Innovations in Buprenorphine Initiation for the Advanced Clinician

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Melissa Weimer, DO, MCR, DFASAM

ASAM Annual Conference 2024

April 6, 2024 1:15-2:30pm

Disclosure Information

- Presenter 1: Pouya Azar, MD, FRCPC, FASAM
  - Commercial Interests: Indivior Advisor for a study on XR buprenorphine, Patent: Apparatus and Methods for Detecting and Quantifying Analytes
- Presenter 2: Andrew Herring, MD
  - Commercial Interests: no disclosures
- Presenter 3: Laura Kehoe, MD, MPH, FASAM
  - Commercial Interests: Indivior Advisory Board
- Presenter 4: Melissa Weimer, DO, MCR, DFASAM
  - Commercial Interests: no disclosures

Learning Objectives

- Describe the current evidence regarding buprenorphine initiation in people using high potency synthetic opioids like fentanyl.
- Discuss the rationale and potential risks and benefits of novel buprenorphine initiation strategies.

**Pre-reading recommended: ASAM Clinical Considerations: Buprenorphine Treatment of OUD for Individuals Using High-potency Synthetic Opioids*

COMMENTARY

A Plea From People Who Use Drugs to Clinicians: New Ways to Initiate Buprenorphine are Urgently Needed in the Fentanyl Era

Kimberly L. Sue, MD, PhD, Shawn Cohen, MD, Jess Tilley, and Avi Yocheved

J Addict Med. 2022 Jul-Aug 01;16(4):389-391.

Concerns and Questions

- **"I can't wait long enough"** Patients are unable to tolerate abstinence long enough to allow sufficient withdrawal to develop permit successful buprenorphine initiation with standard dosing.

- **"It doesn't work for me"** Patient withdrawal symptoms persist despite buprenorphine initiation.

- **"It makes me sick"** patients reports precipitated withdrawal

Workshop Outline

- Case presentation 1 – Dr. Kehoe & Dr. Azar
  - Questions limited to 8 minutes
- Case presentation 2 – Dr. Weimer
  - Questions limited to 8 minutes
- Case presentation 3 – Dr. Herring
  - Questions limited to 8 minutes
- Wrap Up

PRE-READING RECOMMENDED

Buprenorphine Clinical Considerations

REVIEW

ASAM Clinical Considerations: Buprenorphine Treatment of Opioid Use Disorder for Individuals Using High-potency Synthetic Opioids

Melissa B. Weimer, DO, MCR, DFASAM, Andrew A. Herring, MD, Sarah S. Kawasaki, MD, FASAM, Marjorie Meyer, MD, Bethea A. Kleykamp, PhD, and Kelly S. Ramsey, MD, MPH, MA, FACP, DFASAM

Case 1a: Low Dose Outpatient (Kehoe)

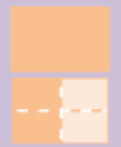
- 27 yo female with 10yr hx severe OUD, hx of necrotizing fasciitis, numerous overdoses, generalized anxiety disorder
- Uses fentanyl IV, intermittent cocaine IV
- Goals: abstinence and transition to XR Buprenorphine
- She is terrified of POW, having experienced it numerous times
- Adamantly opposed to methadone
- Asks to try LDB-OC initiation after a friend's success
- She works part time and is living with her parents

Case 1a continued

- Day 1:
  - You explain LDB-OC initiation process, steps, document shared decision making
  - You review and provider her with patient handout, and send Rx buprenorphine with instructions
  - You administer 0.5 mg buprenorphine/naloxone in clinic which she tolerates well
  - Write Rx 2/0.5 mg and 8/2 mg films with instructions
  - You arrange daily phone check in
  - You reinforce harm reduction strategies and provide safer equipment

"Patient has OUD and would like to start buprenorphine treatment but has had challenges with traditional initiation due to intolerance/withdrawal symptoms which may represent precipitated withdrawal. Patient would like to try low dose buprenorphine initiation as an alternative induction strategy. "

Once you are ready, follow these instructions to start the medication:

	Day 1	Day 2	Day 3	Day 4	Day 5
Total Daily Dose	**0.5mg daily**	**0.5mg twice daily**	**1 mg twice daily**	**2 mg twice daily**	**3 mg twice daily**
# of 2mg films	1/4 Film	1/4 Film x 2	1/2 Film x 2	1 Film x 2	**Return to Clinic** 1 + 1/2 Film x 2
Morning					
Evening					

After returning to clinic, finish the regimen using 8 mg films:

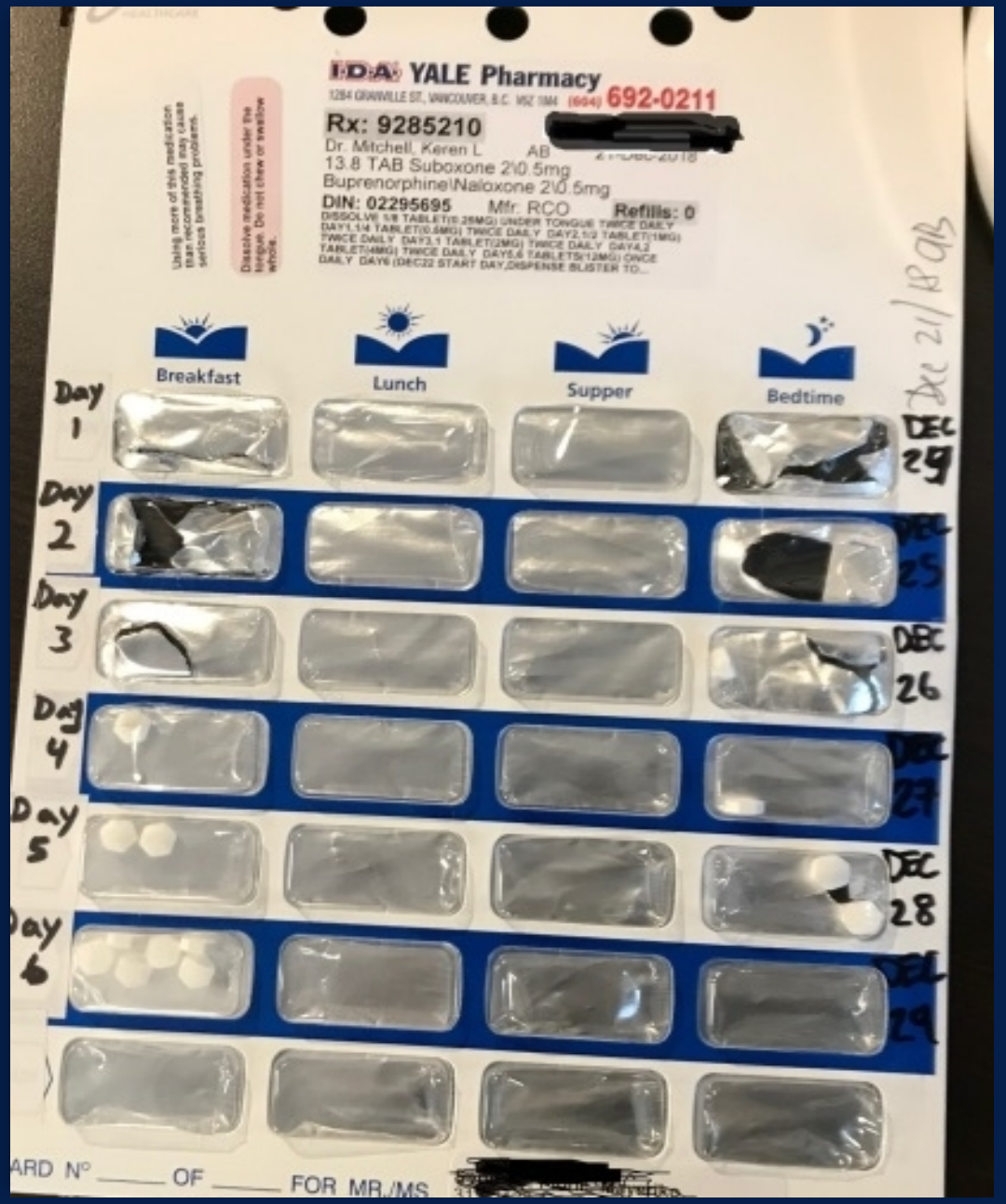
	Day 6	Day 7
Total Daily Dose	**4 mg twice daily**	**8 mg in the AM, 4 mg in the PM**
# of 8mg films	**STOP other opioid use** 1/2 Film x 2	1 Film AM 1/2 Film PM
Morning		
Evening		

Case 1a continued

- Day 2:
  - Did well first night, but experienced POW symptoms after her dose this am

Question: Why would this have happened? Thoughts on next steps?

Blister Packs for LDB-OC

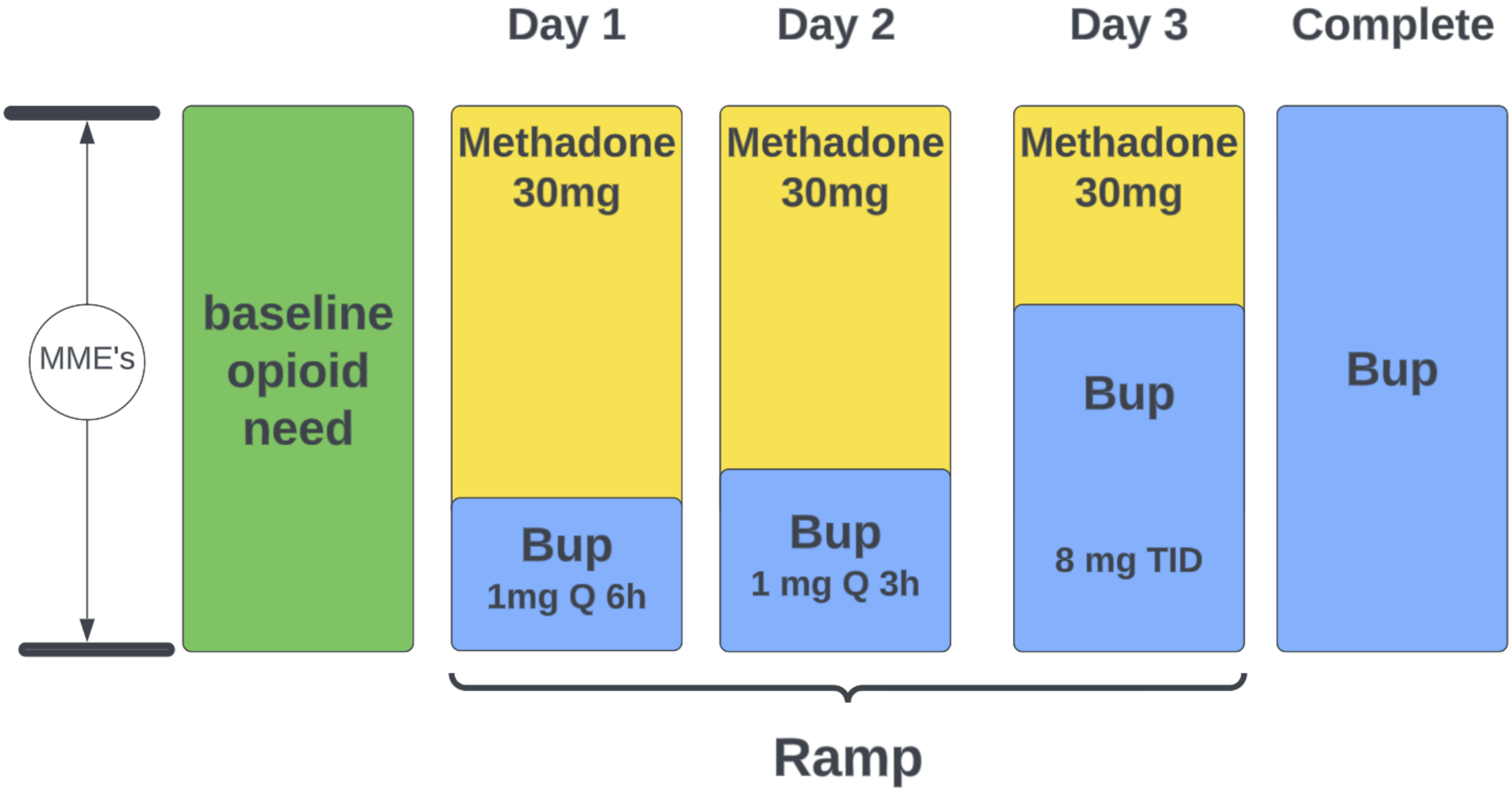


Case 1a continued

- Day 3-5:
  - Restart process, pre-medicate with lorazepam
  - Tolerates well, experiences a little flushing, restlessness day 5, anxious about advancing
  - You slow process and repeat current dose for a couple days, encourage comfort meds

- Day 7-10:
  - Process slowed, continue 8 mg daily x 2 days, increase to 12 mg day 9.
  - Stops fentanyl and advances buprenorphine to 16 mg by day 10
  - Day 10 returns to clinic, and receives Buprenorphine XR 300mg and tolerates well without any withdrawal
  - Supplemental buprenorphine films given
  - Tolerating well, continues with monthly Buprenorphine XR 300mg, engaging, with markedly decreased fentanyl use

Case 1a Option – LDB-OC using DEA exemption



Case 1b: Rapid LDB-OC in Hospital

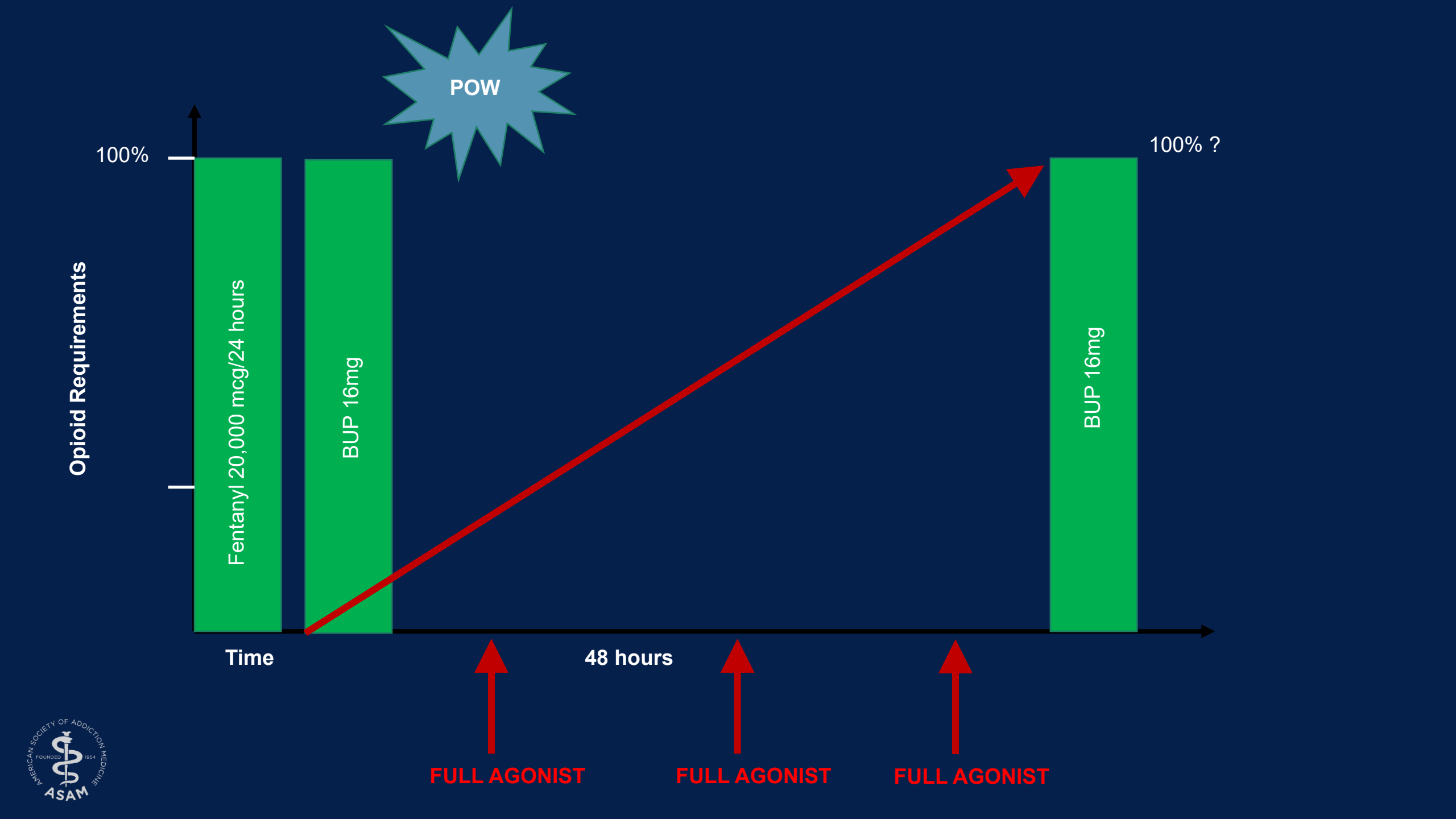
- The maximum plasma concentration
  - 40 minutes-3.5 hours
- The elimination half-life 24-36 hours
- Duration of action is dose-dependent:
  - Low doses 4-8 mg: 4-12 hours
  - Moderate doses 8-12 mg: ~ 24 hours
  - Higher doses >12 mg: 2-3 days

48 hour buprenorphine initiation protocol

☐ **RAPID MICRODOSING INDUCTION** **Start on:** _____ **(date) at** _____ **(hours)**

Doses	buprenorphine dose and interval*	buprenorphine - naloxone strength to use	Quantity per dose
1 to 8	0.5 mg sublingual Q3H x 8 doses	buprenorphine 2 mg - naloxone 0.5 mg	1/4 tab
9 to 16	1 mg sublingual Q3H x 8 doses	buprenorphine 2 mg - naloxone 0.5 mg	1/2 tab
Starting 3 hours after the last dose (i.e. dose number 16), give buprenorphine-naloxone* _____ mg sublingual once daily ***AND*** start buprenorphine-naloxone _____ mg sublingual Q3H PRN withdrawal symptoms ***AND*** discontinue all opioids other than buprenorphine-naloxone.			

* Buprenorphine-naloxone is dosed based on buprenorphine component.


POW
100%
100% ?
Opioid Requirements
Fentanyl 20,000 mcg/24 hours
BUP 16mg
BUP 16mg
Time
48 hours
FULL AGONIST
FULL AGONIST
FULL AGONIST

Case 1b: Pt admitted 3 days later with Fentanyl OD

- Stopped Buprenorphine second day post D/C
- Used with boyfriend
- IV 0.5-1 g illicit fentanyl daily (last use few hours before admit)
- Goal: Abstinence on buprenorphine, agreeable to XR buprenorphine

• **Problem:** Pt should first undergo initiation on 8-24 mg/day transmucosal bup. for a min. 7 days? prior to BUP-XR injection.

Case 1b: Initiation Course

- 48 hour induction directly onto BUP-XR 300mg
- Clinical Opioid Withdrawal Scale (COWS) score maximum 6 throughout induction
  - Unchanged COWS after administration of BUP-XR 300mg
- No indication of precipitated withdrawal at any time
- Discharged home a few hours after administration of BUP-XR 300mg

48 hour buprenorphine initiation protocol

☐ **RAPID MICRODOSING INDUCTION** **Start on:** _____ **(date) at** _____ **(hours)**

Doses	buprenorphine dose and interval*	buprenorphine - naloxone strength to use	Quantity per dose
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* Buprenorphine-naloxone is dosed based on buprenorphine component.

The American Journal on Addictions, 29: 531–535, 2020

ISSN: 1055-0496 print / 1521-0391 online
DOI: 10.1111/ajad.13050

A Case Report: Rapid Micro-Induction of Buprenorphine/Naloxone to Administer Buprenorphine Extended-Release in an Adolescent With Severe Opioid Use Disorder

Pouya Azar, MD, FRCPC,[1] James S.H. Wong, BSc,[2] Sara Jassemi, MD, FRCPC,[3] Eva Moore, MD, MSPH,[3] Dzung X. Vo, MD, FAAP, FSAHM,[3] Mohammadali Nikoo, MD,[2] Samantha Young, MD, FRCPC[4,5]

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[5]Department of Medicine, Interdepartmental Division of Addiction Medicine, St. Paul's Hospital, Vancouver, British Columbia, Canada

Case 2 - Weimer

- 32 yo female with severe OUD, uses fentanyl IV, intermittent cocaine use, history of recent opioid overdose
- Presents with opioid withdrawal (COWS 8), large abscess on her left forearm, severe pain in the arm.
- She would like buprenorphine treatment but has had POW before and does not feel ready to start buprenorphine.
- She is uninsured and unhoused

Case 2 – HDB option

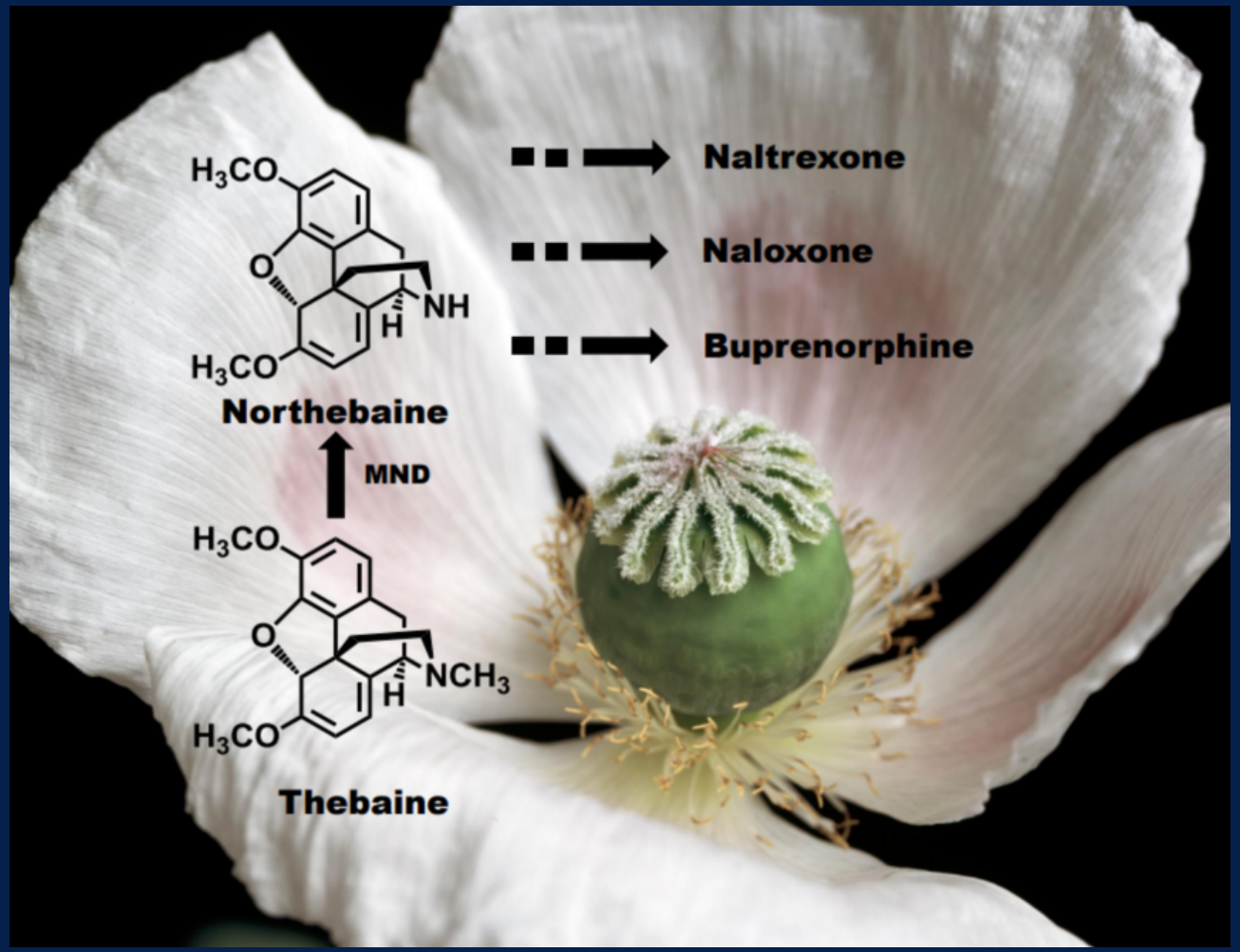
- Stabilize patient with short acting opioids
  - Oxycodone IR 20-30mg every 3-4 hours scheduled
  - Clonidine, hydroxyzine, acetaminophen, ibuprofen, trazodone
- Stop opioids at 10pm on 2nd day of hospitalization
- At 9am on 3rd day, give her 24mg of buprenorphine at once
  - Patient tolerates well, pain is improved
- At 3pm, give patient 300mg of XR buprenorphine (Sublocade®) or 128mg XR buprenorphine (Brixadi®)*

**alternative option – give 32mg of XR Buprenorphine Weekly Injection (Brixadi®)*

Case 2: Other Options, HDB protocols

- Wait 36-48 hours from last use → give >16mg at one time when COWS >8
- Wait 6-12 hours from last use → give >24mg at one time when COWS >8
- Overdose -> naloxone -> give >16mg at one time
- Give more buprenorphine if/when COWS >12
- Give weekly XR buprenorphine when COWS >8

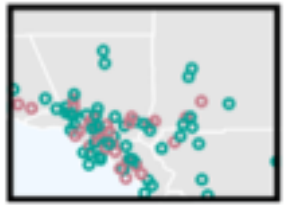
Case 3: Precipitated withdrawal

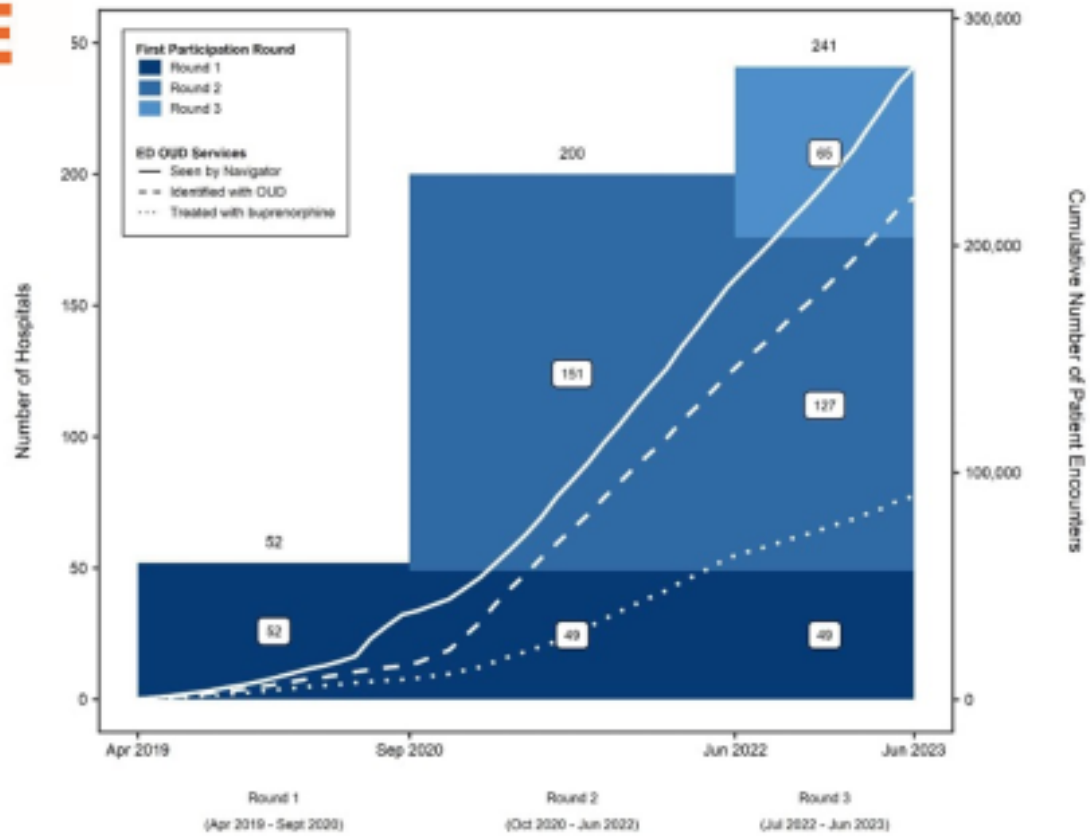


CA BRIDGE

Bay Area

Greater Los Angeles





Goal: 24-7 access to high quality treatment of substance use disorders in all California hospitals by 2025.

Hospitals implementing the CA Bridge program are serving tens of thousands of patients.

208,596

patients seen for substance use disorders

156,599

patients identified with opioid use disorders

71,445

patients provided with buprenorphine

Precipitated withdrawal was rare ≤1%
9 out of 1,200

March 30, 2023

Incidence of Precipitated Withdrawal During a Multisite Emergency Department–Initiated Buprenorphine Clinical Trial in the Era of Fentanyl

Gail D'Onofrio, MD, MS[1,2,3]; Kathryn F. Hawk, MD, MHS[1,3]; Jeanmarie Perrone, MD[4]; Sharon L. Walsh, PhD[5]; Michelle R. Lofwall, MD[5]; David A. Fiellin, MD[1,2,3]; Andrew Herring, MD[6]

Precipitated withdrawal was rare ≤2%

JAMA Network | Open™

Research Letter | Substance Use and Addiction

High-Dose Buprenorphine Initiation in the Emergency Department Among Patients Using Fentanyl and Other Opioids

Hannah Snyder, MD; Brendon Chau, MPH; Mariah M. Kalmin, PhD; Melissa Speener, MPH; Arianna Campbell, PA; Aimee Moulin, MD, MAS; Andrew A. Herring, MD

Let's start Bup!

Smokes 30
fentanyl tablets
per day
3 years

Snorts 1/2 gm
black tar
6 months

Denae Reed, PA-C

Opioid Exposure

"Neuroadaptive Hurdle"

Smokes 30 fentanyl tablets 3 years

→ Profound Desensitization

→ Small changes cause large disruptions

Traumatized
Unsupported

Snorts 1/2 gm black tar per day 6 moths

→ Moderate Desensitization

→ Intact resilience supported

Withdrawal Assessment is a snap shot only

COWS 8

Withdrawal intolerant

Slower less predictable Treatment response

Opioid sensitive

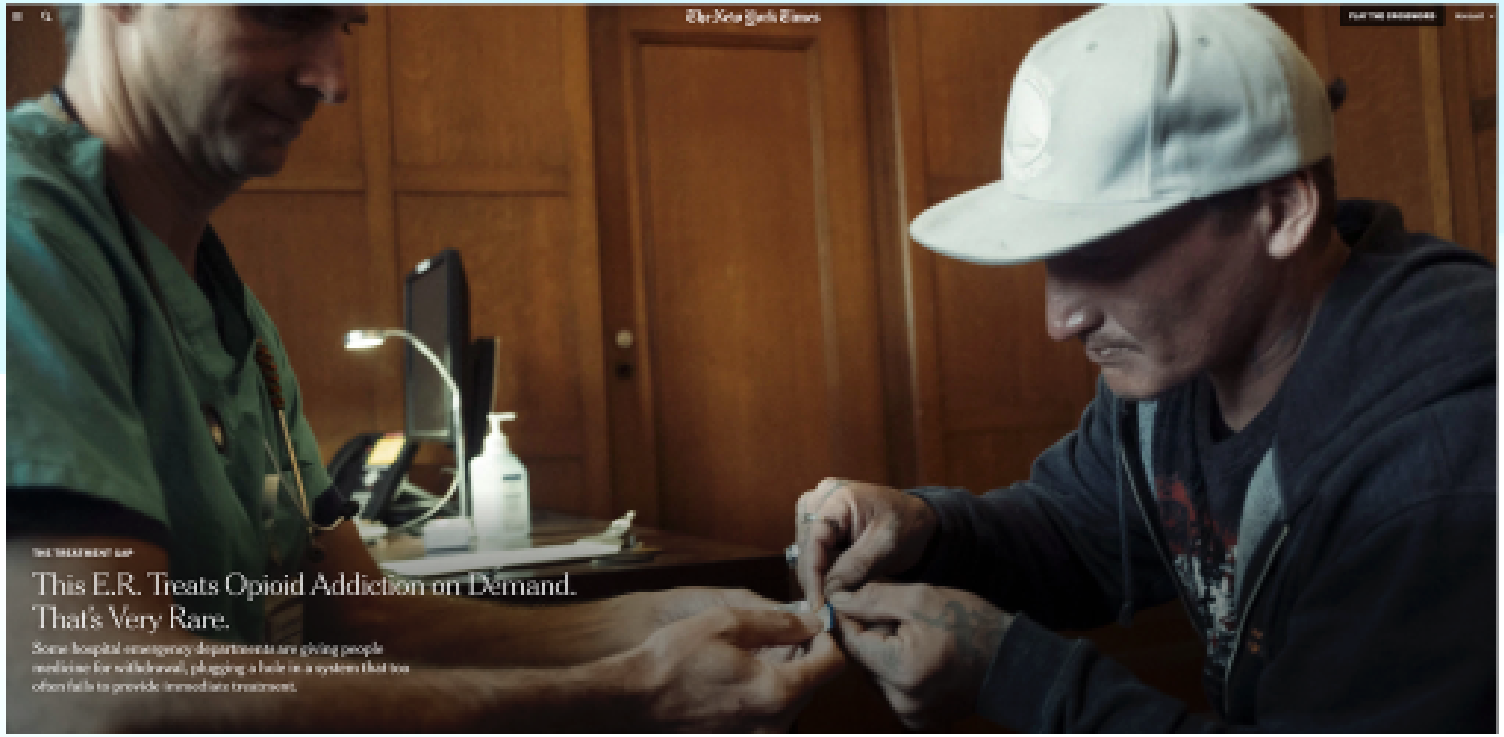
Withdrawal tolerant

Rapid response

Predictable

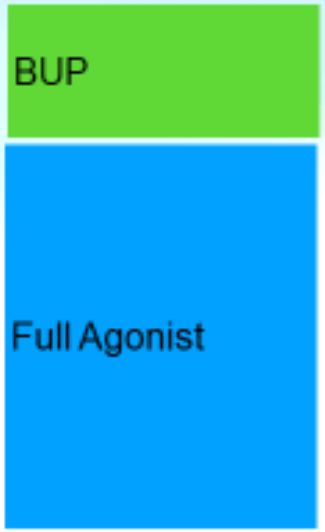
16mg SL BUP

Worsening Sweats
Feels bad
Wants to vomit

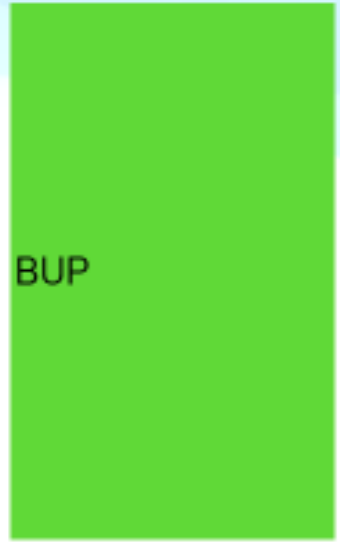


Profound opioid resistance / tolerance

High-dose is the only Option



"Microdose"



"Macrodose"

Caulfield, Mackenzie Duncan Gregory, et al. "Transitioning a patient from injectable opioid agonist therapy to sublingual buprenorphine/naloxone for the treatment of opioid use disorder using a microdosing approach." *BMJ Case Reports CP* 13.3 (2020): e233715.

Two part theory of Precipitated Withdrawal

COWS

Receptor level disruption (Acute)	Opioid deficit (Chronic exposure/physical dependence)
Rate of agonist displacement by Bup	Total mu agonist

Buprenorphine Precipitated Withdrawal

Target	Treatment
Opioid deficit	Full agonist opioids Buprenorphine
Opioid resistance	Ketamine
Symptom Feedback loops	Adjuncts: Alpha-2 agonists, benzodiazepines, anticonvulsants, antipsychotics, loperamide, D2/D3 agonists

Buprenorphine Precipitated Withdrawal

Early

1. Act quickly
2. Calm & confident
3. Benzo PO
4. High-dose Bup (16mg)

Clonidine
D2/3 agonist
Gabapentinoid

Acute

1. Monitored bed
2. Bup- 64mg SL
3. Ketamine 20 IV q 30
4. Fentanyl 200mcg Q 10 min

Residual

1. Pramipexole 0.5mg
2. Clonidine 0.3mg
3. Benzo (loraz 1mg IV)
4. Pregabalin 100-300mg po

Olanzepine 10mg IM

goal

Month-long Bup

Naloxone precipitated Withdrawal

Smokes 30 fentanyl tablets per day
3 years

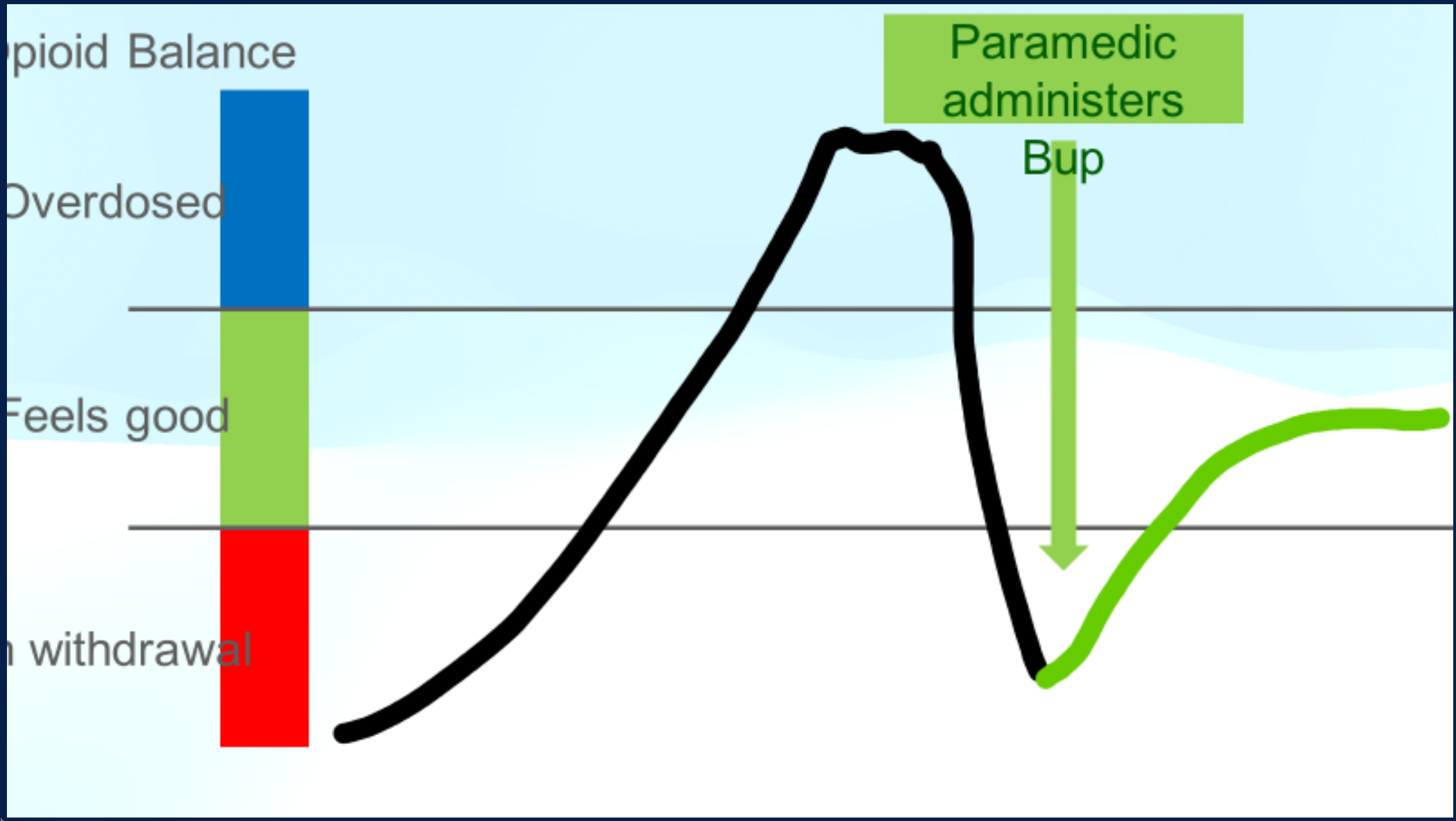
Overdose

Naloxone Reversal

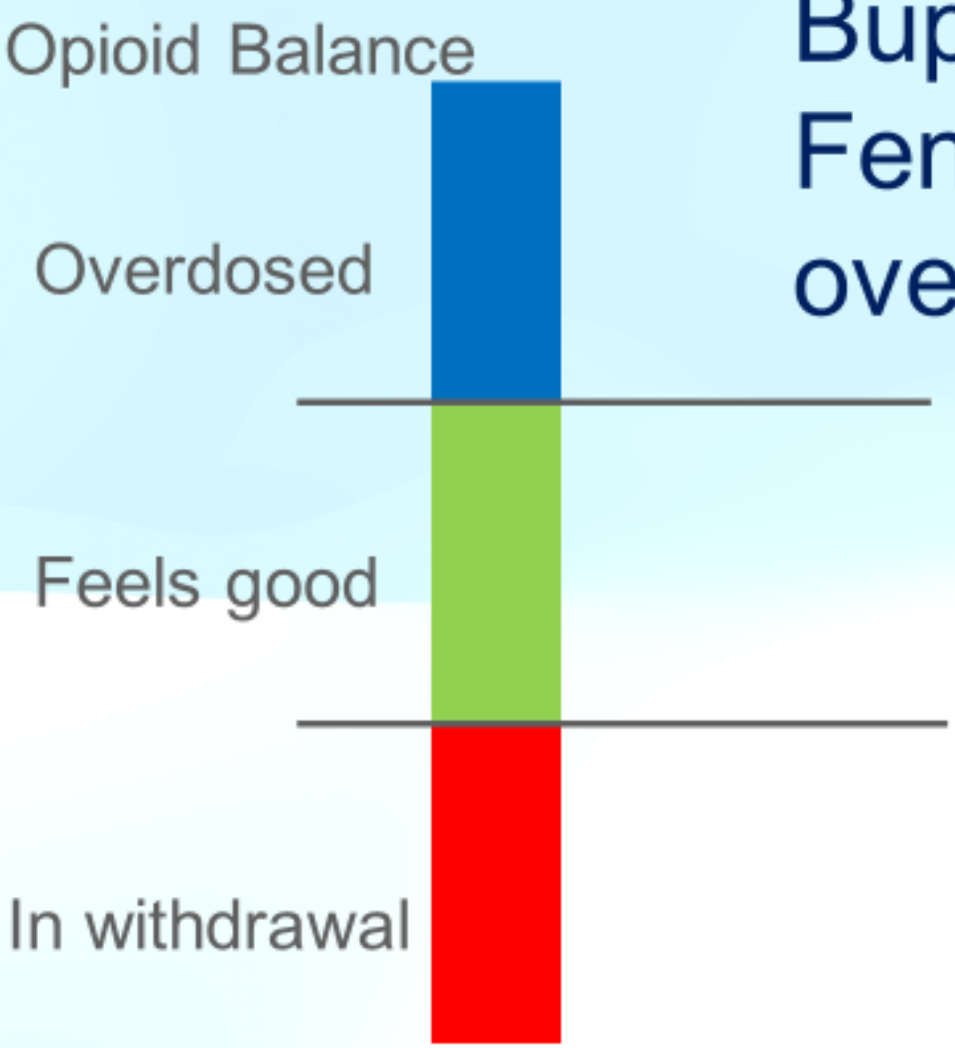
COWS 13

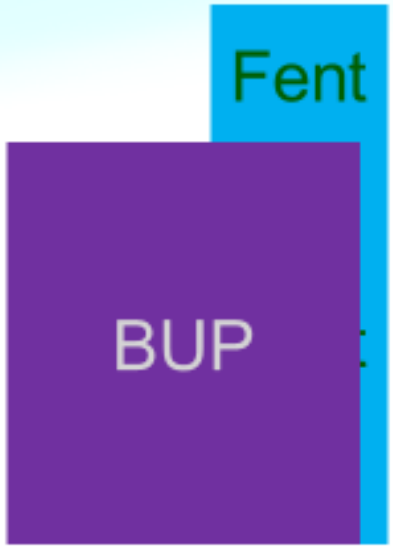
16mg SL Bup

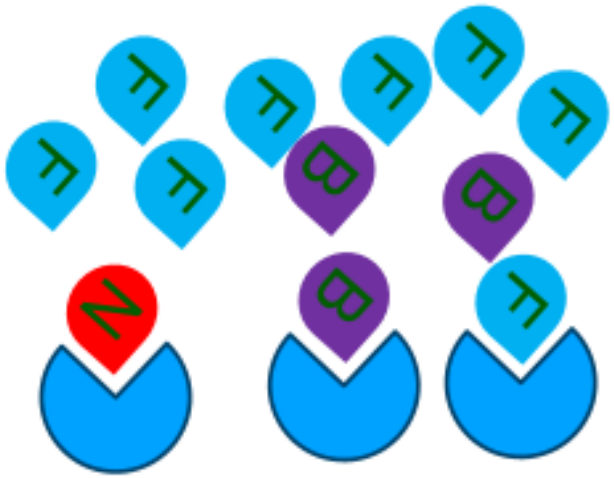
Month Long Injectable Bup


pioid Balance
Overdosed
Feels good
withdrawal
Paramedic administers
Bup

Buprenorphine and Fentanyl are Additive after overdose








YOU CAN'T
STOP THE WAVES
BUT YOU CAN
LEARN TO SURF

Summary of Buprenorphine Initiation Approaches

TABLE 2. Clinical Decision Support for Buprenorphine Initiation Techniques Based on the Clinical Setting

	Fastest	Slowest	
Initiation Strategy*	**HDB†**	**Standard‡**	**LDB-OC§**
Possible advantages	-Quick stabilization -Bridge access barriers to ongoing buprenorphine	-Most common and well-described technique	-Opioid abstinence not initially required
Need for opioid withdrawal?	Yes	Yes	No
Premedicate with adjuvant medications?‖	Consider	Yes	Yes
Initial starting dose¶ (buprenorphine SL formulation)	8–16+ mg	2–8 mg	0.25 mg–1 mg
Duration of initiation until stabilization	≤2 h	1–3 days	3–10 d (may be longer in certain situations)
Need for opioid continuation	No	No	Yes
Full agonist opioid continuation dose	None	None	Examples: Methadone 30 mg PO daily or Hydromorphone 4 mg PO every 4 hr or Self-directed illicit/nonprescribed opioid use
Care coordination required	Moderate	Moderate	High

TABLE 3. Considerations for Buprenorphine Initiation Approach Based on High-Tolerance and High-Potency Synthetic Opioid Exposure—Clinical Setting and Opioid Withdrawal

Situation	Outpatient	Emergency Department	Residential/Hospital Setting*
Opioid withdrawal, COWS ≥8 with 1 objective sign of opioid withdrawal	Standard initiation or HDB	Standard initiation or HDB	Standard initiation or HDB
Opioid withdrawal, COWS <8	Standard initiation or LDB-OC†	Standard initiation or LDB-OC†	Standard initiation or LDB-OC†
Pain + opioid withdrawal, COWS <8	Standard initiation or prescribed FAO for pain with LDB-OC	Standard initiation or prescribed FAO for pain with LBD-OC	Administered FAO + LDB-OC

Final Takeaways/Summary

- Individualize your approach
- Each approach has risks and benefits that should be discussed with patients
- Consider the safety of opioid continuation in patients without close follow up
- Consider the HDB approach a way to quickly stabilize individuals at very high risk

FREE RESOURCES

CA Bridge

ASAM Buprenorphine Clinical Consideration Document

ASAM Advanced Buprenorphine Education

Low Dose Bup 1 hr Education with Resources (fee)

References

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XR BUP Anesthesia -- MGH protocol

Massachusetts General Hospital Substance Use Disorder Bridge Clinic

Optional Lidocaine injection / local anesthetic for XR buprenorphine injections

Purpose:
Some patients find topical ice is insufficient to manage the procedural pain from XR buprenorphine injections, which has led some patients to fear initiating XR buprenorphine or to discontinue injections despite preference for this formulation

Procedure:

1) Identify site for XR buprenorphine in abdominal quadrant
2) Apply ice to site while preparing lidocaine for injection into subcutaneous tissue
3) Prepare 1% Lidocaine, without epinephrine:
    - Wipe top of lidocaine bottle with alcohol pad
    - Draw up 2cc Lidocaine with large bore needle in a 3 or 5 cc syringe
    - Change needle to 1 inch, 25 or 27 gauge
4) Clean abdominal site with alcohol swab
5) Tent skin and Inject 2 cc Lidocaine at ~75 degree angle, releasing lidocaine into tissue while pulling back
6) Apply 2x2 gauze to area and massage gently in circular motion to allow lidocaine to diffuse the area
7) Keep 2x2 resting on skin and reapply ice pack

*Wait at least 3 minutes before injecting XR buprenorphine

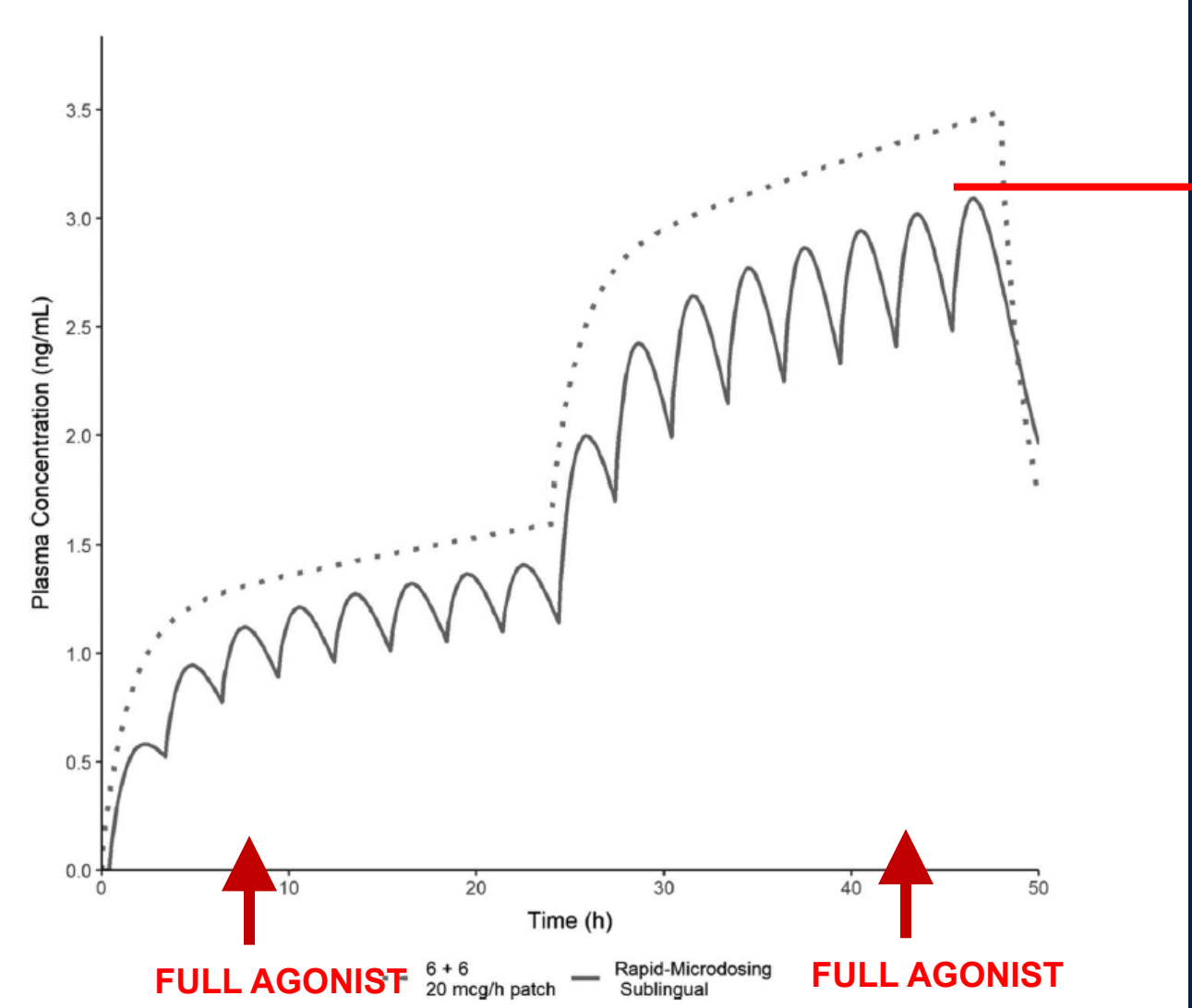
XR Buprenorphine injection:

1) Clean abdominal site with alcohol wipe where lidocaine was injected, identifying the lidocaine puncture site
2) Tent skin and inject XR Buprenorphine into the same puncture site and track of lidocaine
3) Apply band-aid
4) Have patient lay for recommended time per manufacturer

Kehoe, LG, Gray, J, MGH SUD Bridge Clinic

Rapid out-pt low dose bup. initiation strategy.

Transdermal buprenorphine induction



SL BUPRENORPHINE MAINTENANCE

Dr. Anil Maharaj

MEDICATIONS:

First 48 hours:

Date: _____ Time: _____

Apply 6 (six) TD-BUP 20mcg/hr patches (total dose 120mcg/hr). Leave on for 24hrs

Date: _____ Time: _____

Apply an additional 6 (six) TD-BUP 20mcg/hr patches for a total of 12 (twelve) patches (total dose 240mcg/hr). Leave on for 24hrs.

First 48 hours PRN opioids for pain or opioid withdrawal symptoms:
(Hold if sedated, respiratory rate below 12, or SpO_2 below 92%)

☐ HYDROmorphone _____ mg PO Q3H PRN **OR** HYDROmorphone _____ mg SUBCUT Q3H PRN

Post 48 hours:

Date: _____ Time: _____

Remove **all** 12 (twelve) TD-BUP patches.
Upon initiation of SL-BUP tablets, **discontinue all opioids** other than SL-BUP (unless otherwise directed below)

Scheduled:

☐ SL-BUP 8mg/2mg 1 tablet SL once daily

OR

☐ SL-BUP _____ mg 1 tablet SL once daily

PRN:

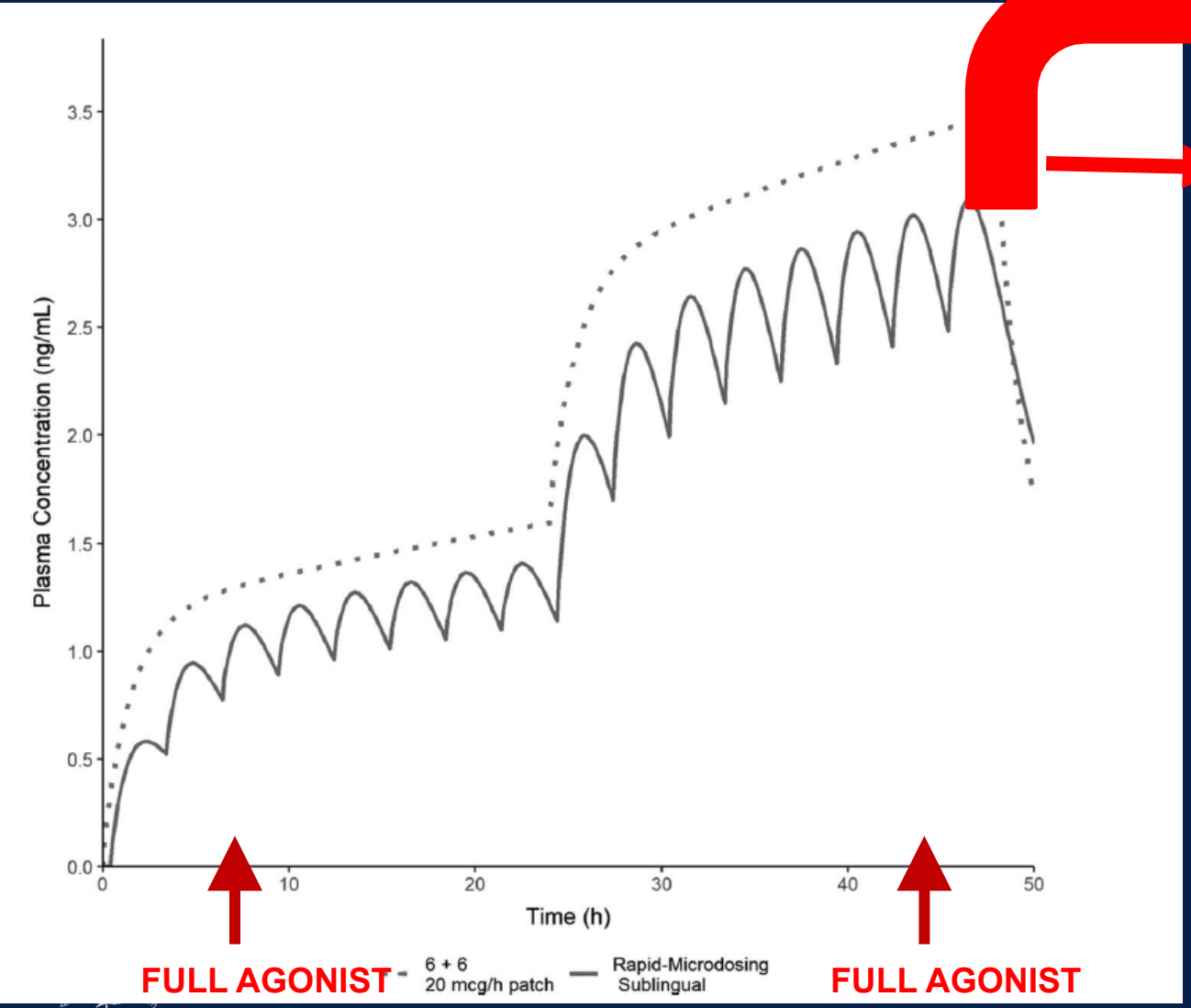
☐ SL-BUP 2mg/0.5mg 1 tablet SL Q3H PRN (no 24 hour max dose)

OR

☐ SL-BUP _____ mg 1 tablet q_____h PRN (no 24 hour max dose)

ADDITIONAL ORDERS: (if continuing orders such as methadone, MUST note below to continue)

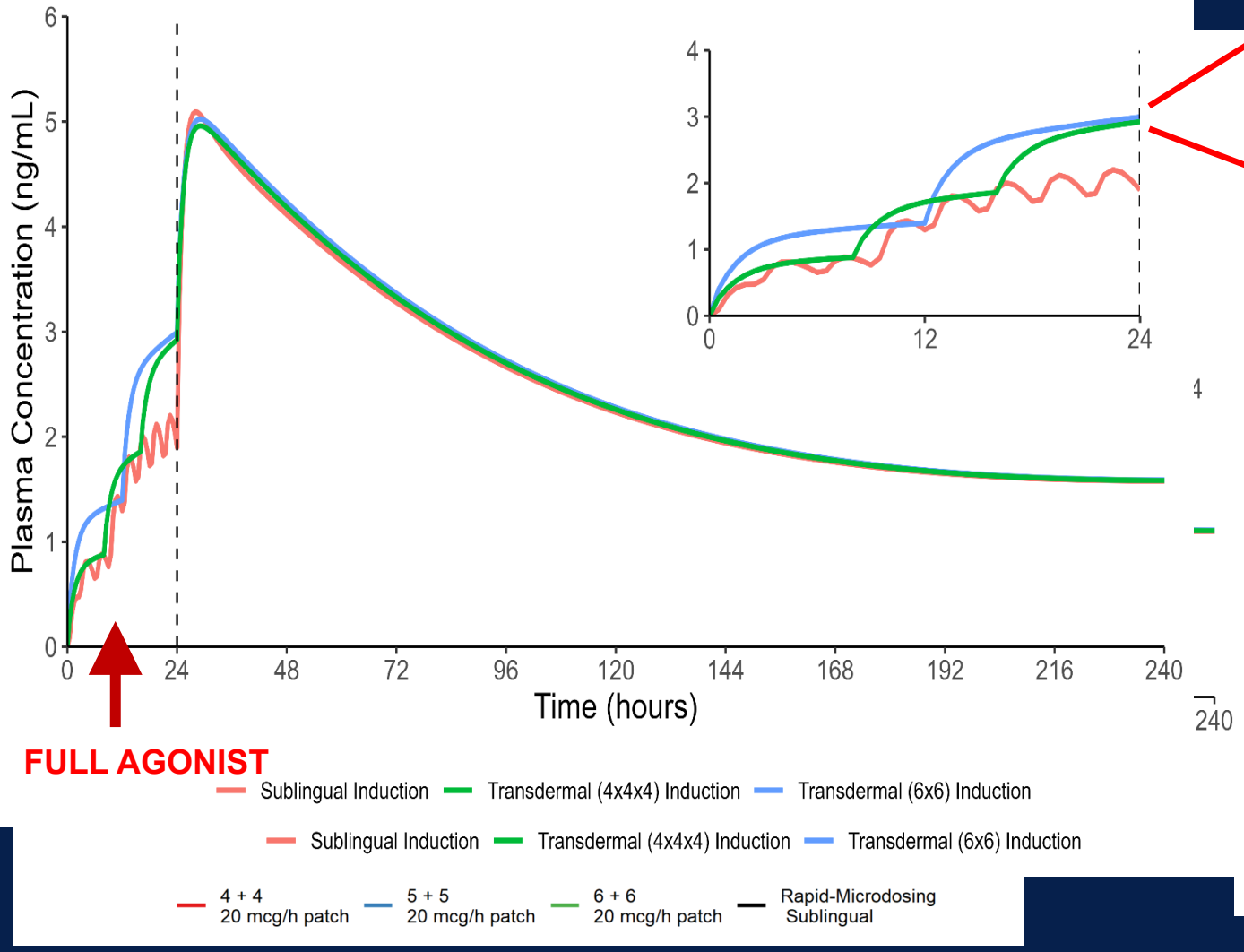
Transdermal buprenorphine induction



SL BUPRENORPHINE MAINTENANCE → BUP-XR MAINTENANCE

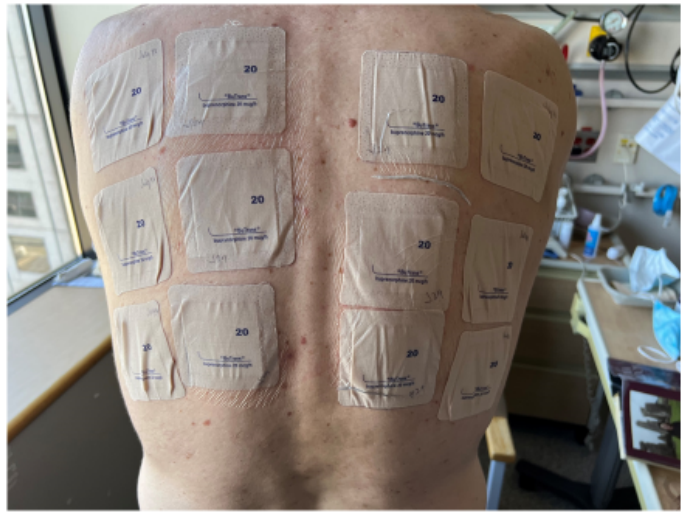
Dr. Anil Maharaj

CLINICAL PROBLEM : NEED FOR OUT PT AND PRACTICAL BUP INDUCTION PROTOCOL



SL BUPRENORPHINE MAINTENANCE

BUP-XR MAINTENANCE



CASE REPORT

48-hour Induction of Transdermal Buprenorphine to Extended-release Buprenorphine

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Nickie Mathew, MD, MSc, ABPN, FRCPC, ABPM, Martha J. Ignaszewski, MD, FRCPC,
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Adedayo Ajidahun, PhD, Sahithi Thotakura, PharmD, Marianne Harris, MD, CCFP,
Rolando Barrios, MD, FRCPC, Julio S.G. Montaner, MD, FRCPC, FRSC, and Anil R. Maharaj, PhD

DIRECT BUP-XR INDUCTION WITHOUT WITHDRAWAL

- What is the risk of precipitated opioid withdrawal?
- Does BUP-XR rate of rise in buprenorphine serum levels equate to a low dose induction?

ANY COWS

DIRECT BUP-XR INDUCTION WITHOUT WITHDRAWAL
CASE: Unregulated Fentanyl Using Patient

PRE-INDUCTOIN COWS 3

PRE-INDUCTOIN FULL AGONIST

- 30mg methadone
- 16mg PO HM
- 32mg SQ HM

300mg BUP-XR injection
(SQ infiltration of 2% lidocaine)

1 hour post administration: COWS score 1

2 hours post administration: COWS score 7

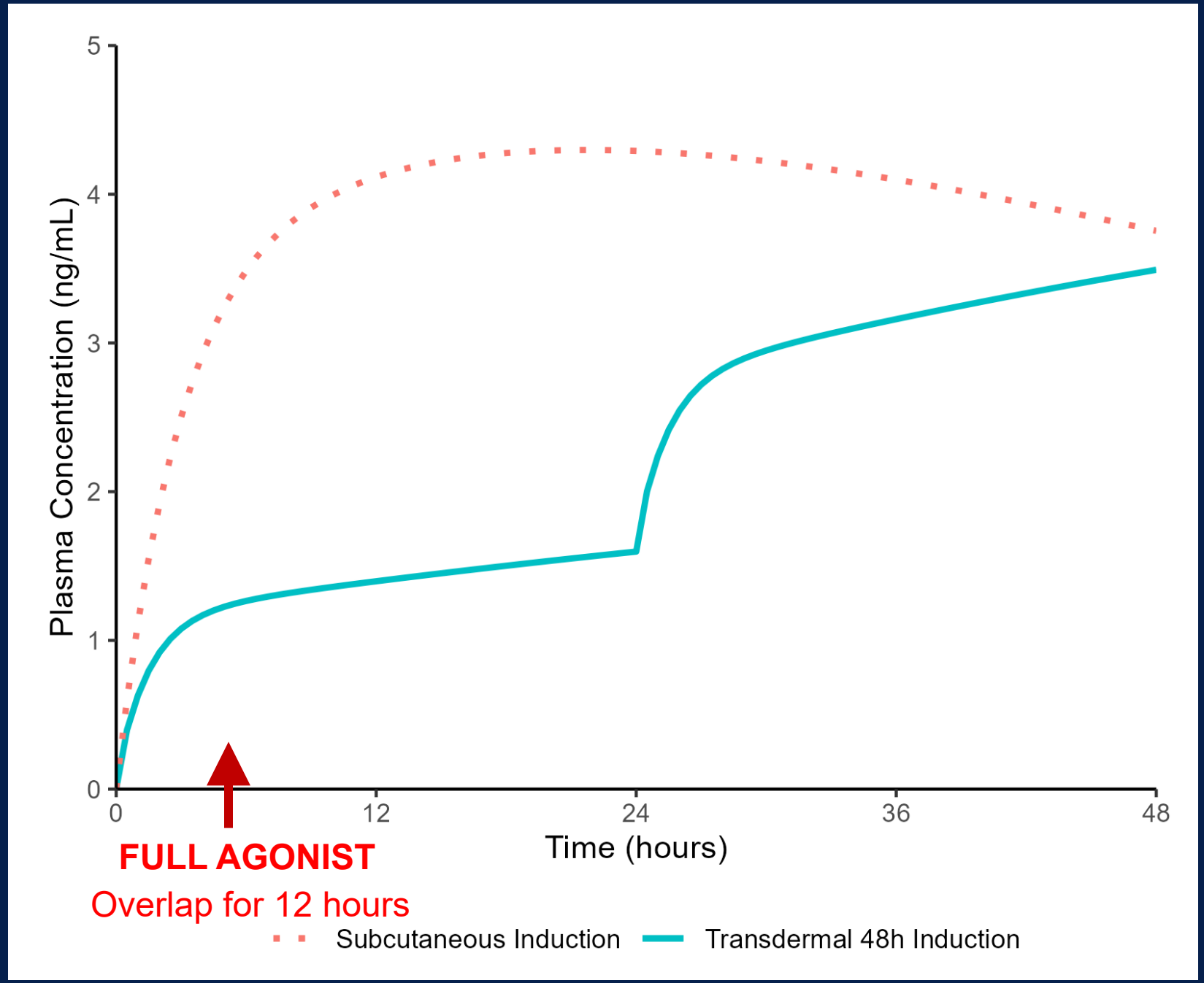
- 32mg SQ HM

3 hours post administration: COWS score 4

- 64mg PO HM
- Next 3 hours: 128mg PO HM

Next day: COWS score 1

Required no further opioid administration during hospitalization;
remained abstinent from unregulated fentanyl


Plasma Concentration (ng/mL)
5
4
3
2
1
0
0
12
24
36
48
Time (hours)
FULL AGONIST
Overlap for 12 hours
Subcutaneous Induction
Transdermal 48h Induction