BUP-XR: Alternative induction strategies for challenging cases in the age of fentanyl

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No Conflicts of Interest

to Disclose

Learning Objectives

- Review standard and off-label options for starting the buprenorphine extended-release (BUP-XR) injection.
- Apply novel strategies to start BUP-XR in clients using fentanyl.

Let’s hear from you!

What are you hearing about BUP-XR in your community?

Is it being used in your community? (E.g. are you prescribing it, administering it and/or is it being prescribed to you?)

Goals of Treatment

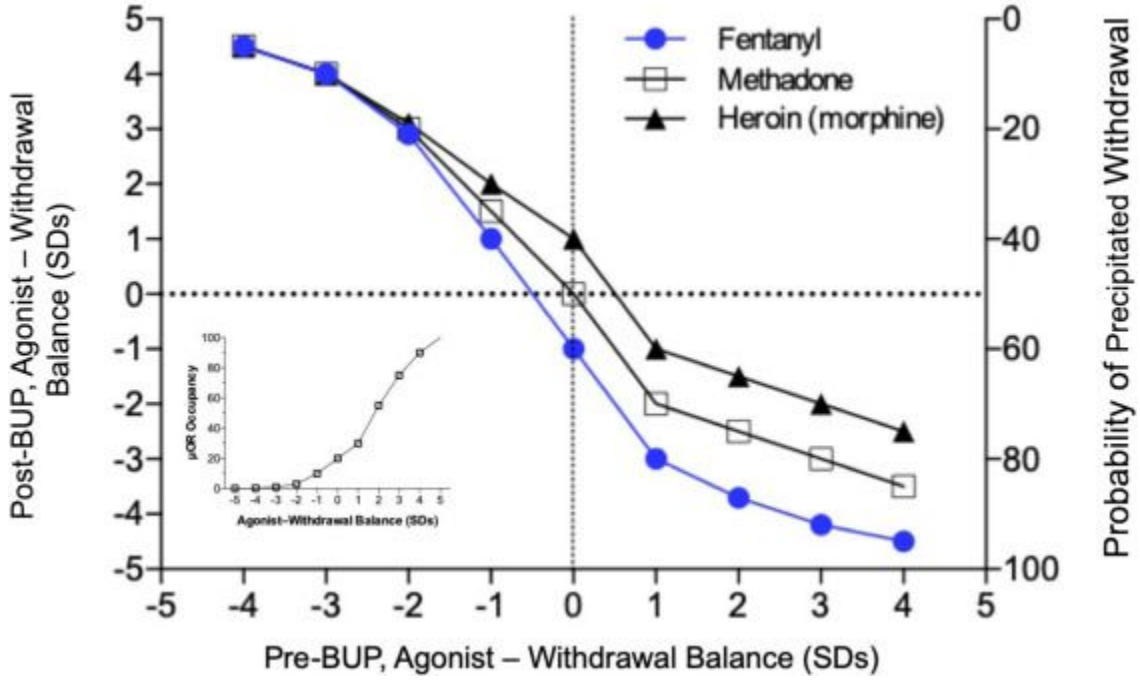
- Keep patients alive:
  - Initiate patients onto OAT/maintain their tolerance
  - OAT substantially reduces mortality, especially overdose deaths
- Stabilize patients:
  - Well enough to engage in other areas of their lives i.e. find housing, employment, gain access to social supports
- Engage patients:
  - Meet people where they are at
  - Recovery-based programming, counseling, treatment of comorbid mental health conditions

Understanding the Pharmacology - Basic Principles

- Buprenorphine is a partial agonist
- Buprenorphine precipitated withdrawal is related to:
  - Initial dose of buprenorphine
  - Mu-opioid receptor affinity
  - Lipophilicity
  - Intrinsic efficacy
  - Elimination pharmacokinetics
- Induction outcomes also related to the level of opioid dependence, genetics, comorbidities and prior buprenorphine experience
- Continued use of fentanyl increases likelihood of desensitization and internalization of the mu-opioid receptors, leading to increased risk of precipitated withdrawal

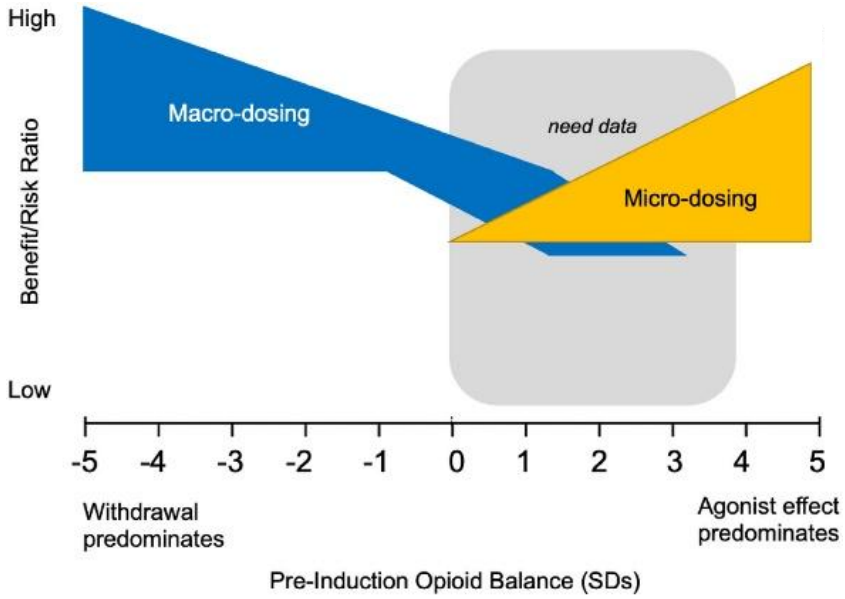
Greenwald et al, 2022

Neuropharmacological Model for Buprenorphine Initiation



Adapted from Greenwald et al, 2023

Decision Tool for Buprenorphine Inductions

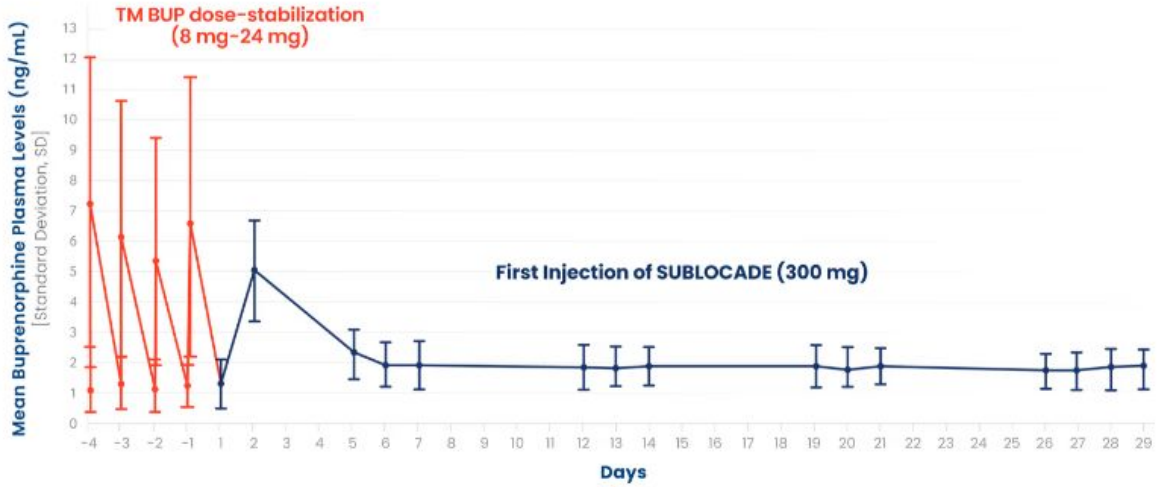


Greenwald et al. 2023

BUPRENORPHINE-XR (Sublocade®)

BUP-XR - Plasma Levels

Mean Buprenorphine Levels During Transmucosal Buprenorphine (TM BUP) Dose-Stabilization and After the First Injection of SUBLOCADE[3]



Indivior, 2016

BUP-XR Clinical Pearls

[BUP] Plasma	Mu opioid receptor occupancy	Outcome
1 ng/ml	50%	Relief of opioid WD
2 ng/ml	70%	Control of WD and cravings
3 ng/ml	80%	Attenuation of reinforcing and euphoric effect of typical doses of commonly used opioids

- Average plasma concentrations of BUP-XR at steady state are 3.21ng/mL for the 100mg dose and 6.54ng/mL for the 300mg dose.
- BUP-XR produces a Css with no daily variation and bioavailability 6-8x > BUP-SL.

Greenwald et al. 2007

Buprenorphine Dosing

	BUP-SL	BUP-XR
Dosing	Daily – q2days	Monthly*
Peak	~ 1.5 hours	24 hours
$T_{1/2}$	24-72 hours	43-60 days
T_{SS}	~ 1 week	4-6 months (injections)

*FDA product monograph now includes update that 2nd injection can be given up to a week after the 1st injection.

BUP-XR Counseling Points

- **No precipitated withdrawal once on BUP-XR:** taking an opioid such as fentanyl won't make you sick
- People usually find that **they get less of a high when they take other opioids** while on BUP-XR**.** Some people like this because it makes them less tempted to use opioids.
- BUP-XR can be helpful for people who continue to use opioids:
  - Because **BUP-XR helps to control cravings and withdrawal symptoms,** you won't have to keep taking your usual opioid to avoid being sick; becomes more of a choice
  - BUP-XR makes you **less likely to die of an overdose** if you keep using opioids.
- Time to peak is 24 hours post-injection **– you may notice the effect get stronger** over this period (monitor for sedation) AND with repeat injections

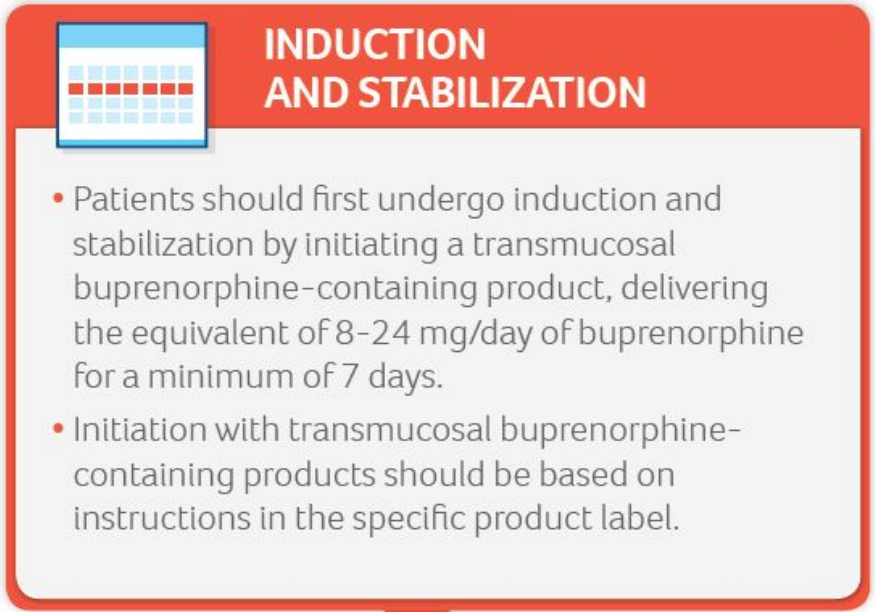
BUP-XR Considerations

	Precautions / Contraindications	Monitoring / Counseling
CNS + Respiratory	BUP-XR serum levels > BUP-SL serum levels – may have sedation, resp depression after depot.	Advise self-monitor for the first few days.
Cardiac	QT prolongation noted in monograph but not found in clinical studies.	Consider ECG before and after depot.
Hepatic	Case reports of severe liver disease and death in patients on buprenorphine; unclear correlation. C/I in severe hepatic impairment (physical findings of cirrhosis, liver failure i.e. encephalopathy, ascites, jaundice).	Monitor LFTs closely. Use caution in moderate hepatic impairment/cirrhosis + impaired liver function. Transaminitis without clinical/lab evidence of dysfunction not a contraindication
Pregnancy	Fetotoxic ingredient in the depot product	Urine βhcg if may be pregnant prior to injection. Contraception advised.

BUP-XR Dosing

1. Traditional induction
2. New* FDA product monograph updates
3. Macrodosing BUP-SL followed by BUP-XR
4. Cold Induction

1. Traditional Induction

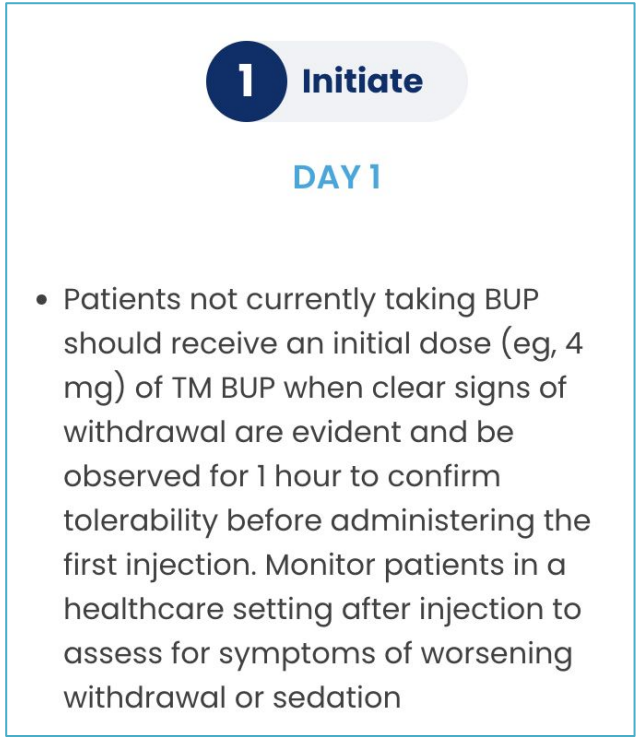


Potential Issues:

- Time consuming – requires patient to present for daily doses and follow up, sometimes needing to restart.
- May cause withdrawal if actively using or longer start with micro-induction
- Delays getting on to treatment

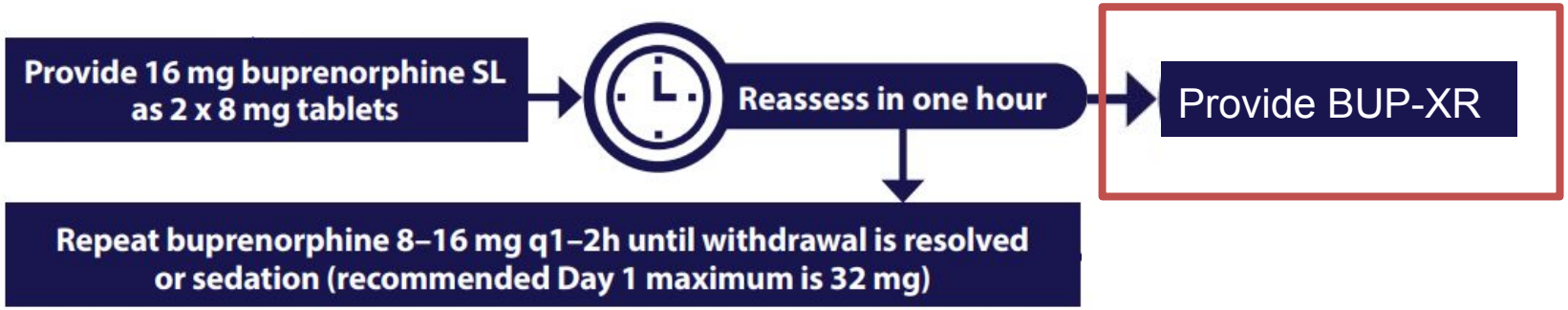
2. New* Rapid Start - FDA Product Monograph Updates

- Initial dose of 4mg BUP-SL followed by BUP-XR 300mg 1 hour later
- Oral Presentation at CSAM-SMCA 2024 Scientific Conference:
  - Randomized sub-study; evaluated treatment retention at injection 2 administered 1 week after injection using standard induction (SI) vs. rapid induction (RI) onto BUP-XR injection
  - RI treatment was superior to SI with respect to participant retention through Injection 2. Retention rate difference (RI-SI) was 11.82%



3. Macrodosing BUP-SL followed by BUP-XR

- Macrodosing allows for a faster induction onto BUP-XR, less time in withdrawal and increased OD prevention sooner!



4. “Cold Induction”

- BUP-XR is administered without BUP-SL
  - Considered a rapid micro-induction … BUP-XR has a slower onset (peaking at 24h).
  - Buprenorphine is slowly displacing fentanyl and allowing the receptors to re-sensitize (buprenorphine becomes primary agonist)
  - Further doses should add cumulative agonist effect and suppress WD sx

- On META-PHI several sites and providers report doing this with minimal PW

- This approach can also be considered when managing missed doses (e.g. several months of missed doses while continuing to use fentanyl)

Considerations for “cold induction”

1. **Have they tried buprenorphine before and tolerated mod-high doses?**
   If yes, this would make me feel more comfortable to pursue this approach (I,e. r/o allergy, ensure tolerance)
2. **Are they using fentanyl?**
   If yes, this would make me feel more comfortable as well – they are high risk , they have tolerance
3. **Have they had recent overdoses?**
   If yes, this would strongly make me consider this approach – the benefits of giving Bup-XR almost certainly outweigh the risks.
4. **Are they using alcohol or knowingly using illicit benzos, or other sedating substances?**
   If no, this would make me feel more comfortable.
5. **Do they have any known medical comorbidities i.e. hepatopathology, renal dysfunction, respiratory compromise?**
   If no, this would make me feel more comfortable as well.
6. **Is their POCT UDS neg for methadone?**
   If yes, much safer to proceed
7. **Are they pregnant?**
   If no and not on contraception, ensure to counsel before proceeding
8. **Are they elderly?**
   If yes, consider more conservative induction method, particularly in absence of recent BW

Case 1

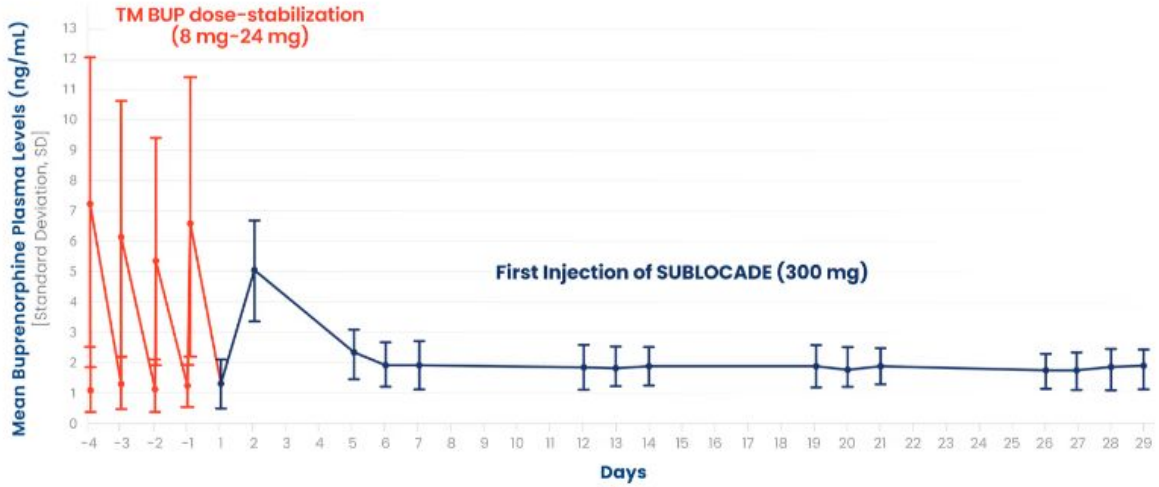
- 31 year-old male – previously on bup/nal tabs and on sublocade.
- Found the injection worked best.
- Lost to care but presented wanting to restart.
- Multiple attempts to re-start on SL bup:
  - Micro-induction – missed days of observed at pharmacy, had to restart.
  - 2nd attempt: Blister pack to take home – missed follow up and had to restart.
  - 3rd attempt: Offered same-day induction if he could come in without using for 6hrs… not able to do this.
- CONTINUED TO USE VERY HIGH DOSES OF IV FENTANYL
- Offered “cold induction” and got back on Sublocade.

Case 2

- 24 year old female admitted to hospital for cellulitis at tertiary care facility
- Received BUP-XR 300mg x 2 doses >6 months prior while incarcerated, tolerated/responded well
- Multiple recent overdoses requiring Narcan, frequently leaves AMA
- Wanting to restart buprenorphine XR
- LU FYL > 30 hours prior (pt seen on Monday morning) ; COWS = 20
- WBC = 14, otherwise unremarkable, betaHCG neg
- Afebrile, HR = 96, BP= 126/78; 02%= 98%; UDS pending, pt denies using methadone
- GIM says she may be discharged later today or tomorrow morning
- Do you macrodose?
- Do you provide buprenorphine XR today or tomorrow?

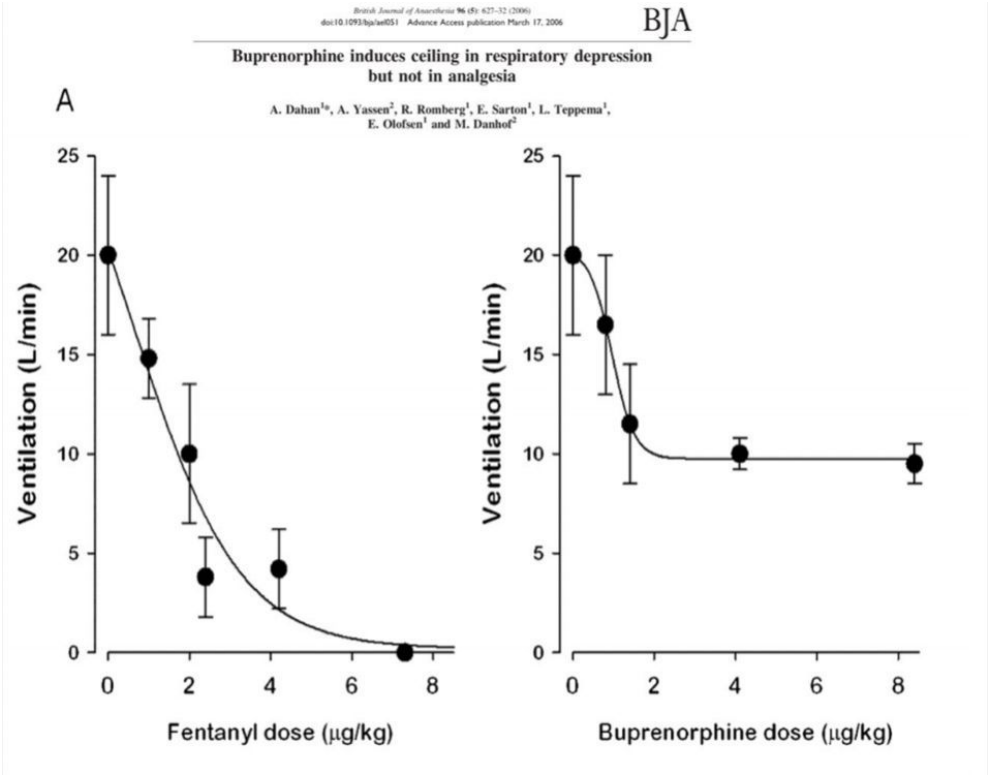
BUP-XR - Plasma Levels

Mean Buprenorphine Levels During Transmucosal Buprenorphine (TM BUP) Dose-Stabilization and After the First Injection of SUBLOCADE[3]



Indivior, 2016

Partial Opioid Agonist → Ceiling Effect



Case 3 - For the clients that just can't stick around…

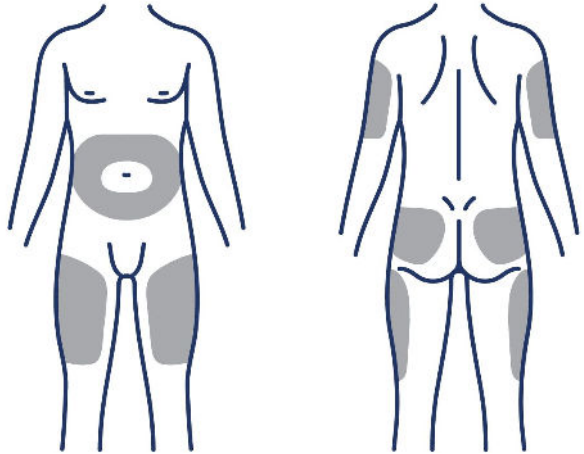
DTC client - 48 y.o. Male, severe OUD and stimulant use disorder,

- Received buprenorphine XR 300 mg during brief admission post overdose
- Missed doses for 6 months, can't tolerate being in clinic for longer than an hour
- Patient is having repeated overdoses on fentanyl AND frequent run-ins with the law because of their uncontrolled SUDs
- Has HTN but no other comorbidities
- UDS neg for methadone, pos for fentanyl consistently
- They are adamant they do not want to go to pharmacy every day
- They are willing to receive buprenorphine XR again; we review benefits and risks, and they demonstrate understanding that initiating BupXR immediately would be off-label
- Would you do cold induction with this patient?

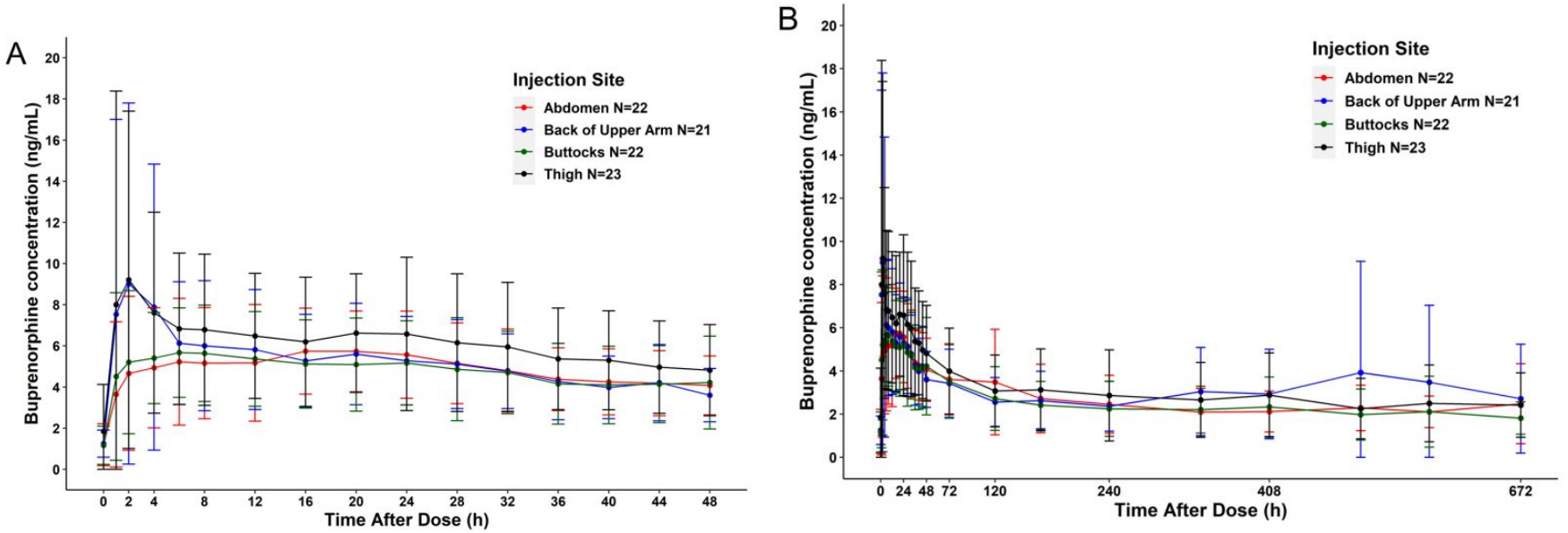
Additional FDA Product Monograph Updates

- More injection sites added (FDA):

✓ Abdomen	✓ Buttock
✓ Thigh	✓ Back of the upper arm



- Single dose study by Laffont et al (2024):
  - Eligible participants were aged 18–65 years with a body mass index (BMI) ≥ 18.0 to ≤ 33.0 kg/m2, OUD, stabilized on 12mg SL-BUP for 7-14 days.
  - Participants (n=88) were administered one dose of BUP-XR and serial blood draws were done over 28 days.



Laffont et al, 2024

Additional FDA Product Monograph Updates

- *The recommended dose for the second injection is 300 mg. The second injection may be administered as early as 1 week and up to 1 month after the initial injection, based on patient need*
    - May want to consider this in clients who have failed previous BUP-XR initiation
    - Experiencing w/d symptoms or cravings within the first week post BUP-XR
    - Required top-up BUP-SL during previous trial(s)
    - High opioid tolerance

Polling Question?

Which of the following FDA product updates have you adopted in your practice and what was your experience? **Please comment in the chat.**

a. Rapid Induction (1 hour after single 4mg BUP-SL)
b. Injections at different sites
c. Second injection given 1 week after first injection

Management of Precipitated Withdrawal post BUP-XR

- Similar to how you manage precipitated withdrawal with SL-BUP
- Can provide additional SL-BUP take home doses to manage withdrawal symptoms (e.g. 8-16mg PRN)

Substance Abuse and Rehabilitation

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Initiation and Dosing of Extended-Release Buprenorphine: A Narrative Review of Emerging Approaches for Patients Who Use Fentanyl

Kenneth W Lee[1], Annabel Mead[2], Imran Ghauri[3], Bruce Hollett[4], Martine Drolet[5], Jan-Marie Kozicky[5]

Table 1 BUP-XR Initiation Protocols with <7-Day TM-BUP Stabilization Periods Described in Patients Using Fentanyl

Citation	Location	Study Description	Day 1	Day 2	Day 3	Day 4	Day 5
BUP-XR initiated without any immediate prior TM-BUP dose, in patients with previous exposure to TM-BUP							
Wethern, 2023[29]	Denver, Colorado, USA	Case study (n=2)	300 mg BUP-XR				
Mooney 2024[48]	Portland, Oregon, USA	Case study (n=2)	300 mg BUP-XR				
BUP-XR initiated after single TM-BUP dose							
Hassman 2023[37]	Berlin, NJ, USA	Open label, uncontrolled (n=26)	4 mg TM-BUP 300 mg BUP-XR				
Ochalek, 2023[39]	Richmond, VA, USA	Open label, uncontrolled (n=19)	4 mg TM-BUP 300 mg BUP-XR				
Shiwach 2024[14]	Multiple Sites, Canada/ USA	Randomized controlled trial (n=489)	4 mg TM-BUP 300 mg BUP-XR				
BUP-XR initiated after macro/high-dose TM-BUP induction							
Mariani, 2021[41]	New York, NY, USA	Open label, uncontrolled (n=5)	24 mg TM-BUP (divided) 300 mg BUP-XR				
Taylor 2024[30]	Boston, MA, USA	Case study (n=1)	12mg IN-NAL 16mg TM-BUP 300 mg BUP-XR				
Kahan, 2023[32]	Timmins, ON, Canada	Case study (n=2)	28–32 mg TM-BUP (divided)	32 mg TM-BUP 300 mg BUP-XR			
LeSaint 2024[42]	San Francisco, CA, USA	Case study (n=1)	32mg TM-BUP (divided)	32 mg TM-BUP 300 mg BUP-XR			
Mariani, 2020[40]	New York, NY, USA	Open label, uncontrolled (n=5)	10–24 mg TM-BUP (divided)	16–24mg TM-BUP (divided) 300 mg BUP-XR			
				8–24mg TM-BUP (divided)	16 mg TM-BUP (divided) 300 mg BUP-XR		

Thank you!

Let’s discuss:

- Challenging cases you’ve encountered
- Questions about our presentation