Best Practices for Starting Buprenorphine for Fentanyl Use

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DISCLOSURES

None

LEARNING OBJECTIVES

1. Examine “traditional” buprenorphine starts and new challenges in the fentanyl era
2. Review different formulations of buprenorphine
3. Distinguish withdrawal (“high-dose”) and overlapping (”low-dose”) buprenorphine starts and predict circumstances where each might be preferable
4. Explore strategies to start long-acting injectable buprenorphine, including direct-to-inject protocols
5. Practice formulating plans for buprenorphine starts through clinical vignettes

CASE 1

- Your patient is 42 y/o woman who has a PMHx of severe opioid use disorder (fentanyl), methamphetamine use disorder, PTSD, depression, and unstable housing who comes into your clinic in withdrawal hoping to start MOUD (medications for opioid use disorder).

- She has tried methadone in the past but didn't like going to the clinic frequently and didn't feel it worked well for her. She has had heard from friends about buprenorphine but has some concerns about starting it.

The Flood of Questions

Who is the right provider to start buprenorphine?

Do I need special training or an X-waiver?

Are they using fentanyl?

How much fentanyl have they been using?

What if they are using other substances too?

How long do we have to wait since last use?

What dose will help prevent overdose?

Are they in withdrawal?

Is it ENOUGH withdrawal?

What's a COWS score?!

Do I need to calculate a COWS score?!

WHAT EVEN IS PRECIPITATED WITHDRAWAL?!!

REDUCING BUPE-XIETY…

- Starting buprenorphine can feel stressful and overwhelming
- Withdrawal is a reality but choosing the right start and **good anticipatory guidance** can set the stage for a successful initiation
- Your addiction medicine colleagues are always willing to help!

WHO CAN PRESCRIBE?

YOU should feel empowered to start Buprenorphine!

- Can be started in many clinical settings
- No dedicated training or certification needed

X-Waiver History

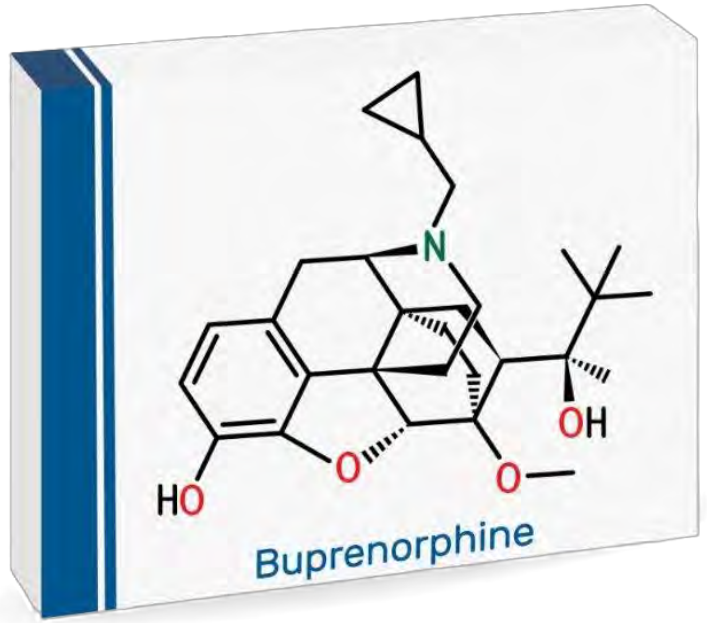
- The Drug Addiction Treatment Act of 2000 (DATA 2000)
  - Mandatory structured training
  - Prescriber ID # from DEA (X-waiver)
  - Limited amount of prescribing providers
- Consolidated Appropriations Act of 2023
  - Removed X-Waiver requirement
  - Expanded to all providers with standard DEA license

WHY BUPRENORPHINE?

- Decreased mortality!!!!
- Overdose protection
- Blockade of opioids rewarding effects
- Dose related retention in care
- Access to outpatient care outside of an OTP (methadone clinic)

WHAT IS BUPRENORPHINE?

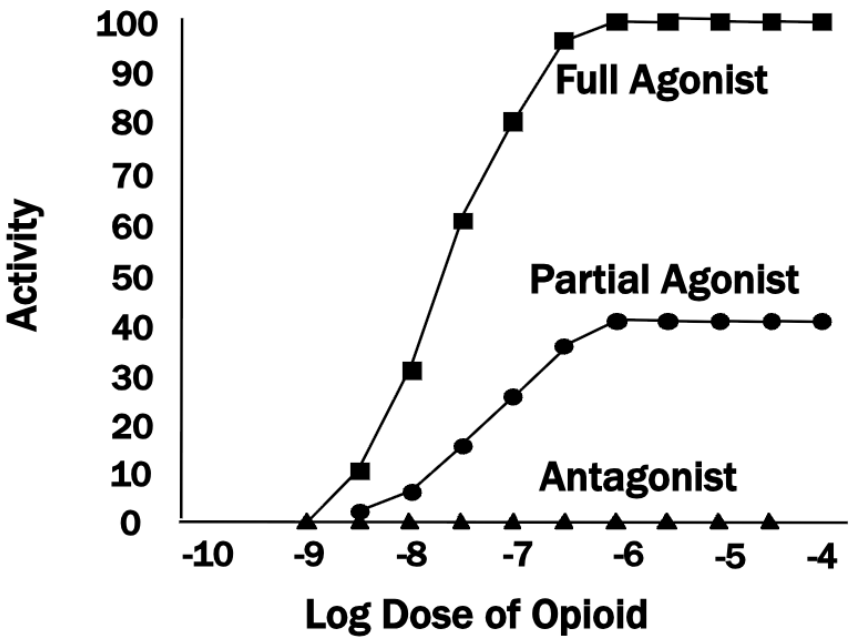
- Synthetic analog of thebaine an alkaloid found in poppy flowers
- Partial agonist at the mu-opioid receptor
- Exhibits ceiling effects on respiratory depression
- Metabolized in liver by CYP3A4 enzymes into the active metabolite norbuprenorphine
- FDA approved for pain and opioid use disorder



BUPRENORPHINE PHARMACOKINETICS

- Partial agonist
  - Only partially activates the MOR
- Very high affinity
  - Lower Ki value = stronger binding affinity
  - Blocks other opioids
- Slow dissociation (average half-life 38 hrs)

Drug	K_i (nM)	Drug	K_i (nM)
Hydrocodone	41.58	Butorphanol	0.7622
Oxycodone	25.87	Levorphanol	0.4194
Diphenoxylate	12.37	Oxymorphone	0.4055
Alfentanil	7.391	Hydromorphone	0.3654
Methadone	3.378	Buprenorphine	0.2157
Nalbuphine	2.118	Sufentanil	0.1380
Fentanyl	1.346		
Morphine	1.168		



OVERVIEW OF BUPRENORPHINE FORMULATIONS

- **Sublingual**
  - Buprenorphine-naloxone: 2-0.5mg, 8-2mg
  - Buprenorphine monoproduct: 2mg, 8mg
- **Long-acting injectable options**
  - 1st generation (Sublocade) - 2018
    - Monthly dosing (q28 days) with two dose options: 100mg, 300mg
  - 2nd generation (Brixadi) - 2023
    - Weekly and monthly options with multiple dosing ranges
- Patches, Buccal films
  - Primarily used for chronic pain
- Intravenous or Intramuscular

CASE 1, cont.

Your patient states she is in withdrawal and that she last use fentanyl about 12 hours ago. She states she feels anxious, has mild joint pain, a little restless, and some slight nausea. She does not have a tremor, lacrimation, rhinorrhea, or piloerection. Her heart rate is 91 and pupils are 2mm.

CASE 1, cont.

Your patient states she is in withdrawal and that she last use fentanyl about 12 hours ago. She states she feels anxious, has mild joint pain, a little restless, and some slight nausea. She does not have a tremor, lacrimation, rhinorrhea, or piloerection. Her heart rate is 91 and pupils are 2mm.

- You give 4mg of sublingual buprenorphine

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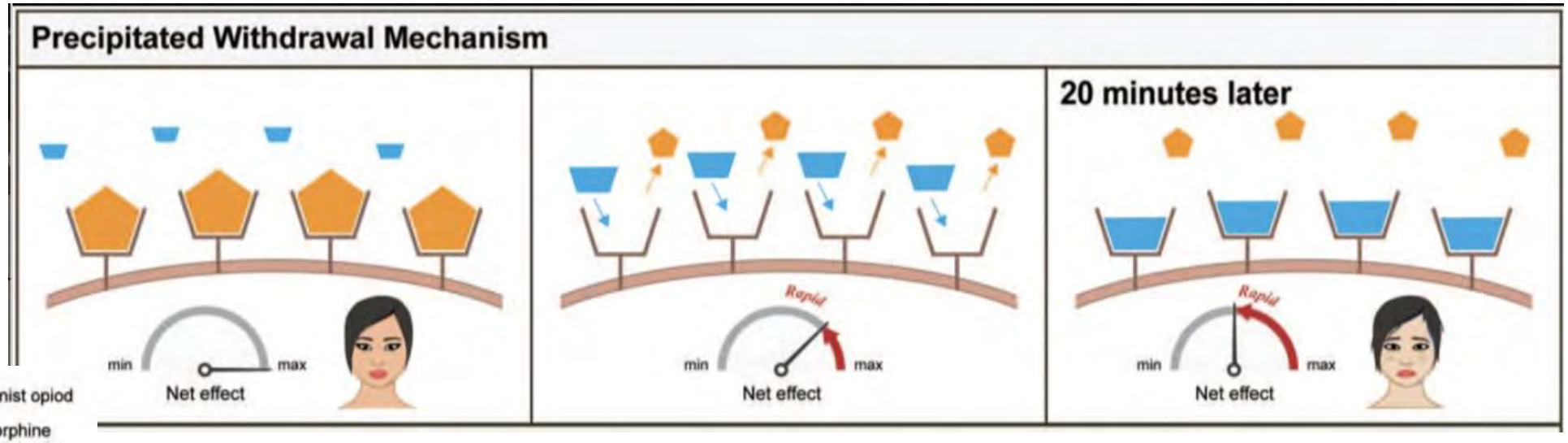
- You give 4mg of sublingual buprenorphine
- Within 15 minutes, you re-eval your patient. She is now extremely uncomfortable with emesis, restlessness, and muscle cramping.
- What happened?!?

PRECIPITATED WITHDRAWAL

- Definition (loose): COWS score increase ≥5 within 1-2 hours of taking partial agonist
- Mechanism: abrupt displacement of full agonist opioids from opioid receptors by a partial agonist or antagonist



Source: Ghosh et al (2019)

PRECIPITATED WITHDRAWAL

- Definition (loose): COWS score increase ≥5 within 1-2 hours of taking partial agonist
- Mechanism: abrupt displacement of full agonist opioids from opioid receptors by a partial agonist or antagonist
- Differs from spontaneous withdrawal which is milder, longer in duration
- Severe cases may require hospitalization and medical treatment

CASE 1 – WHY DID THIS HAPPEN?

- Attempted a withdrawal-based start too early
  - 12 hours since last use of fentanyl
- Mild withdrawal with COWS = 7
- No objective signs of withdrawal
  - No lacrimation, rhinorrhea, piloerection, pupils 2mm

OBJECTIVE ITEMS ON COWS

Resting Pulse Rate: Measured after patient is sitting or lying for 1 minute ☐ 0… pulse rate 80 or below ☐ 1… pulse rate 81-100 ☐ 2…pulse rate 101-120 ☐ 4… pulse rate greater than 120	**GI Upset:** Over last ½ hour ☐ 0…no GI symptoms ☐ 1…stomach cramps ☐ 2…nausea or loose stool ☐ 3…vomiting or diarrhea ☐ 5…multiple episodes of diarrhea or vomiting
Sweating: Over past ½ hour not accounted for by room temperature or patient activity. ☐ 0…no report of chills or flushing ☐ 1…subjective report of chills or flushing ☐ 2…flushed or observable moistness on face ☐ 3…beads of sweat on brow or face ☐ 4…sweat streaming off face	**Tremor:** Observation of outstretched hands ☐ 0…No tremor ☐ 1…tremor can be felt, but not observed ☐ 2…slight tremor observable ☐ 4…gross tremor or muscle twitching
Restlessness: Observation during assessment ☐ 0…able to sit still ☐ 1…reports difficulty sitting still, but is able to do so ☐ 3…frequent shifting or extraneous movements of legs/arms ☐ 5…Unable to sit still for more than a few seconds	**Yawning:** Observation during assessment ☐ 0…no yawning ☐ 1…yawning once or twice during assessment ☐ 2…yawning three or more times during assessment ☐ 4…yawning several times/minute
Pupil size: ☐ 0…pupils pinned or normal size for room light ☐ 1…pupils possibly larger than normal for room light ☐ 2…pupils moderately dilated ☐ 5…pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability:** ☐ 0…none ☐ 1…patient reports increasing irritability or anxiousness ☐ 2…patient obviously irritable anxious ☐ 4…patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches: ☐ 0…not present ☐ 1…mild diffuse discomfort ☐ 2…patient reports severe diffuse aching of joints/ muscles ☐ 4…patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin:** ☐ 0…skin is smooth ☐ 3…piloerection of skin can be felt or hairs standing up on arms ☐ 5…prominent piloerection
Runny nose or tearing: Not accounted for by cold symptoms or allergies ☐ 0…not present ☐ 1…nasal stuffiness or unusually moist eyes ☐ 2…nose running or tearing ☐ 4…nose constantly running or tears streaming down cheeks	The total score is the sum of all 11 items… Total Score:

WHAT WE WERE DOING BEFORE…

- Traditional buprenorphine starts in heroin era
  - Wait 12 hours since last opioid (heroin) use
  - Confirm COWS >8
  - Administer 2-4 mg SL buprenorphine up to 12 mg first day
  - Full dose 16mg daily

WHAT MAKES FENTANYL DIFFERENT

- Highly potent and short-acting → high opioid tolerance
- Highly lipophilic
  - Rapid distribution to CNS
  - Slower distribution to larger tissues (skeletal muscle, adipose tissue)
  - Chronic exposure can lead to sequestration and "depot effect"
  - Subjective withdrawal may occur even if mu-receptors are still occupied by fentanyl from adipose tissue
    - Urine testing may remain positive for weeks
- May have higher risk of precipitated withdrawal, even 24-48h after last use

SO NOW WHAT?

- Development of new buprenorphine start methods:
  - Overlapping start
  - Withdrawal-based start
    - High-dose start
    - Traditional start

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OVERLAPPING START

- AKA "Bernese method", "microdosing", "low-dose start"
- Principles:
  - Repetitive administration of very small buprenorphine doses
  - Long receptor binding time allows buprenorphine to accumulate at the receptor
  - Buprenorphine will gradually replace full agonist at receptor
- Important: patient should continue use of full opioid agonists throughout or withdrawal will develop
- Don't forget comfort meds

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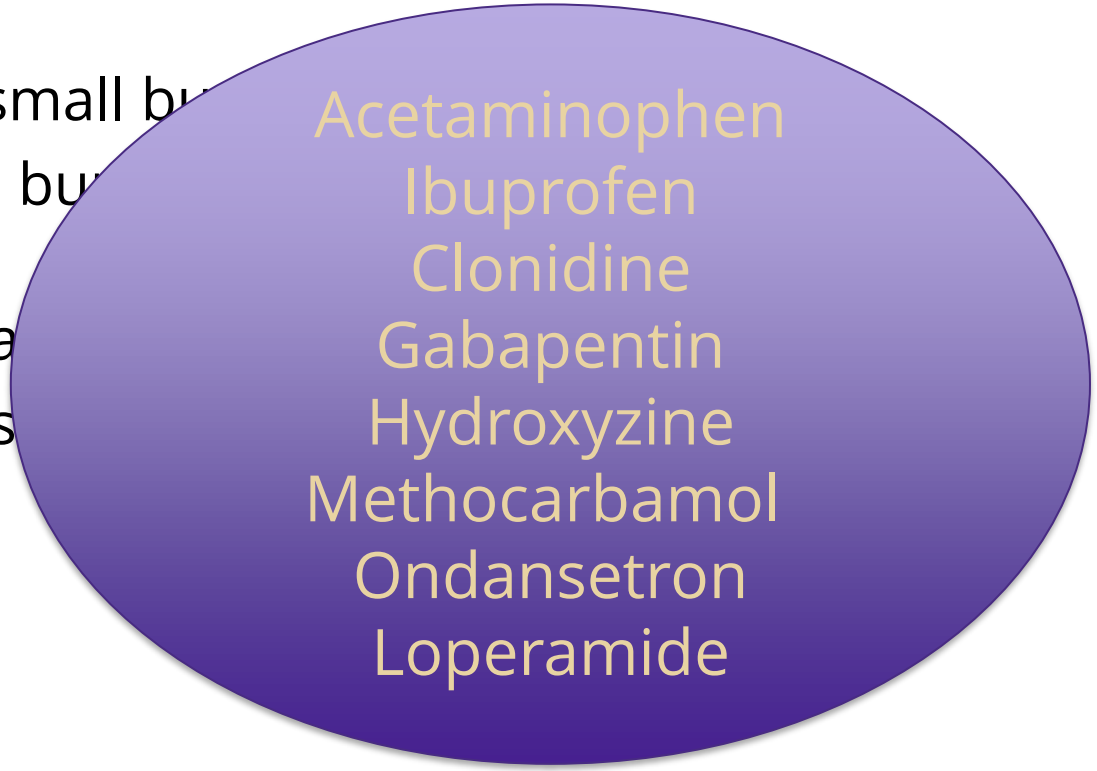
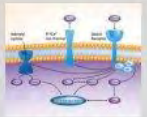
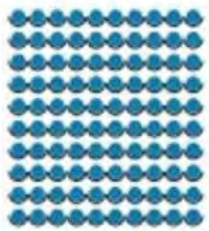
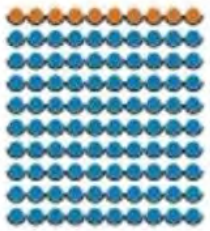
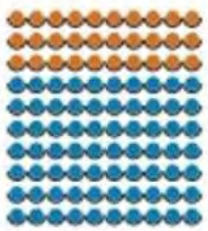
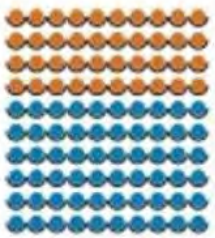
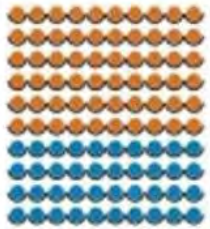
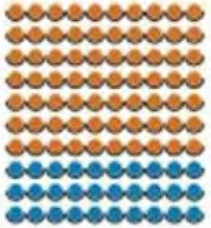
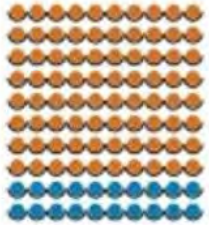


EXAMPLE PROTOCOL: SL

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Old opioid								
2/0.5 mg buprenorphine-naloxone								
	0 mg	1/4 = **0.5 mg**	1/4 BID = **1 mg**	1/2 BID = **2 mg**	1/2 TID = **3 mg**	1 BID = **4 mg**	2 BID = **8 mg**	2 TID = **12 mg**
 Opioid receptor binding								

Source: King County Bupe Pathways Clinic

OVERLAPPING START

Pros	Cons
• No withdrawal period required • Lower risk of precipitated withdrawal • Can continue full agonist opioids, such as short-acting opioids for acute pain • Can be used to transition from methadone	• Longer and more complicated regimen with frequent dosing • Low rates of outpatient completion • Often requires ability to split medications • Requires ongoing use to avoid withdrawal

SO NOW WHAT?

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  - Overlapping start
  - Withdrawal-based start
    - High-dose start
    - ~~Traditional start~~

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WITHDRAWAL-BASED START

- AKA "macro-dosing", "high-dose start"
- Principle: rapid saturation of receptors to overcome withdrawal symptoms and achieve high receptor occupancy
- Patient must be in moderate to severe withdrawal
  - No consensus on COWS or timing
  - Most studies used COWS >8 with at least one objective sign
  - If no objective signs, consider COWS ≥12
  - Great option following naloxone administration
- Don't forget comfort meds

WITHDRAWAL-BASED START

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  - G
- Don't

WHAT WE WERE DOING BEFORE...

- Traditional buprenorphine starts in heroin era
  - Wait 12 hours since last opioid (heroin) use
  - Confirm COWS >8
  - Administer 2-4 mg SL buprenorphine up to 12 mg first day
  - Full dose 16mg daily

Caption

EXAMPLE PROTOCOL: SL

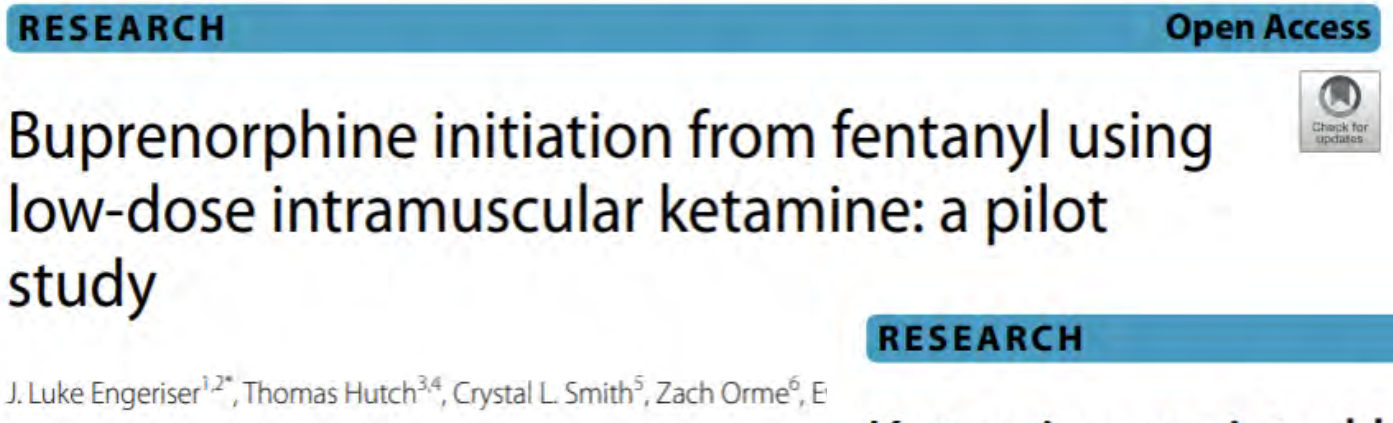
1. Confirm at least moderate withdrawal
2. Give sublingual buprenorphine 8-16mg
3. Observe for 30-60 min
4. If COWS improves or stays the same and withdrawal symptoms persist, give another 8-16mg every 30-60 minutes as symptoms persist up to 64mg total

Day 1 total dose target: at least 24-32mg

If precipitated withdrawal develops, give more buprenorphine (up to 64mg+) + adjuncts

Safety: across large-scale studies, high-dose starts were not associated with increased respiratory depression or excessive sedation

HOT OFF THE PRESS!



RESEARCH Open Access

Buprenorphine initiation from fentanyl using low-dose intramuscular ketamine: a pilot study

J. Luke Engeriser[1,2*], Thomas Hutch[3,4], Crystal L. Smith[5], Zach Orme[6], E

RESEARCH Open Access

Ketamine-assisted buprenorphine initiation: a pilot case series

Lucinda A. Grande[1,6*], Tom Hutch[2,6], Keira Jack[2], Wendy Mironov[2], Jessica Iwuoha[2], Martin Muy-Rivera[2], Jacob Grillo[3], Stephen A. Martin[4] and Andrew Herring[5]

WITHDRAWAL-BASED START

Pros	Cons
• Rapid stabilization and achievement of therapeutic doses • Low complexity	• Requires moderate to severe withdrawal • Some risk of precipitated withdrawal

COMPARING METHODS

	Overlapping start	Withdrawal-based start
Need for withdrawal?	No	Yes
Initial starting dose	0.25-1mg	8-16mg
Day 1 total dose	0.5-1mg	16-32mg
Time to stabilization	3-10 days	2-6 hours
Continue full agonist opioids?	Yes	No
Complexity of regimen	High	Low

INCORPORATING LONG-ACTING INJECTABLES (LAI-B)

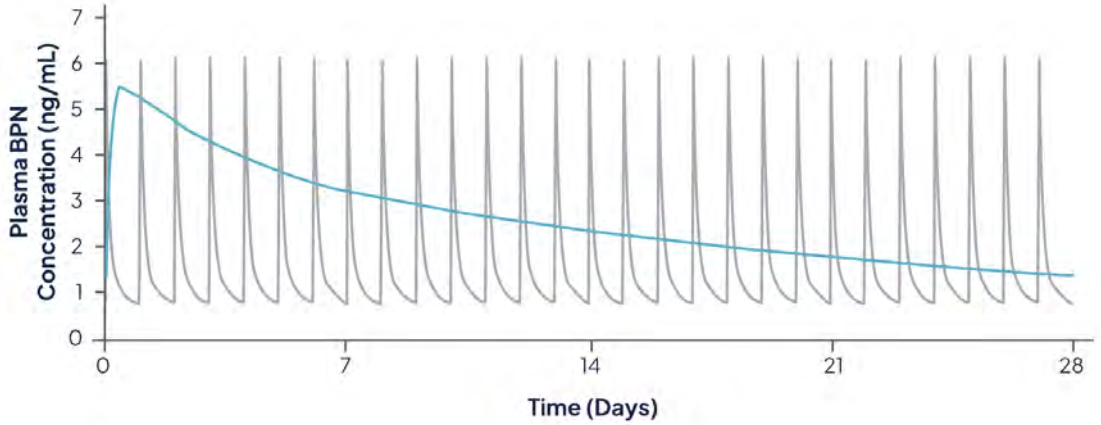
Good options for patients with:

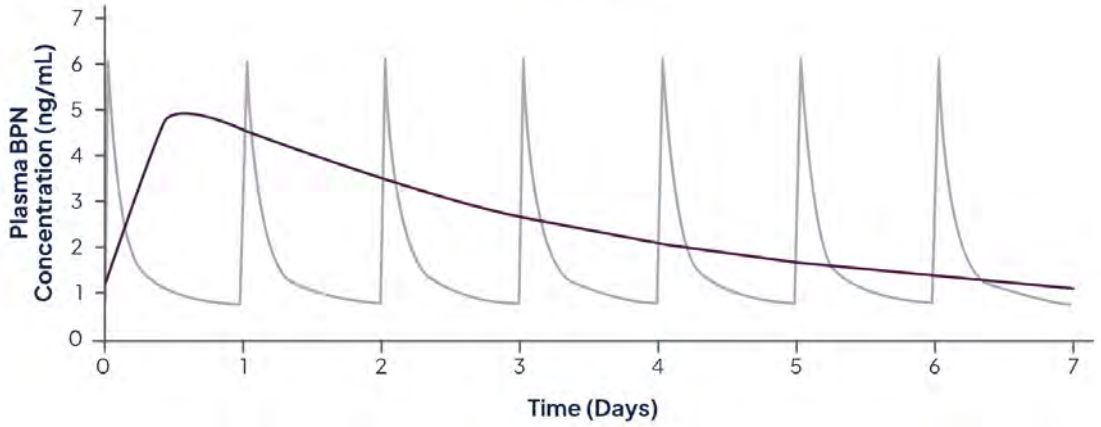
- Difficulty with daily medication adherence
- Concerned about stigma related to daily buprenorphine
- Dislike taste or other characteristics of sublingual buprenorphine
- Challenges with buprenorphine access (e.g. incarceration, residential treatment)
- Concerns with safe storage of medication

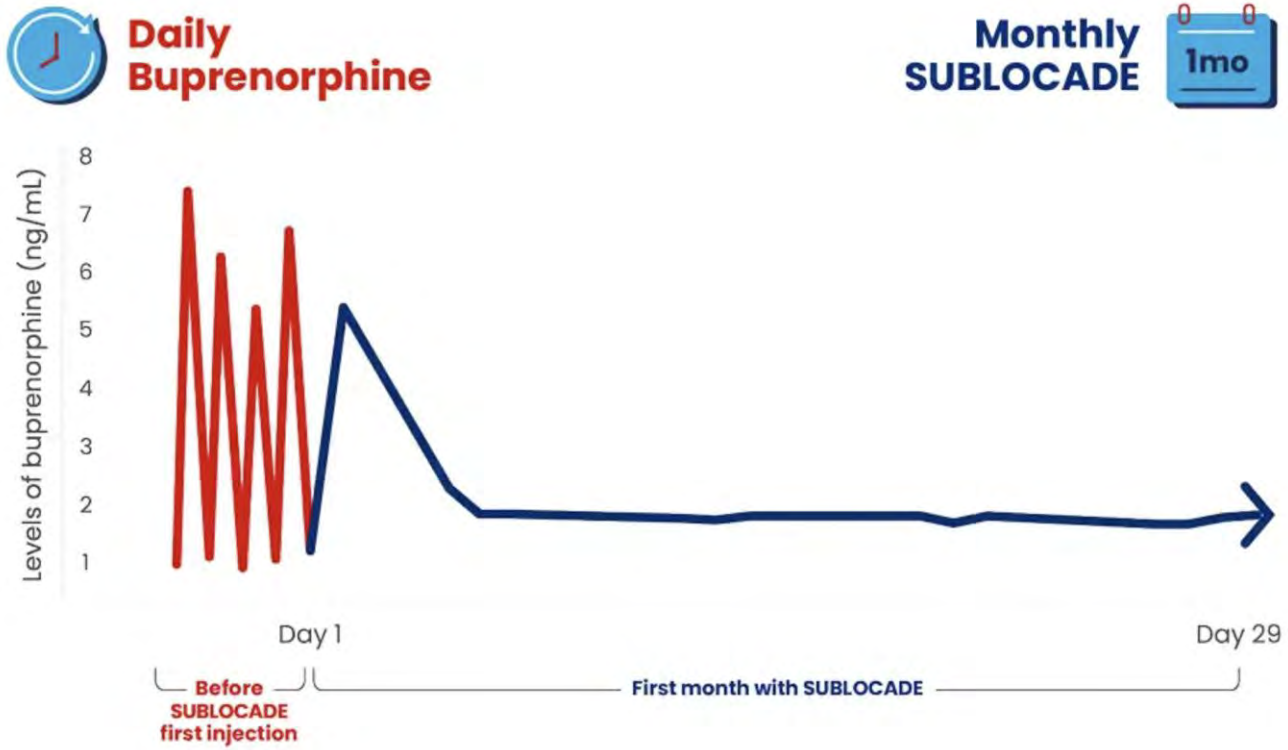
LAI-B OPTIONS

	1st generation (Sublocade)	2nd generation (Brixadi)
Dose options	100mg, 300mg	Weekly: 8, 16, 24, or 32mg Monthly: 64, 96, or 128mg
Dose interval	Minimum 26 days	Weekly: 5-9 days Monthly: 21-35 days
Medication delivery	Depot injection with formation of lump at site	Depot injection, minimal to no detectable lump
Administration site	**Abdomen**, thigh, buttock, or back of upper arm	Abdomen, thigh, buttock, or **back of upper arm**
Needle size	19 gauge, 5/8"	23 gauge, ½"
Use of lidocaine?	Recommended	Optional, generally not needed
Requires refrigeration?	Yes	No

COMPARING SUBLINGUAL VS. LAI-B







Half-life comparison: SL = 24-42h, Brixadi weekly 3-5 days, Brixadi monthly 19-26 days, Sublocade 43-60 days

Sources: Brixadi and Sublocade manufacturer websites

COMPARING SUBLINGUAL VS. LAI-B

Serum levels (ng/mL)	Sublingual					Brixadi weekly			Brixadi monthly			Sublocade		
	8	12	16	24	32	16	24	32	64	96	128	100 (ss)	300 (1st)	300 (ss)
Minimum	**0.66**	**0.87**	**1**	**1.37**	**~2.8**	**0.8**	**1.4**	**2.6**	**1.3**	**2**	**2.1**	**2.46**	**1.42**	**5.47**
Average	1.2	1.79	1.8	2.5	~3	2.1	2.9	4.2	2	2.9	3.9	2.87	2.19	6.32
Maximum	4.27	5.6	6.5	8.2	13.2	4.3	5.5	6.9	4	6	11.1	5.1	5.37	11.81

Time to steady state:

- Sublingual: 7-10 days
- LAI-Bs: typically 4-6 injections

FDA-APPROVED STARTS FOR LAI-Bs

1st gen

Give 4mg SL buprenorphine → Observe for 1 hour → If no PW or adverse effects, give 300mg injection

Sequence: 300mg --> 300mg (as soon as 7 days later) --> 100mg or 300mg

2nd gen

Give 4mg SL buprenorphine → Observe for 1 hour → If no PW or adverse effects, give 16mg weekly injection

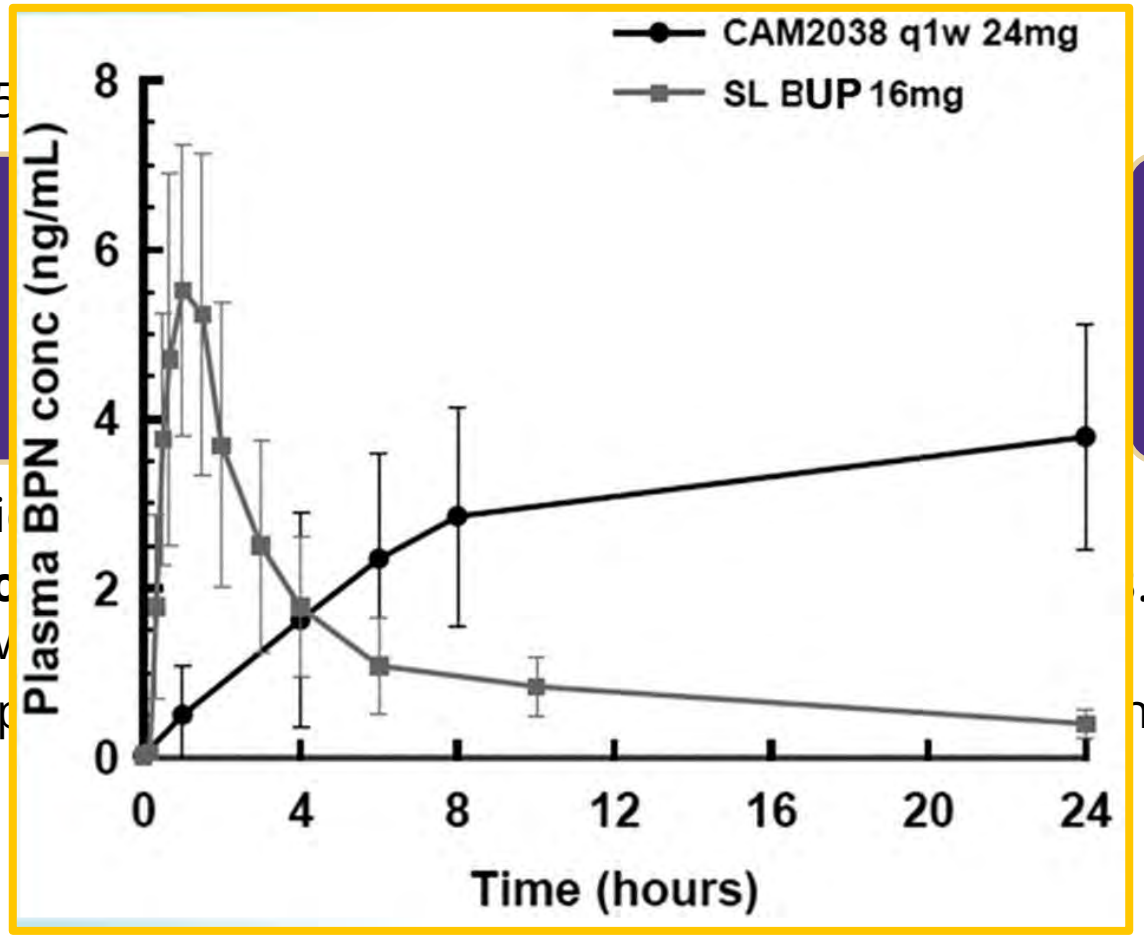
Give up to 32mg in first week --> continue weekly vs transition to monthly

FDA-APPROVED STARTS FOR LAI-Bs

OVERLAPPING START: DIRECT-TO-INJECT

Waters et al (2025): N=95

Day 1: weekly 8mg injection (2nd gen)



Day 3: monthly 300mg injection (1st gen) or monthly 128mg injection (2nd gen)

- Provide comfort medi
- Counsel patients to **cc** . Some withdrawal is expected and severe v
- Patients may use supp nthly injection

OVERLAPPING START: DIRECT-TO-INJECT

Waters et al (2025)

Day 1: weekly 8mg injection (2nd gen) → Day 2: weekly 16mg injection (2nd gen) → Day 3: monthly 300mg injection (1st gen) or monthly 128mg injection (2nd gen)

- Provide comfort medications
- Counsel patients to **continue full agonist opioid use** until at least day 3. Some withdrawal is expected and severe withdrawal is possible
- Patients may use supplemental SL buprenorphine starting 24h after monthly injection

Results: 75% completion and 64% 2-month retention

WITHDRAWAL-BASED START: DIRECT-TO-INJECT

- Direct to weekly or monthly injection with 1st or 2nd generation LAI-B
  - Ideally patient should be in moderate withdrawal prior to injection
  - PW is possible, may have protracted course of withdrawal
- Provide comfort medications and supplemental SL buprenorphine

WITHDRAWAL-BASED START: DIRECT-TO-INJECT

Published protocols:

- Direct to weekly injection: D'Onofrio (2024, 2026)
  - COWS ≥4 (including objective sign) → 24mg weekly LAI
  - Low rates of PW: <1% within 2 hours
- Direct to weekly injection: Rosenwohl-Mack (2026)
  - COWS ≥4 → 8 (4%), 16 (27%), 24 (62%), or 32mg (7%) weekly LAI
  - Withdrawal (24h): none (37%), mild/moderate (31%), severe (11%), unknown (21%)
  - 67% subsequently received monthly injection and 43% retained after 90 days

Unpublished:

- Direct to monthly injection: 1st gen 300mg/2nd gen 128mg + supplemental SL bup
  - 1st generation: peak in 24h
  - 2nd generation: peaks in 6-10h

SUPPLEMENTING LAI-B

- Sublingual:
  - Provide supplemental SL buprenorphine for PRN use for withdrawal or cravings, typically 8mg BID up to QID PRN
- Booster dosing:
  - 1st generation monthly (Sublocade): eligible for booster dose of 300mg 7 days after 1st monthly injection
  - 2nd generation weekly (Brixadi): eligible for booster of weekly 8mg or 16mg within 3 days of first dose to reach total 32mg weekly
- Comfort medications

PRACTICE CASES

CLINICAL VIGNETTE 1

Your patient is a 21-year-old male with PMHx of MRSA endocarditis of the tricuspid valve, opioid use disorder (daily fentanyl), methamphetamine use disorder (daily intravenous), currently stably housed with his father.

- Questions?

CLINICAL VIGNETTE 1

Your patient is a 21-year-old male with PMHx of MRSA endocarditis of the tricuspid valve, opioid use disorder (daily fentanyl), methamphetamine use disorder (daily intravenous), currently stably housed with his father.

- He is interested in stopping fentanyl use as quickly as possible. He uses 1-1.5g daily. He has never tried methadone or buprenorphine before. He last used fentanyl yesterday morning and reports subjective withdrawal today.
- Exam?

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- He is interested in stopping fentanyl use as quickly as possible. He uses 1-1.5g daily. He has never tried methadone or buprenorphine before. He last used fentanyl yesterday morning and reports subjective withdrawal today.
- On exam, his pupils are 4mm. His pulse is 102 bpm. He denies nausea or vomiting, does note some anxiety, restlessness, and back ache. He is sniffling a bit in the interview. He is mildly diaphoretic. He yawns once over the course of your assessment. He does not have piloerection.

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- Which start might you recommend?

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Withdrawal-based start

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Phone a friend!

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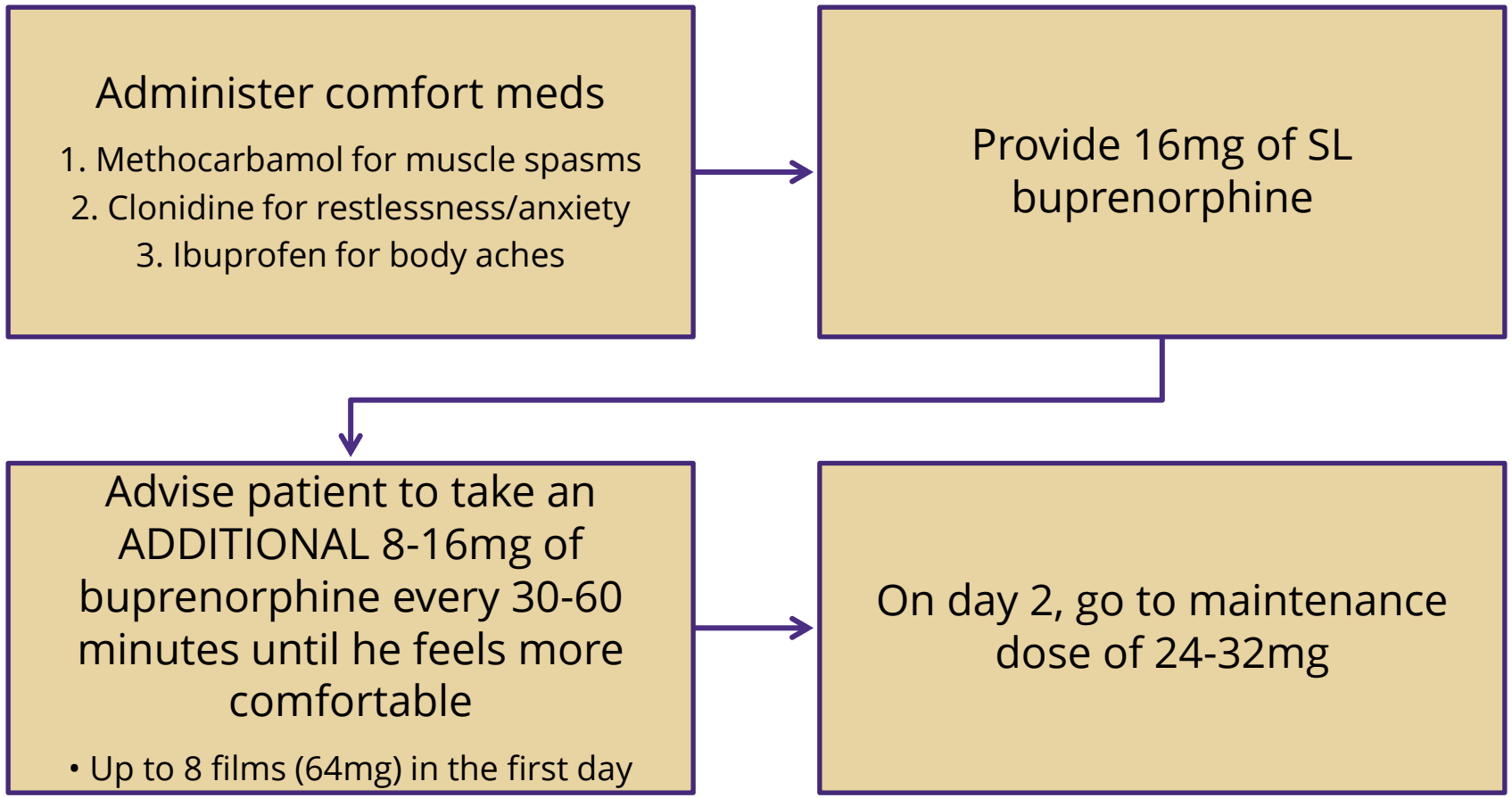
WITHDRAWAL-BASED START: SL



CLINICAL VIGNETTE 1: PLOT TWIST!

Your patient hates the taste of both films and tablets and wants to be on an LAI anyway – he asks if he has to start out with the films?

WITHDRAWAL-BASED START: LAI-B

1. Administer comfort meds
2. Give 24-32mg 2nd Gen LAI (Brixadi weekly) OR give 300mg 1st gen LAI (Sublocade)

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3. Tip: Give ADDITIONAL SL bupe to take as a PRN

CLINICAL VIGNETTE 2

A 65-year-old woman is evaluated for OUD. She has a PMH of alcohol use disorder in remission, opioid use disorder (daily fentanyl via smoking), and currently lives in permanent supportive housing.

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- Exam?

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OUTPATIENT OVERLAPPING START: SL

1. Send home with comfort meds based on their symptoms
2. Ideally, find a pharmacy comfortable with preparing the start
3. Select a start with simple dosing (BID ideal)
4. Counsel the patient on what to do about missed doses
5. Counsel the patient on continued full agonist use
6. Send with maintenance dose of 24-32mg/day

CLINICAL VIGNETTE 2: PLOT TWIST!

You prescribe your patient a SL overlapping 7-day start. She calls you back on day 3 reporting significant withdrawal – she's worried she's precipitating!

- What question do you ask next?

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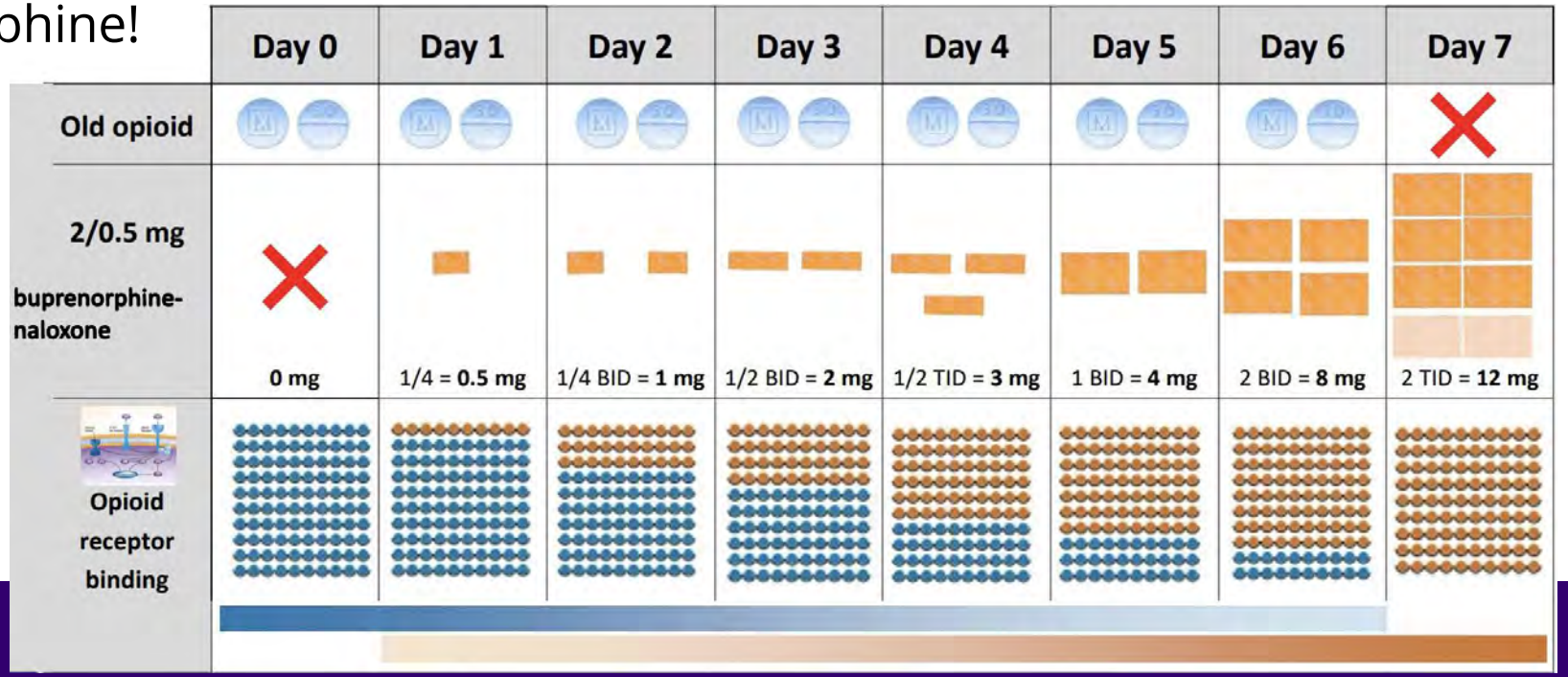

CLINICAL VIGNETTE 2: ANOTHER PLOT TWIST!

Your patient calls you back. She is now on day 5 of her start; she last took half of a 2mg bupe-nal film yesterday, but FORGOT to take her evening dose last night – what do you advise?

How to start buprenorphine _____ at home without going into withdrawal first

Cut your 2 mg films and take according to the schedule below. Each day you will increase the total amount of medication you are taking. On Day 7 you should follow-up in clinic and begin trying to decrease you opiate use.

1 film (2 mg) | 1/2 film (1 mg) | 1/4 film (0.5 mg)

Time of Day	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Morning	1/4 film	1/4 film	1/2 film	1/2 film	1 film	2 film	2 film
Afternoon				1/2 film			2 film
Evening/Night		1/4 film	1/2 film	1/2 film	1 film	2 film	2 film

CLINICAL VIGNETTE 2: MISSED DOSE

a) Give up - restart the whole thing!

b) Take the 1mg dose she missed right now instead

c) Forget about the missed dose and take the next 2mg dose tonight as planned

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CLINICAL VIGNETTE 2.5

A 65-year-old woman is evaluated for OUD. She has a PMH of alcohol use disorder in remission, opioid use disorder (daily fentanyl via smoking), and currently lives in permanent supportive housing.

- She is interested in buprenorphine but hasn't ever been able to go more than 12 hours without fentanyl in recent years. She has mild cognitive impairment and struggles to organize her medications.
- Which start do you choose?

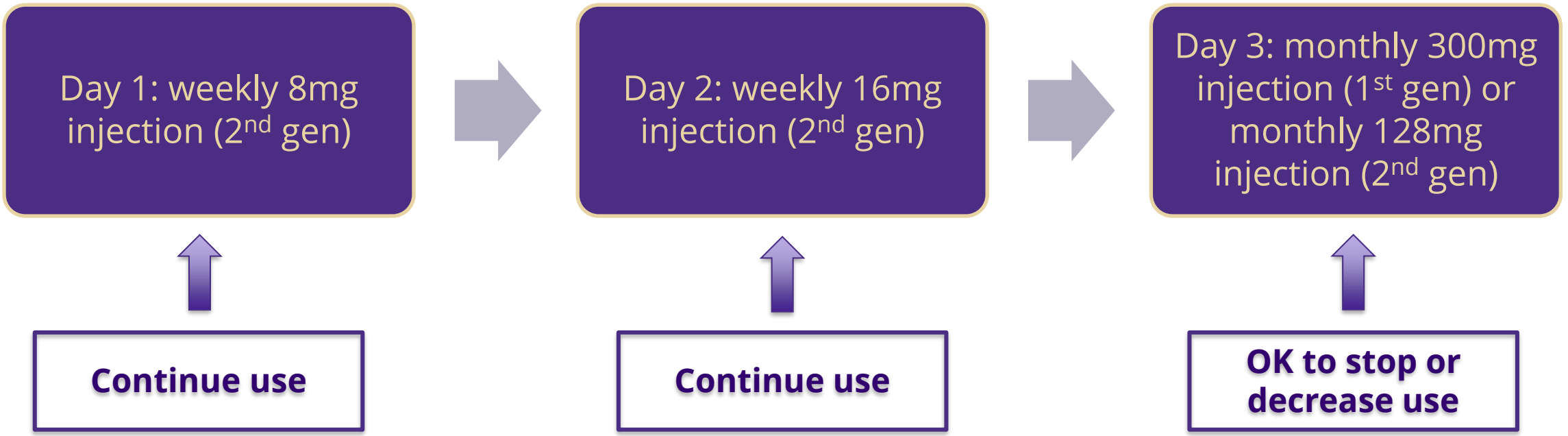
OVERLAPPING START: LAI-B

Day 1: weekly 8mg injection (2nd gen)

Day 2: weekly 16mg injection (2nd gen)

Day 3: monthly 300mg injection (1st gen) or monthly 128mg injection (2nd gen)

OVERLAPPING START: LAI-B



YOU DID IT! Your patient started bupe!

WHEN TO PHONE A FRIEND (REFER TO ADDICTION MED)

- Unclear use/diagnosis history
- Pt has history of precipitated withdrawal or unsuccessful starts in the past
- Transitioning from methadone
- You have questions!

TAKE-HOME POINTS

- Buprenorphine is a high-affinity, partial mu opioid agonist which can pose withdrawal risks in the fentanyl era
- Buprenorphine is a LIFE-SAVING medication
- Choose your start based on clinical exam and patient preference
  - Withdrawal-based (high dose)
  - Overlapping (low dose)
- Good anticipatory guidance and counseling can promote success!

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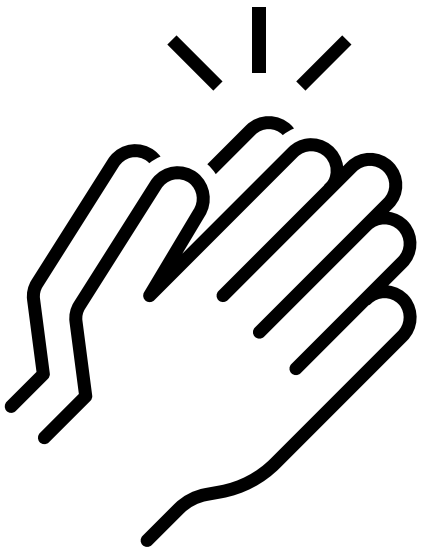
  - Dr. Jared Klein
  - Dr. Amy Kennedy
  - Dr. Sarah Leyde
- King County Pathways for Buprenorphine Clinic



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QUESTIONS?

THANK YOU!