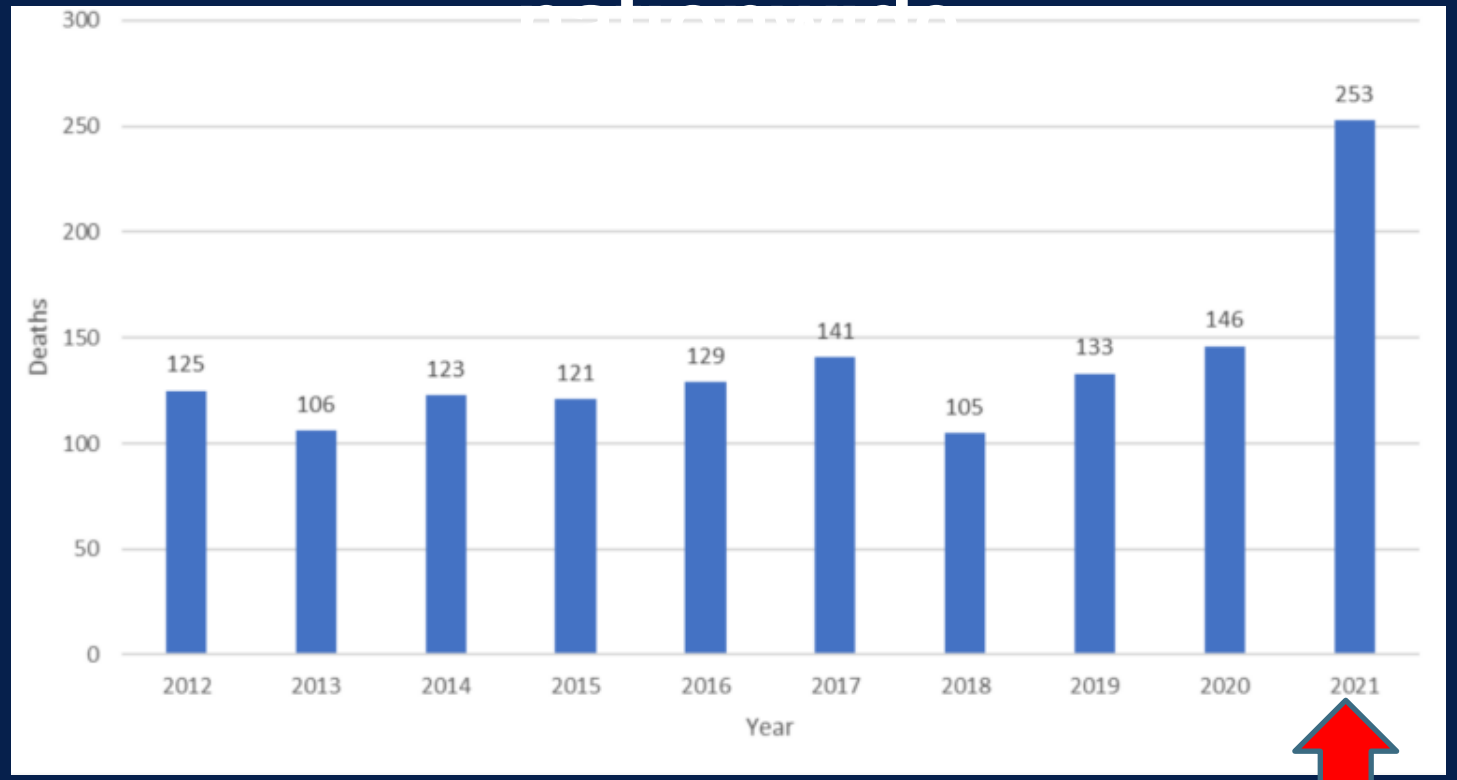
- About 20% AK Native
- 200 miles from nearest OTP
- 1 addiction med specialist



Barriers to MOUD Access in Rural AK

- Travel/Transportation/Gas
- Weather Holds/ Rx delayed in the Mail
- No local licensed medical providers (only CHAPS)
- No local pharmacies
- **STIGMA**

Overdose deaths in Alaska rose by 75% in 2021, highest increase



- Alaskan Natives
OD rate 77/110K

- White
OD rate 28/100K

- Meth OD up 150%

- Fentanyl OD up 150%

https://health.alaska.gov/dph/VitalStats/Documents/PDFs/DrugOverdoseMortalityUpdate_2021.pdf

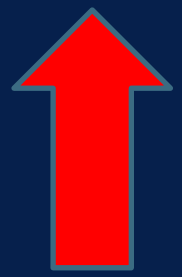
DEA Laboratory Testing Reveals that 6 out of 10 Fentanyl-Laced Fake Prescription Pills Now Contain a Potentially Lethal Dose of Fentanyl

DEA illustration of 2 mg of fentanyl, a potentially lethal dose

https://www.dea.gov/alert/dea-laboratory-testing-reveals-6-out-10-fentanyl-laced-fake-prescription-pills-now-contain

Use of stimulants with opioids has been increasing nationwide

Past month methamphetamine use by people who use heroin

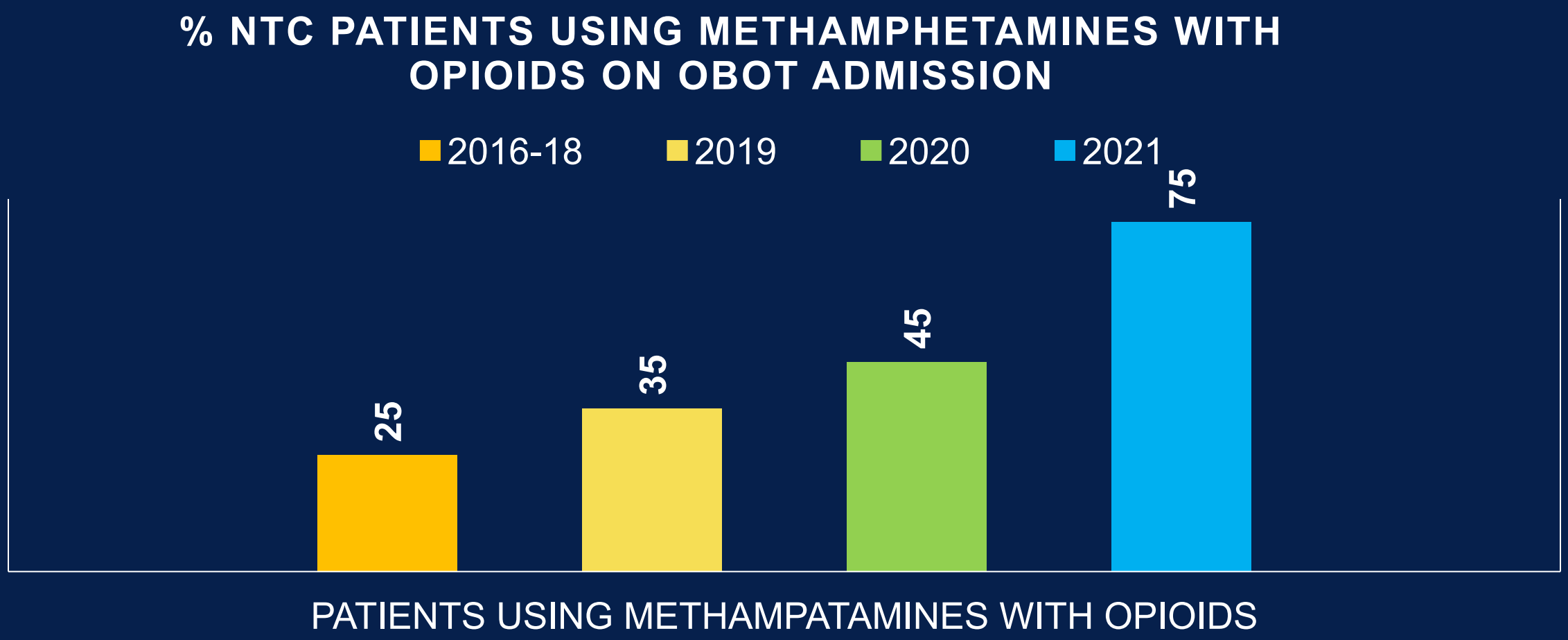


9.0% to 44.0%

from 2015-2019

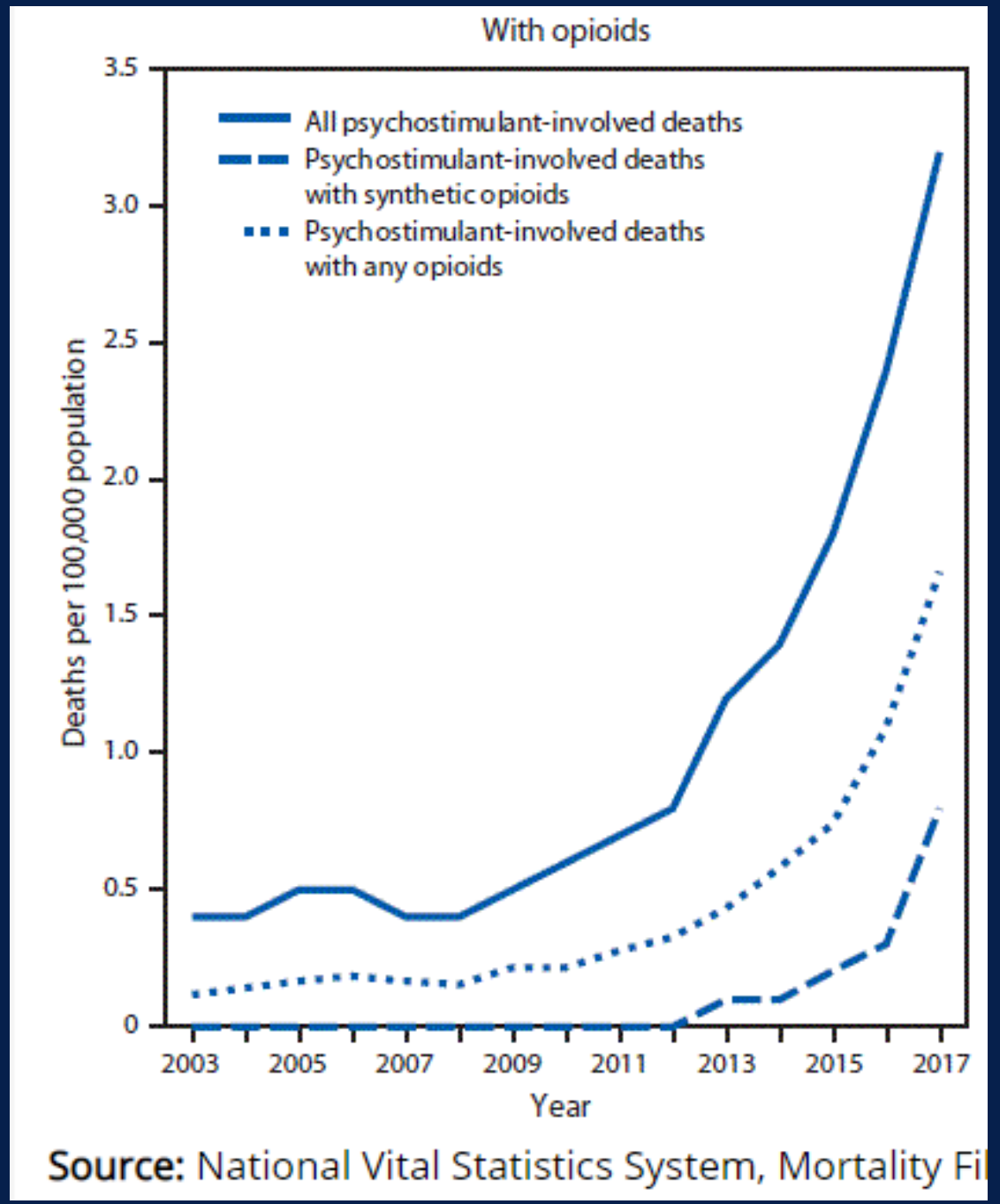
Strickland et al, The continued rise of methamphetamine use among people who use heroin in the United States. Drug Alcohol Depend. 2021

NTC Community Clinic



Roughly ½ of methamphetamine overdoses involve fentanyl

Injecting meth with opioids "goof-balling" is more likely to result in overdose than injecting opioids alone



August 15, 2022

Association of Methamphetamine and Opioid Use With Nonfatal Overdose in Rural Communities

P. Todd Korthuis, MD, MPH[1,2]; Ryan R. Cook, PhD, MSPH[1]; Canyon A. Foot, BA[1]; et al

» Author Affiliations | Article Information

JAMA Netw Open. 2022;5(8):e2226544. doi:10.1001/jamanetworkopen.2022.26544

Findings In this cross-sectional, multistate study of rural communities, 79% of people using drugs reported past-30-day methamphetamine use; nonfatal overdose was greatest in people using both methamphetamine and opioids (22%) vs opioids alone (14%), or methamphetamine alone (6%). People using both substances reported the least access to treatment; only 17% of those using methamphetamine alone had naloxone.

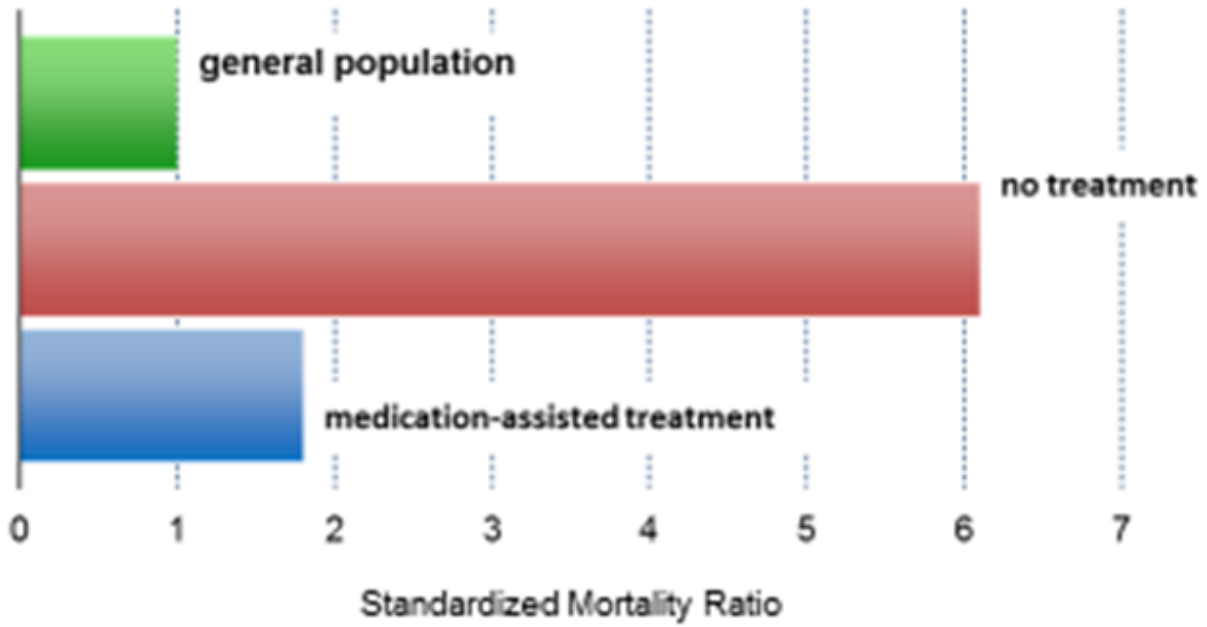
Why do people use stimulants with opioids?

- To prolong the effects of fentanyl
- To counteract the negative effects of opioids (reduce the chance of “nodding out”)
- To foster energy and enhance euphoria

https://www.sciencedirect.com/science/article/abs/pii/S0955395922002079

Benefits of MAT: Decreased Mortality

Overdose risk the first 2 weeks after leaving treatment rises dramatically



MOUD can reduce death rates by 80%

Dupou
Evans
Sordo

PCSS Providers Clinical Support System

Krawczyk N, Mojtabai R, Stuart EA, et al. Opioid agonist treatment and fatal overdose risk in a state-wide US population receiving opioid use disorder services. Addiction. 2020;115:1683–1694.

Retention in MOUD treatment and methamphetamine use

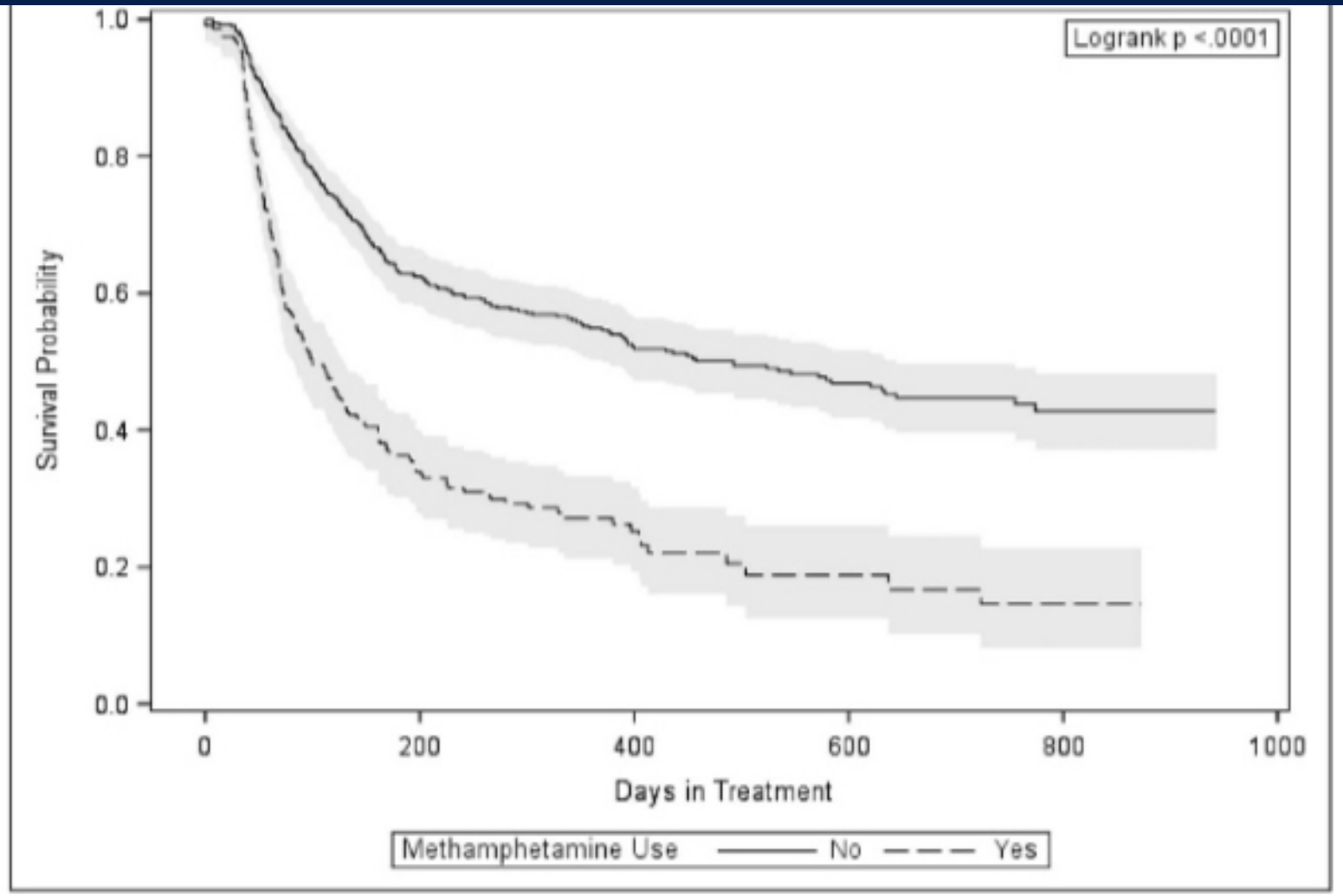


Fig. 1. Kaplan-Meier survival curves for methamphetamine users and non-users with 95% confidence bands (n = 770).

People who use methamphetamine may have poorer retention in MOUD programs

But those who stay in treatment may reduce their use

https://www.journalofsubstanceabusetreatment.com/article/S0740-5472(19)30250-8/fulltext

The impact of methamphetamine/amphetamine use on receipt and outcomes of medications for opioid use disorder: a systematic review

Madeline C. Frost *Addiction Science & Clinical Practice* Oct 2021 https://ascpjournal.biomedcentral.com/articles/10.1186/s13722-021-00266-2

Results

Methamphetamine/amphetamine use or use disorder was negatively associated with receiving methadone and buprenorphine... Overall, existing research suggests people who use methamphetamine/amphetamines may have lower receipt of MOUD, retention in MOUD, and opioid abstinence during MOUD. Future research should examine how specific policies and treatment models impact MOUD outcomes for these patients and seek to understand the perspectives of MOUD providers and people who use both opioids and methamphetamine/amphetamines. Efforts to improve MOUD care and overdose prevention strategies are needed for this population.

Low Threshold Care

A potential strategy to retain people who use stimulants with fentanyl in MOUD treatment

Predictors of engagement and retention in care at a low-threshold substance use disorder bridge clinic https://doi.org/10.1016/j.jsat.2022.108848 , Patient experiences with a transitional, low-threshold clinic for the treatment of substance use disorder: A qualitative study of a bridge clinic https://doi.org/10.1016/j.jsat.2019.09.003

“Low-threshold treatment”

An alternative approach that attempts to remove as many barriers to treatment as possible.

1) Same-day treatment entry
2) Harm reduction approach
3) Flexibility
4) Wide availability in places where people with opioid use disorder go

Jakubowski A, Fox A. Defining Low-threshold Buprenorphine Treatment. JAddict Med. 2020 Mar/Apr;14(2):95-98. doi: 10.1097/ADM.0000000000000555. PMID: 31567596; PMCID: PMC7075734.

Harm Reduction Based Low Threshold Care
(Our clinic's approach)

- Don't discharge patients for ongoing drug use
- Create patient centered care plans
- Flexible walk-in/same day/tele-med appointments
- Co-located/tele-behavioral health/digital apps
- Motivational interviewing
- Peer support (via text)
- Treatment of co-morbid medical/MH issues
- Contingency Management

Harm Reduction Based Low Threshold Care (continued)

- Assistance with transportation
- Assistance with filling out applications for treatment or social services
- Contraception
- Rapid Hep C/HIV testing
- Hep C treatment/ PREP for active users
- Naloxone kits
- Injection and smoking supplies
- Fentanyl test strips

Advantages of XRBUP In Remote Native Alaskan Villages

No concern for diversion

Diversion concerns and stigma around SLBUP can be a barrier. It's difficult to monitor medication compliance in remote locations, and it's difficult to arrange medication counts and drug testing

Reduces risk of withdrawal and relapse related to Rx interruption

Mail delivery in the bush frequently interrupted due to weather holds and logistics (reduced flights during COVID) that can result in delayed Rx refills→ acute withdrawal → relapse → overdose

Flexible dosing q4-6 weeks, slow reduction in levels reduces w/d sxs

Excellent and long-lasting opioid blockade

Reduces overdose risk for patients with extended lack of medication access (fishermen, oil field workers, incarcerated)

Mainstreaming Addiction Treatment (MAT) Act
Alaska specific changes

- Allows for telemedicine starts of buprenorphine without in person visit if patient is located at a village clinic staffed only by a Community Health Aid Practitioner (CHAP)

- Allows CHAPS to administer and dispense buprenorphine per order of remote prescriber

https://www.congress.gov/bill/117th-congress/senate-bill/445/text

Mainstreaming Addiction Treatment (MAT) Act
Alaska specific changes

- Allows for telemedi… …prenorphine without in person visit if pati… …cated a… …illage clinic staffed only by a Community …alth… …Practi… …er (CHAP)

- Allows CHAPS to …minister… …pense buprenorphine per order of remote… …rib…

Not included in Omnibus Bill!!

https://www.congress.gov/bill/117th-congress/senate-bill/445/text

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- **And, still cannot ship XRUP to the village clinic if there is no DEA licensed prescriber registered there…**

Not included in Omnibus Bill!!

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- Allows CHAPS to …minister… …pense buprenorphine per order of remote …rib…

- **And, still cannot ship XRUP to the village clinic if there is no DEA licensed prescriber registered there… And rural native run clinics cannot bill Medicaid for medication (no buy&bill)!**

Not included in Omnibus Bill!!

https://www.congress.gov/bill/117th-congress/senate-bill/445/text

XRBUP Patient Selection

- Useful for patients who have difficulty with medication continuity, who have fallen out of care multiple times
- Patients who cannot reliably attend scheduled appointments or have difficulty filling frequent prescriptions due to transportation (no vehicle or license), location (lives off road system) or employment barriers (slope workers, commercial fishermen) or at risk for med interruption (incarceration, moves, loss of insurance)
- Patients who do better on high dose buprenorphine (still struggle with cravings at 24mg/day)

XRBUP Patient Selection (Continued)

- Patients who don't tolerate SLBUP due to nausea
- Patients who have difficulty securing their medication
- Patients actively using other non-RX substances (stimulants/benzo/ETOH) or otherwise high overdose risk
- Patients who are at high diversion risk, patients who have sold their buprenorphine in the past

J Subst Abuse Treat. 2020 Mar;110:1-8. doi: 10.1016/j.jsat.2019.11.004. Epub 2019 Nov 15.

Effects of monthly buprenorphine extended-release injections on patient-centered outcomes: A long-term study

Walter Ling [1], Vijay R Nadipelli [2], Caitlyn T Solem [3], Naoko A Ronquest [2], Yu-Chen Yeh [4],

Results: Statistically significant improvements from baseline to end of study were noted for the SF-36v2 mental component summary score. Significant improvements ($P < .05$ for all comparisons) on the ASI-Lite were seen for all problem areas except alcohol use from baseline to end of study. Employment rate increased 7% whereas health insurance status remained stable from baseline to end of study.

Medication satisfaction … was >88%

Conclusions: Treatment with BUP-XR monthly injections for up to 12 months in this cohort of treatment-seeking individuals with OUD led to positive PCOs and high treatment satisfaction, which correspond to personal recovery.

"This open-label RCT showed significantly **higher global treatment satisfaction… after 24 weeks with depot buprenorphine than SL buprenorphine**. The depot buprenorphine group also showed **significant improvements in measures of treatment convenience and effectiveness, patient satisfaction, treatment burden, treatment effectiveness, quality of life**. The magnitude of the improvements in the treatment-related PROs in the depot buprenorphine group are noteworthy, as shown by the NNT of 5.1 to achieve the TSQM threshold for satisfaction of 80% or greater between the 2 groups."

Lintzeris N, Dunlop AJ, Haber PS, et al. (2021). Patient-Reported Outcomes of Treatment of Opioid Dependence With Weekly and Monthly Subcutaneous Depot vs Daily Sublingual Buprenorphine: A Randomized Clinical Trial. JAMA Netw Open. 2021;4(5):e219041

Real patient testimonials regarding XR-BUP

"It works great! Anyone that says that it doesn't is full of s#!t!"

"I love that I just feel normal every day when I wake up."

"I was glad that I didn't feel any withdrawal symptoms when I went to jail."

"I don't even think about heroin anymore."

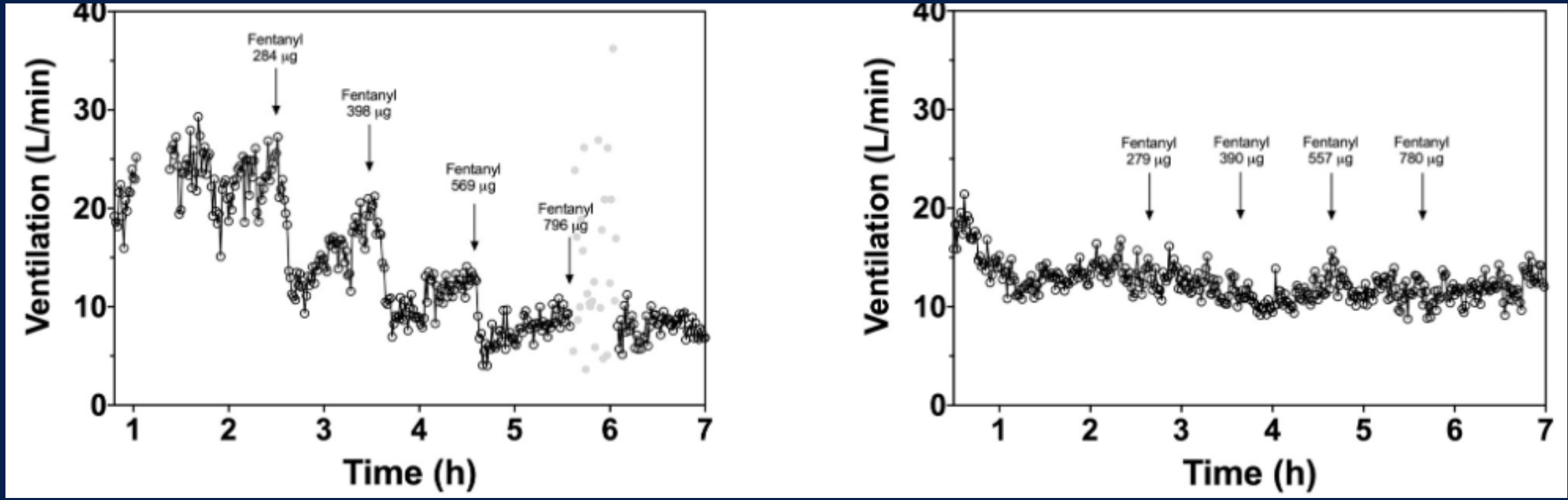
"I tried using heroin and it was totally blocked."

High Dose XRBUP blocks fentanyl induced respiratory depression

C. High-Dose Buprenorphine

S202, Placebo

S202, Buprenorphine 5ng/ml



Blockade was lost under 2 ng/ml

https://journals.plos.org/plosone/article/figure?id=10.1371/journal.pone.0256752.g004

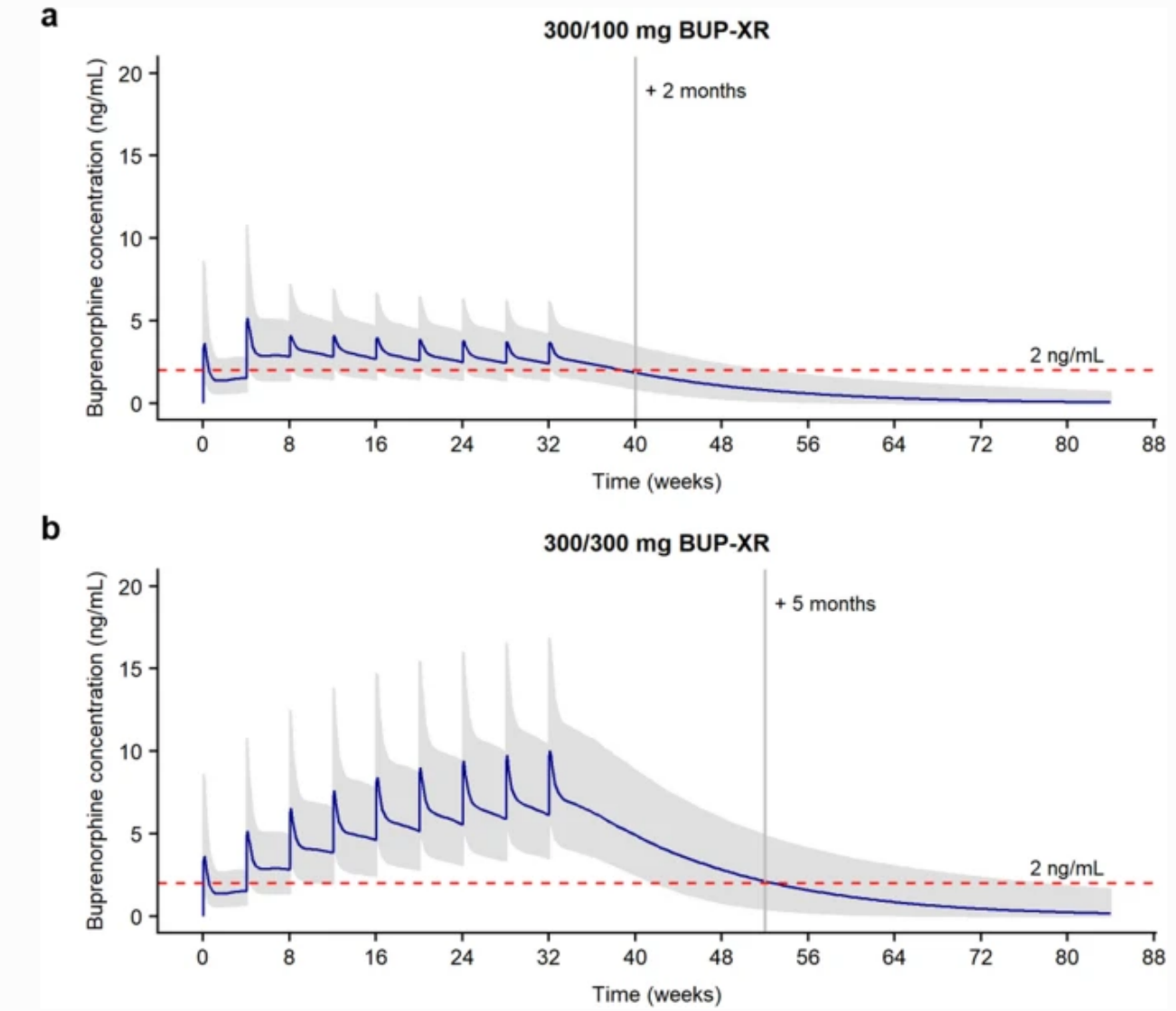
Pharmacokinetic parameters	SUBUTEX daily stabilization		SUBLOCADE		
Mean	12 mg (steady-state)	24 mg (steady-state)	300 mg# (1st injection)	100 mg* (steady-state)	300 mg* (steady-state)
$C_{avg,ss}$ (ng/mL)	1.71	2.91	2.19	3.21	6.54
$C_{max,ss}$ (ng/mL)	5.35	8.27	5.37	4.88	10.12
$C_{min,ss}$ (ng/mL)	0.81	1.54	1.25	2.48	5.01

During the first month of XRBUP, the serum drug levels drop to levels that may not be therapeutic for some patients, thus supplemental SLBUP is indicated in patients who experience craving or withdrawal in early treatment

https://www.sublocade.com/Content/pdf/prescribing-information.pdf

Extended opioid blockade after medication cessation

Fig. 6



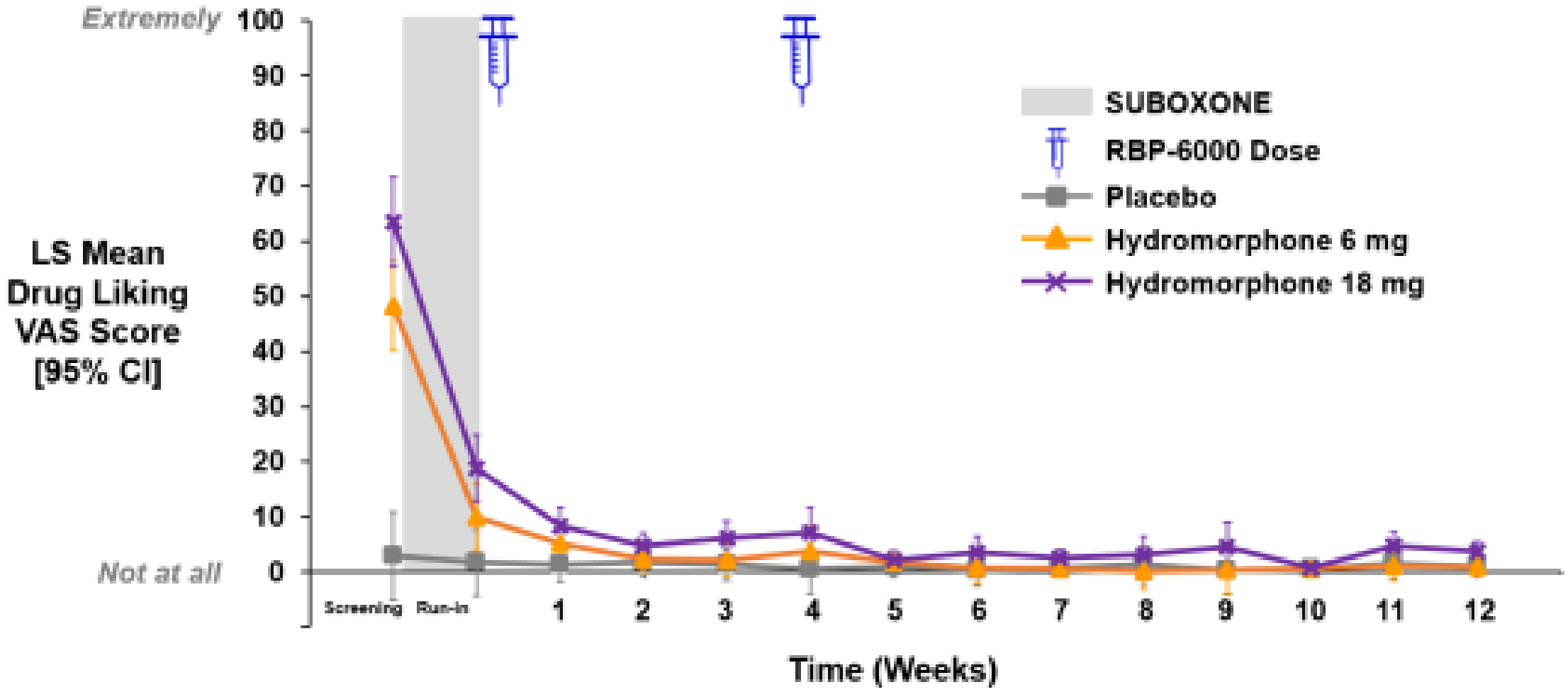
Predicted decrease in buprenorphine plasma concentrations for BUP-XR dosing regimens following treatment interruption. **a** 300/100-mg dosing regimen 2; **b** 300/300-mg dosing regimen. Blue solid lines: median of the simulated data; gray shaded areas: 90% prediction intervals of simulated data. A total 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

Patients stable on 100 mg may have blockade for 2 months (1 missed shot)

Patients stable on 300 mg may have blockade for 5 months (4 missed shots)

https://link.springer.com/article/10.1007/s40262-020-00957-0

Figure 8: Mean Drug-Liking VAS Scores from Opioid Blockade Study (Study 13-0002)



https://www.sublocade.com/Content/pdf/prescribing-information.pdf

XR-BUP may be started **sooner than 7-day stabilization period**, may be **empirically kept at 300mg monthly**, and may require **supplemental SL BUP** during early treatment months

Real-world outcomes with extended-release buprenorphine (XR-BUP) in a low threshold Bridge clinic

Alyssa M. Peckham, PharmD, BCPP
Laura G. Kehoe, MD, MPH, FASAM
Jessica R. Gray, MD
Sarah E. Wakeman, MD, FASAM

The authors have no relevant conflicts of interest or financial disclosures.

MASSACHUSETTS GENERAL HOSPITAL

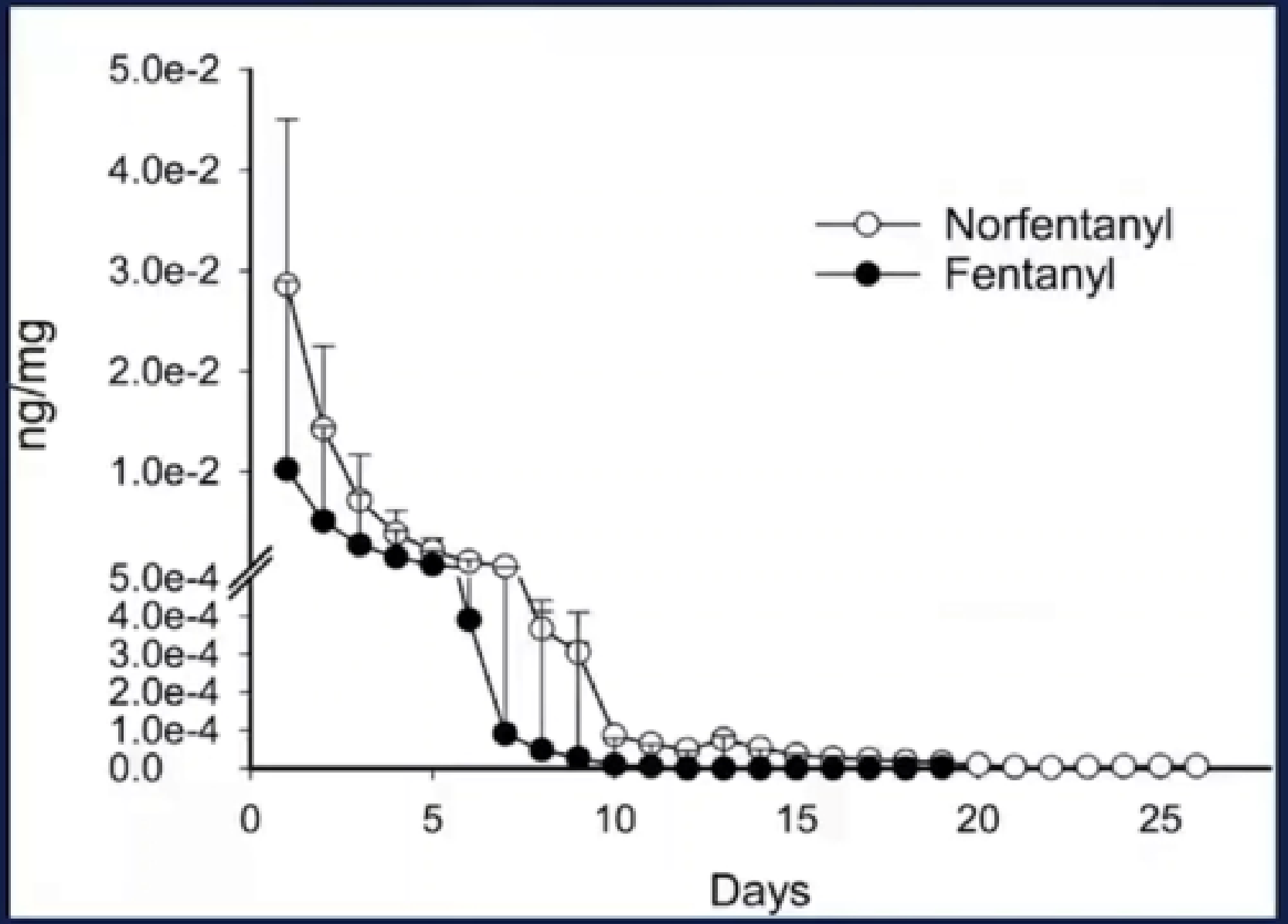
2019 ASAM poster

Low Threshold XR-BUP

- Given regardless of active drug/alcohol use
- No required drug testing
- Flexible schedule
- Walk-in appointments for injections
- Single day medication start for opioid tolerant patients
- Flexible dose
- SL supplementation available
- Available in pregnancy (2^{nd}/3^{rd} trimester)

Rapid XRBUP Initiation

FENTANYL NORFENTANYL ELIMINATION IN URINE



Huhn SA et al. Protracted renal clearance of fentanyl in persons with opioid use disorder. Drug Alcohol Depen. 2021

Int J Drug Policy. 2019 Dec;74:76-83. doi: 10.1016/j.drugpo.2019.09.003. Epub 2019 Sep 25.

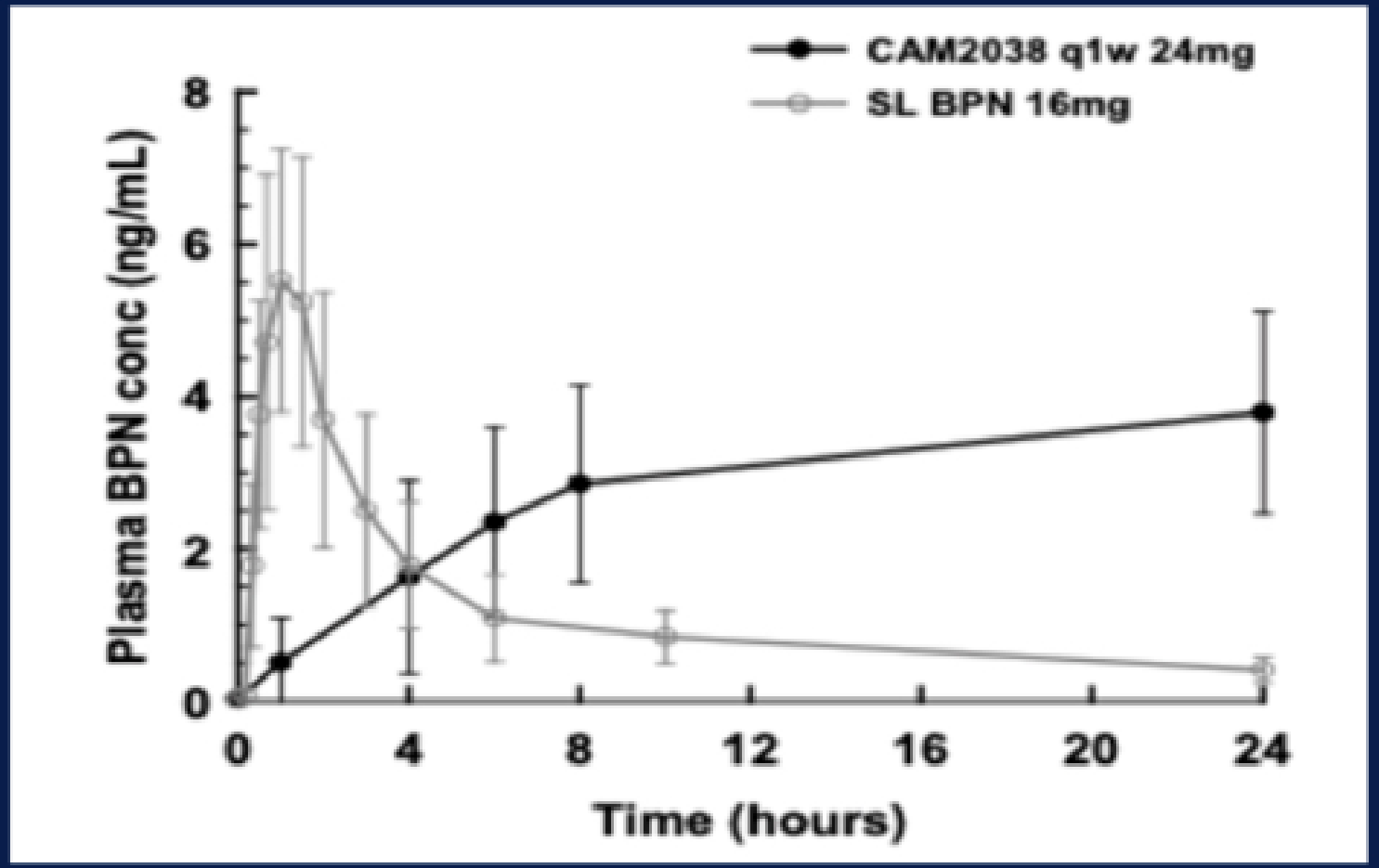
"Everything is not right anymore": Buprenorphine experiences in an era of illicit fentanyl

Sydney M Silverstein [1], Raminta Daniulaityte [2], Silvia S Martins [3], Shannon C Miller [4],

"I was almost 72 hours into withdrawal…and I took it [Suboxone] and it made me… I couldn't believe it. Cuz I don't puke or get diarrhea, I don't have that happen ever…But immediately—Bam! Not even five minutes after I took it I was dripping sweat. It felt like water had just gotten dumped all over me, I'm puking and it's coming out every end"

"You have to be clean four or five days before you can even take the Suboxone. So you're sick four or five days and it's like, it's not, no. It's like you can't do it…, I tried it a couple of times and I just couldn't do it."

ED-INitiated BupreNOrphine VAlidaTION Network Trial ED INNOVATION



Pharmacokinetics of XR- & SL- Buprenorphine

https://www.sciencedirect.com/science/article/pii/S1551714421000951

Rapid XRBUP Initiation Studies

Am J Addict. Author manuscript; available in PMC 2020 Jul 27.
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Published in final edited form as:
NIHMSID: NIHMS1611380
Am J Addict. 2020 Jul; 29(4): 345–348.
PMID: 32167629
Published online 2020 Mar 13. doi: 10.1111/ajad.13018

Case Series: Rapid Induction Onto Long Acting Buprenorphine Injection for High Potency Synthetic Opioid Users

John J. Mariani, MD,[1,2] Amy Mahony, LMHC,[1] Muhammad N. Iqbal, MD,[1] Sean X. Luo, MD,PhD,[1,2] Nasir H. Naqvi,

Open-label, rapid initiation pilot study for extended-release buprenorphine subcutaneous injection

Howard Hassman, **Stephanie Strafford** ✉, Sunita N. Shinde, Amy Heath, Brent Boyett & Robert L. Dobbins

Received 04 Apr 2022, Accepted 23 Jul 2022, Published online: 24 Aug 2022

Download citation https://doi.org/10.1080/00952990.2022.2106574 Check for updates

Contemp Clin Trials. 2021 May; 104: 106359.
PMID: 33737199
Published online 2021 Mar 16. doi: 10.1016/j.cct.2021.106359

The Design and Conduct of a Randomized Clinical Trial Comparing Emergency Department Initiation of Sublingual versus a 7-day Extended-Release Injection Formulation of Buprenorphine for Opioid Use Disorder: Project ED INNOVATION

Gail D'Onofrio, MD, MS,[1,2] Kathryn F. Hawk, MD, MHS,[1] Andrew Herring, MD,[3] Jeanmarie Perrone, MD,[4] Ethan Cowan,

XRBUP (monthly injectable extended-release buprenorphine) is indicated for the first dose to be administered to patients who have taken at least 8 mg of buprenorphine sublingual (under the tongue) for the last 7 days.

A traditional weeklong start is recommended in patients who have time to wait for their injection and the ability to follow up for an injection appointment. It is also highly recommended for patients who have not been using much or any opioids recently (low tolerance) or have not tried high-dose buprenorphine before.

Benefits of a traditional 1-week start:

- Your body has time to adjust to buprenorphine and to gradually increase the dose
- May reduce side effects such as nausea and sleepiness
- May reduce chance of shot causing withdrawal symptoms
- You can make sure you like buprenorphine if you haven't taken it before

Risks of traditional 1-week start:

- You may have difficulty sticking to the schedule of taking your meds everyday or trouble keeping your follow up appointment and risk missing your shot administration. Stopping buprenorphine can cause withdrawal symptoms, return to opioid use and increased risk of overdose
- Daily sublingual buprenorphine might not control withdrawal symptoms

A rapid start of XRBUP (off-label start) is when a patient has taken buprenorphine for only 1-2 days, or not at all, before the first injection of XRBUP is given. The injection should be given no sooner than 12 hours after last opioid use, and longer if you have been using methadone. Because the buprenorphine from the injection takes time to be absorbed into your system and takes 24 hours to reach peak levels, precipitated withdrawal might be less likely to occur with XRBUP administration than sublingual buprenorphine administration. A rapid start is recommended for patients who have tried a traditional 1 week start and have not been able to follow through, patients who are unable to return for a follow up appointment in the next few weeks and are at high risk to return to use, patients at very high overdose risk, patients in the emergency room and hospital and those who are facing time restrictions due to impending moves/incarceration/residential treatment.

Benefits of a rapid start:

- You will get your medication administered more quickly without having to return for additional appointments.
- You will achieve high levels of medication (buprenorphine) more rapidly than with a traditional start. These higher levels may be more effective for cravings and withdrawal symptoms and provide a better opioid blockade to reduce overdose risk.

Risks of a rapid start:

- You won't have as much time to adjust to the effects of buprenorphine or to gradually increase the dose.
- You may experience increased side effects such as sleepiness and nausea. You should be cautious about driving until you are sure how the medication is affecting you.
- You may experience precipitated withdrawal. Precipitated withdrawal is when a medication makes your withdrawal symptoms suddenly feel worse for a little while before they feel better.

Counseling for XRBUP patients

- You won't feel 100% the first month, its normal to have uncontrolled cravings and use, especially the end of the month. Please call us if you need help with withdrawal symptoms and cravings, supplemental SLBUP can be provided for the first 2 months

- Your medication levels will continue to rise for 4-5 months if you stay on high dose XRBUP, so most people find their cravings better controlled the more shots they get

- Nausea, sweating and drowsiness are common the first week after the first shot. Call us if you need more anti-nausea medication. As your body adjusts to the buprenorphine levels the side effects should go away, and most people find each shot is easier.

Counseling for XRBUP patients

- You might not feel the injection wearing off, however if you don't return for your next injection the medication will wear off and most people will have return of cravings and return to use.

- As the shot wears off you may lose your opioid blockade and tolerance and return to use could result in higher risk of overdose. Always keep naloxone on hand, go slow and don't use alone.

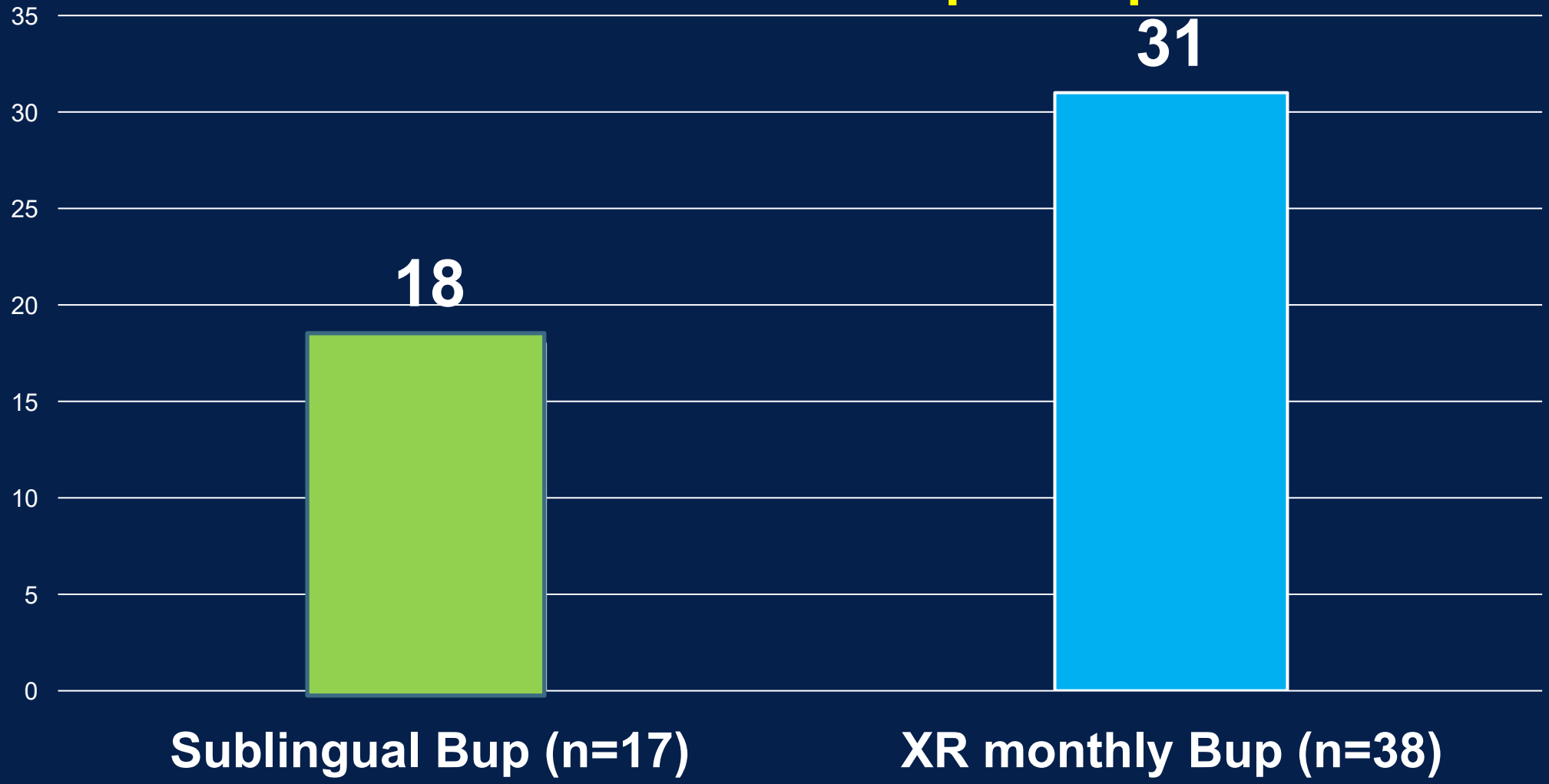
- You can always get your injection no matter what drugs you have been using. Don't be afraid to talk with us about your drug use. If you want support to reduce your drug use, we can help.

Methods

- Reviewed NTC prescriber PDMP records from Jan 2016-Jan 2022
- Identified patients admitted on or after May 2018 and before Aug 2021 who used Methamphetamines with Opioids (n=55)
- Compared duration of treatment (cumulative weeks of buprenorphine therapy)
  - SLBUP vs XRBUP 2018-2022 (at least 1 XRBUP shot)
  - SLBUP 2016-2018 vs SLBUP 2018-2022 (no change)

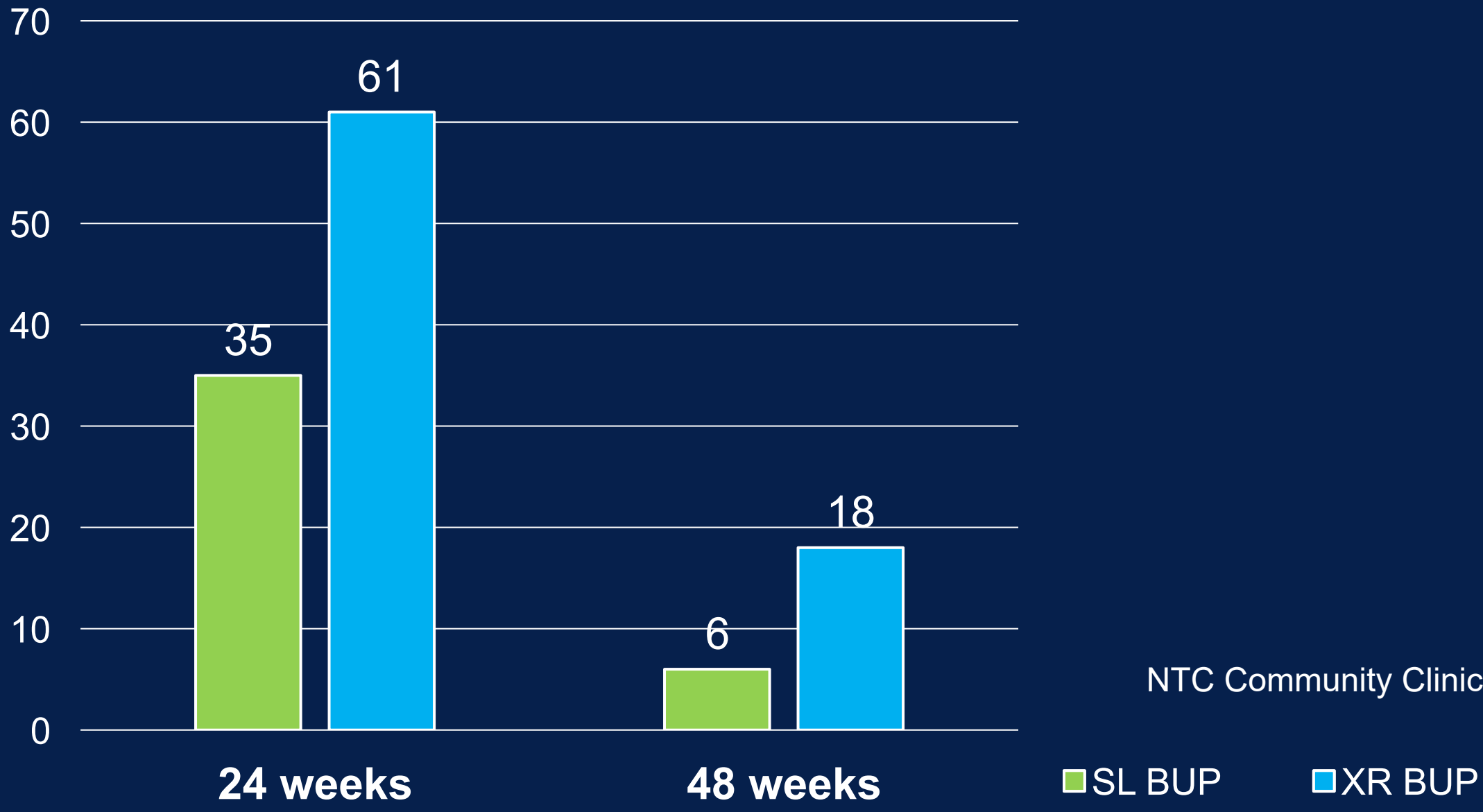
Treatment Retention SL vs XR Buprenorphine

Cumulative Weeks of Buprenorphine



NTC Community Clinic

% Patients with 24 and 48 week cumulative therapy on SL BUP vs XR BUP



NTC Community Clinic

Case Study Discussions

Case #1

- A 35 yo Alaska native male who lives in a roadless village with no local providers is seeing you via telemedicine today for a consult to start buprenorphine. He has been smoking 10-15 fentanyl pills “blues” daily for the past year. He wants to get on the XRBUP monthly injection because “the subs make me deathly ill, even when I waited for a day and a half after stopping the blues, I took a half a strip and it made me sicker than a dog. My friend got the shot and said it’s great”. He gets very anxious when you tell him that he will need to take SL BUP prior to getting his injection. “ I have to work, I can’t be home sick all week”. He only has 1 day off work per week available to fly into the clinic for his injection administration. His dealer just got arrested and he only has enough fentanyl to last him about 3 days. The village receives mail on M,W,F.

Case #1 questions

- How do we reduce his risk of precipitated withdrawal?
- How to we reduce his days away from home/work?

High dose buprenorphine initiation

California ED Bridge Program
https://cabridge.org/tools/resources/

Buprenorphine Self-Start

Guidance for patients starting buprenorphine outside of hospitals or clinics

1. Plan to take a day off and have a place to rest.
2. Stop using and wait until you feel very sick from withdrawals (at least 12 hours is best, if using fentanyl it may take a few days).
3. Dose one or two 8mg tablets or strips UNDER your tongue (total dose of 8-16mg).
4. Repeat dose (another 8mg-16mg) in an hour to feel well.
5. The next day, take 16-32mg (2-4 tablets or films) at one time.

If you have started bup before:

- If it went well, that's great! Just do that again.
- If it was difficult, talk with your care team to figure out what happened and find ways to make it better this time. You may need a different dosing plan than what is listed here.

If you have never started bup before:

- Gather your support team and if possible take a "day off."
- You are going to want space to rest. Don't drive.
- Using cocaine, meth, alcohol or pills makes starting bup harder, and mixing in alcohol or benzos can be dangerous.

Place dose under your tongue (sublingual).

If you have a light habit: *(For example, 5 "Norco 10's" a day)*

- Consider a low dose: start with 4mg and stop at 8mg total.
- **WARNING:** Withdrawal will continue if you don't take enough bup.

If you have a heavy habit: *(For example, injecting 2g heroin a day or smoking 1g fentanyl a day)*

- Consider a high dose: start with a first dose of 16mg.
- For most people, the effects of bup max out at around 24-32mg.
- **WARNING:** Too much bup can make you feel sick and sleepy.

Case #2

- A 25 yo female at 16 WGA with first pregnancy, is referred to your addiction specialty clinic from a local midwife practice to take over her buprenorphine prescribing. She has been intermittently taking prescribed buprenorphine but has moved between 3 different practices in the past 2 months due to chaotic life circumstances. She frequently no-show for visits and has many gaps in medication continuity. She reported to her PCP last week that she has been struggling to take her SLBUP daily and has continued to use fentanyl pills most days and it also using about 6mg/day of non-prescribed alprazolam as well as methamphetamine. She has had 2 attempts at admitting to withdrawal management but has left AMA on day 1 both times. The nearest OTP is 200 miles away and she refuses residential treatment.

Case #2 questions

- Is this pregnant woman a candidate for XRBUP?
- How can we support her and reduce immediate risks to herself and her fetus?

XRBUP in Pregnancy

Patients presenting to antenatal services who are also receiving treatment with long acting depot buprenorphine

Long acting depot buprenorphine has been approved for the treatment of opioid dependence in Australia

The Therapeutic Goods Administration (TGA) in Australia has approved two long-acting injected depot buprenorphine medications: Buvidal™ and Sublocade™. The Buvidal™ product was listed on the PBS on 1 September 2019.

What does this mean for antenatal, maternity and neonatal health services?

Increasing numbers of patients may present to these health services who are being treated with depot buprenorphine.

These formulations of buprenorphine are administered weekly or monthly

Buvidal™ is a modified release formulation of buprenorphine which is administered via subcutaneous (SC) injection in *weekly* or *monthly* intervals.

Sublocade™ is an extended-release formulation of buprenorphine which is administered via subcutaneous injection in *monthly* intervals.

Depot buprenorphine can be considered for pregnant women

Under the NSW Clinical Guidelines, depot buprenorphine may be considered for pregnant women if the risks of transferring her to sublingual buprenorphine or methadone outweigh the benefits.

https://www.health.nsw.gov.au/aod/resources/Pages/depot-buprenorphine-info-for-non-aod-clinicians-antenatal.aspx

There is a component in the inactive depot gel of XRBUP that has been associated with birth defects in rats. There are no studies in humans. If feasible, XRBUP should be avoided in women planning pregnancy or the first trimester when teratogenic risks are highest. In women who are unable to safely be maintained on SL BUP, XRBUP may be considered for use throughout pregnancy when benefits outweigh risks and the mother consents.

Patient Consent for Monthly extended-release buprenorphine (XRBUP)

For Pregnant women and women not on contraception

Women who have opioid use disorder and who are pregnant or at risk of becoming pregnant should be treated with buprenorphine or methadone to reduce return to use and overdose risk. Although there is good data on the safety of these medications in pregnancy, we do not have studies looking at the affects of XRBUP in pregnancy. Studies testing the effect of this drug in animals (rats) have shown the possibility of birth defects and miscarriages related to an ingredient in the depot gel. There are no studies to show if XRBUP causes birth defects or miscarriage in humans. The highest risk of birth defects and miscarriages in humans occurs in the first trimester of pregnancy, however some risk might still exist later in pregnancy. XRBUP depot gel stays in the body for up to 4 months or possibly more after administration, so women who choose this medication should be on a reliable form of birth control to prevent unintended pregnancy. Women who discover they are pregnant should switch to SLBUP during 1st trimester

Patient Consent for Monthly extended-release buprenorphine (XRBUP)

For Pregnant women and women not on contraception (continued)

Women who have not been successful with staying on daily dosing of buprenorphine or whose cravings are not adequately controlled on this medication, might choose to switch to XRBUP during their 2nd and 3rd trimester of pregnancy if it is decided that the risks of returning to opioid use outweigh any risks of the XRBUP medication.

I, _____ am pregnant or at risk of pregnancy and have decided after a conversation with my medical provider that XRBUP is the best medication option to treat my opioid addiction and to reduce my risk of returning to use and overdose. I understand the risks of this medication in pregnancy are not fully understood and that it may increase risk of birth defects and miscarriage, especially during the first trimester.

Case #3

- 42 yo female with fentanyl and methamphetamine use disorders presents to initiate XRBUP. She reports on her telemedicine intake that for the past 2 years she been unable to successfully initiate SLBUP due to precipitated withdrawal. Prior to this she had success with the use of non-prescribed buprenorphine to reduce cravings and use. She has friends who have received XRBUP injections and have encouraged her to do the same. She would prefer to start XRBUP without having to take SLBUP first. She lives 40 miles from the clinic and relies on friends for rides.

Case #3 questions

- What initiation strategies might reduce her risk of precipitated withdrawal?

Low-dose Overlapping SLBUP Start

How to

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Buprenorphine dose	0.5mg daily	0.5mg BID	1mg BID	2mg BID	4mg BID	4mg TID	8mg BID
Film size	2mg	2mg	2mg	2mg	2mg	2mg	8mg
Morning dose							
Afternoon Dose							
Night dose							
Full agonist	Continue	Continue	Continue	Continue	Continue	Continue	STOP

https://journals.lww.com/journaladdictionmedicine/Fulltext/2022/07000/Low_Dose_Initiation_of_Buprenorphine__A_Narrative.9.aspx

Case #3 (cont.)

- You provide her instructions for low-dose overlapping start of SLBUP and with prescriptions for clonidine and ondansetron
- She misses the next 2 scheduled appointments and presents to your office 3 weeks later for her injection
- She reports taking no SLBUP (still has the whole Rx), last use of fentanyl was 12 hours prior, COWS 13.
- She wants to get her XRBUP injection today but is worried about withdrawal symptoms

Case #3 questions

- How can we counsel patient on risks and benefits of rapid XRBUP injection?
- How can we support her after injection, and address her concerns about minimizing withdrawal symptoms?

Additional buprenorphine doses are the treatment of choice for precipitated withdrawal

Evidence for Additional Buprenorphine Doses

Buprenorphine has been well established as an effective treatment for opioid withdrawal and thus it is an attractive option to Macrodosing give additional doses of buprenorphine to treat precipitated withdrawal if the first dose of buprenorphine made symptoms worse.[1] Extrapolating from the management of naltrexone induced POW, 3 case reports and one case series described the use of buprenorphine to treat precipitated withdrawal, with resolution of precipitated withdrawal within hours using doses of 4mg to 22mg.[20-23] Buprenorphine has also been described as a treatment for naloxone precipitated opioid withdrawal in a case report.[24] In case reports of buprenorphine to manage buprenorphine POW, doses of 8-16mg were given with improvement of symptoms within 1-2 hours of receiving the additional doses.[11,25]

http://www.emdocs.net/buprenorphine-precipitated-opioid-withdrawal-tips-for-prevention-and-management-for-the-emergency-clinician/

If you experience precipitated withdrawal:

- Immediately take 16 mg of Buprenorphine (2 strips or tablets) dissolve under tongue for 20 mins. You may repeat 8-16 mg of buprenorphine again in 1-2 hours if needed (max 40 mg)

- Take Ondansetron 4-8 mg dissolve under tongue for nausea

- Take Clonidine 0.1 mg 1-2 tabs every 4 hours for restlessness and sweating

Final Takeaways/Summary

- Patients who use methamphetamine with fentanyl are at an increased risk of overdose death, while also having multiple barriers to accessing and retaining on MOUD
- XRBUP has a high patient satisfaction rating and a unique pharmacology resulting in an excellent blockade of fentanyl induced respiratory depression that can extend beyond the cessation of medication which may reduce overdose risk.
- Harm reduction based low-threshold access to XRBUP may help patients stay on buprenorphine longer. OBOT programs should work to reduce barriers to access this medication.

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