Innovative Strategies for Medication Initiation in Opioid Use Disorder

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Melissa Weimer, DO, MCR, DFASAM
Laura Kehoe, MD, MPH, FASAM

ASAM Annual Conference 2026

Disclosure Information

- Presenter 1: Pouya Azar, MD, FRCPC, DABAM
  - Receives honoraria for presentations organized by Indivior.
- Presenter 2: Andrew Herring, MD
  - No Disclosures.
- Presenter 3: Melissa Weimer, DO, MCR, DFASAM
  - No Disclosures.
- Presenter 4: Laura Kehoe, MD, MPH, FASAM
  - Received honoraria for advisory board, presentation organized by Indivior

Learning Objectives

- Describe the unique pharmacology of high-potency synthetic opioids and their implications for initiating medications for opioid use disorder.
- Summarize the current evidence base supporting novel methadone, buprenorphine, and extended-release buprenorphine, initiation strategies.
- Discuss the pharmacologic rationale, clinical applications, and relative risks and benefits of each initiation approach.

Introduction

JAMA Network Open

Original Investigation | Substance Use and Addiction

Hospital-Based Methadone and Buprenorphine Initiation Practices by Addiction Consult Services

Shawn M. Cohen, MD; Elana Straus, BA; David A. Fiellin, MD; Jamie L. Pomeranz, PhD; Joji Suzuki, MD; Jeanette M. Tetrault, MD; Melissa B. Weimer, DO, MCR; E. Jennifer Edelman, MD, MHS; Paul J. Joudrey, MD

ORIGINAL RESEARCH

Opioid Agonist Therapy for Fentanyl-Related Opioid Use Disorder: A Systematic Review

Austin Daniel Solak, MD(c), MHI, BSc, Jack Boynton, MD(c), MSc, Jacob Riches, MD(c), MSc, Allison Souter, MD(c), BScH, Kathryn Dong, MD, MSc, FRCPC, DRCPSC, Maryam Zaree, MD, CCFP-EM, Nicolas Woods, MScFN, MSc, Alla Iansavitchene, MLIS, and Christopher Byrne, MD, MSc

Current Addiction Reports (2025) 12:44
https://doi.org/10.1007/s40429-025-00655-6

Methadone for Opioid Use Disorder in the Fentanyl Era: Navigating Challenges and Evolving Strategies- a Narrative Review

Eugene Osagie[1,2] · Jacob Horton[1,6] · David Lawrence[3,4] · Gretchen Hermes[1,5,6] · Gabriela Garcia-Vassallo[1,2]

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

Cohen SM, Straus E, Fiellin DA, et al. Hospital-based methadone and buprenorphine initiation practices by addiction consult services. *JAMA Netw Open.* 2025;8(8):e2526077. doi:10.1001/jamanetworkopen.2025.26077

Weimer MB, Herring AA, Kawasaki SS, Meyer M, Kleykamp BA, Ramsey KS. ASAM clinical considerations: buprenorphine treatment of opioid use disorder for individuals using high-potency synthetic opioids. *J Addict Med.* 2023;17(6):632-639. doi:10.1097/ADM.0000000000001202

Osagie E, Horton J, Lawrence D, Hermes G, Garcia-Vassallo G. Methadone for opioid use disorder in the fentanyl era: navigating challenges and evolving strategies—a narrative review. *Curr Addict Rep.* 2025;12(1):44.

Solak AD, Boynton J, Riches J, et al. Opioid agonist therapy for fentanyl-related opioid use disorder: a systematic review. *J Addict Med.* 2024. doi:10.1097/ADM.0000000000001379

Methadone Initiations

Methadone Pharmacology

It has a high oral bioavailability and a prolonged duration of action, making it suitable for both chronic pain management and opioid dependence treatment.

Mechanism of Action

- Synthetic opioid
- Primarily acts on the mu-opioid receptors
- NMDA blockade
- SNRI-like reuptake inhibition

Pharmacokinetics

- Long and variable half-life, 8 to 59 hours due to its extensive tissue distribution and slow metabolism.
- It is primarily metabolized in the liver by cytochrome P450 enzymes, particularly CYP3A4 and CYP2B6.

Paladin Labs Inc. Metadol-D (methadone hydrochloride) product monograph. Paladin Labs Inc; 2022.

Slow-Release Oral Morphine (SROM) Pharmacology

SROM is administered via once-daily oral doses

SROM is released over 24 hours

- Because of the sustained-release properties of SROM, dosage increases should generally be separated by at least 24 hours.

Peak plasma levels are achieved within 8.5 to 10 hours

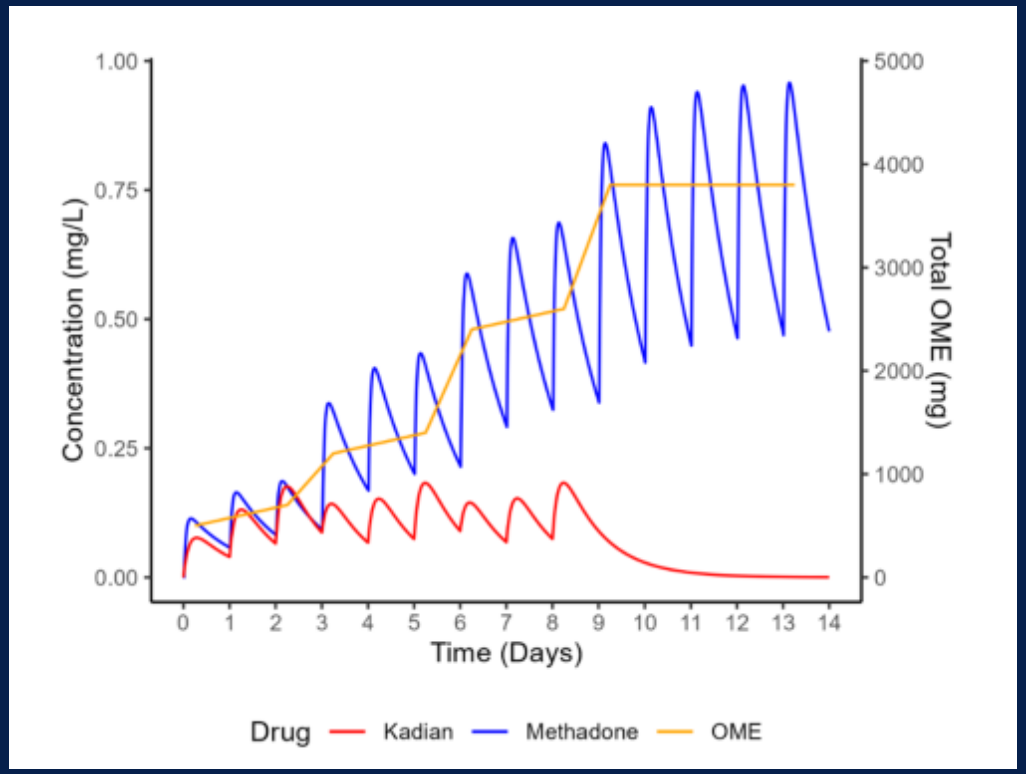
Elimination half-life

- The terminal elimination half-life of morphine following a single dose of SROM administration is approximately 11 to 13 hours. However, this is primarily due to the delayed absorption of the pellets.
- Once absorption is complete, the plasma elimination half-life is the same as immediate-release morphine (2 to 4 hours).

META:PHI. Methadone as opioid agonist therapy: guidance for prescribers. META:PHI; 2025. Accessed March 11, 2026. https://www.metaphi.ca/wp-content/uploads/MethadoneGuidance.pdf

Cheema K, Kahan M, Rodgers J, Smoke A, Turner S, Wyman J, Zhang M. Recommendations for use of slow-release oral morphine as opioid agonist therapy. META:PHI; 2023.

Rapid Methadone Titration with Slow-Release Oral Morphine (SROM) Bridging



Day	1	2	3	4	5	6	7	8	9	10-14
Methadone (mg)	40	40	40	90	90	90	140	140	140	190
SROM (mg)	300	400	500	300	400	500	300	400	500	0

Rapid Methadone Titration with SROM Bridging - Case

Adult male presenting for re-initiation of OAT at community clinic

- Severe opioid use disorder
- Unhoused
- Psychiatric history – schizophrenia
- Declined buprenorphine, past methadone patient

Substance Use

- Fentanyl: ~1 g daily smoked
- Solitary use pattern
- Cocaine use history with stimulant-induced psychosis
- UDS + for amphetamines, methamphetamines, benzos, hydromorphone, fentanyl

Goal: restart Methadone, abstinence.

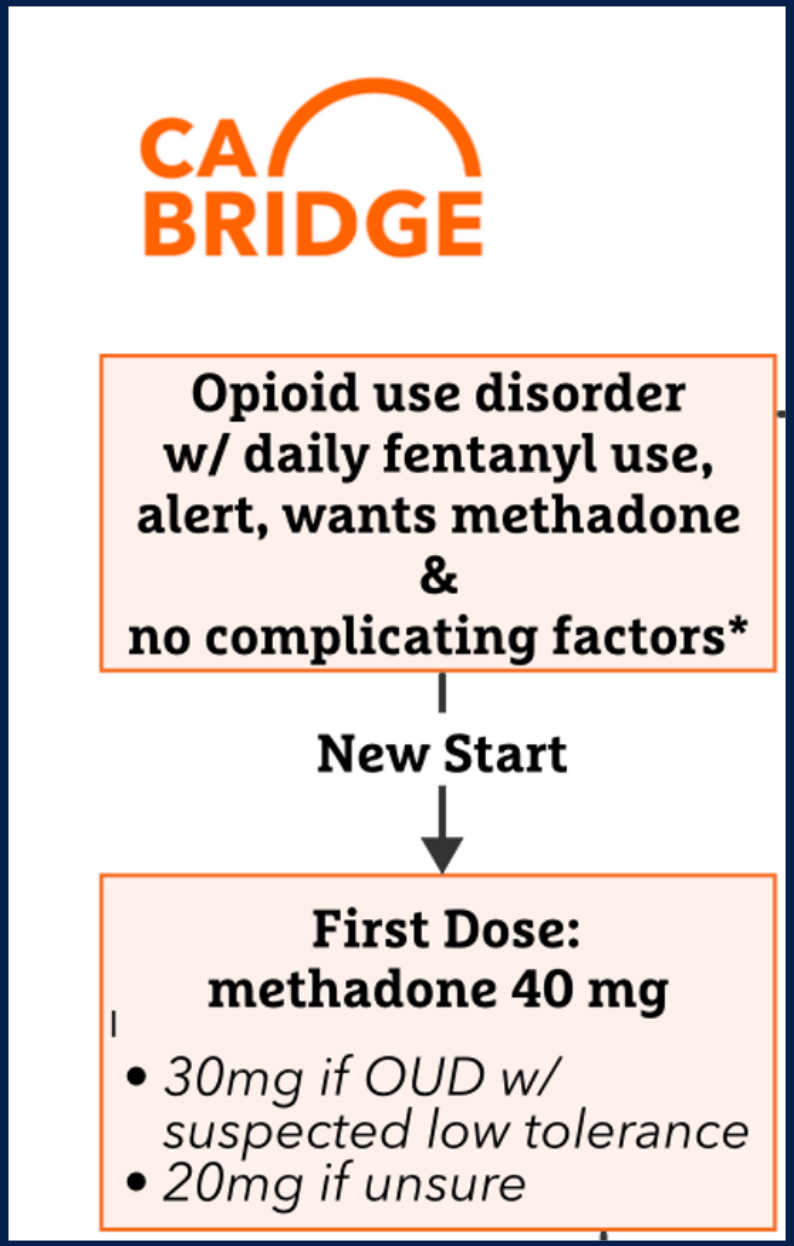
Rapid Methadone Titration with SROM Bridging - Case

Day	Methadone	SROM	UDS	Cravings / Withdrawal	Fentanyl Use
Day 1	50 mg PO daily	300 mg PO daily		Active withdrawal; significant cravings	Ongoing daily use (prior baseline ~1 g/day)
Day 2	50 mg PO daily	400 mg PO daily		Withdrawal ongoing	Ongoing daily use
Day 3	50 mg PO daily	500 mg PO daily		Withdrawal improving	Ongoing daily use
Day 5	100 mg PO daily	300 mg PO daily			
Day 6	100 mg PO daily	400 mg PO daily			
Day 7	100 mg PO daily	500 mg PO daily			

Rapid Methadone Titration with SROM Bridging - Case

Day	Methadone	SROM	UDS	Cravings / Withdrawal	Fentanyl Use
Day 8	150 mg PO daily	300 mg PO daily			
Day 9	150 mg PO daily	400 mg PO daily			
Day 10	150 mg PO daily	500 mg PO daily			
Day 11	200 mg PO daily	Discontinued		Cravings reduced; no withdrawal	Reports 2 days abstinent
Day 13	200 mg PO daily	Discontinued		Cravings largely resolved; mild residual withdrawal	1 point previous day and 1 point morning of visit
Day 15	200 mg PO daily	Discontinued		No withdrawal; denies cravings	~0.5 point related to stress
Day 18	240 mg PO daily	Discontinued		Withdrawal absent; mild cravings persist	~0.25 point most days
Day 21	240 mg PO daily	Discontinued		Not documented	Ongoing intermittent use
Day 22	240 mg PO daily	Discontinued	NEG (+ EDDP)	Not documented	No reported use
Day 46	240 mg PO daily	Discontinued	NEG (+ EDDP)	No cravings/No withdrawal	No reported use

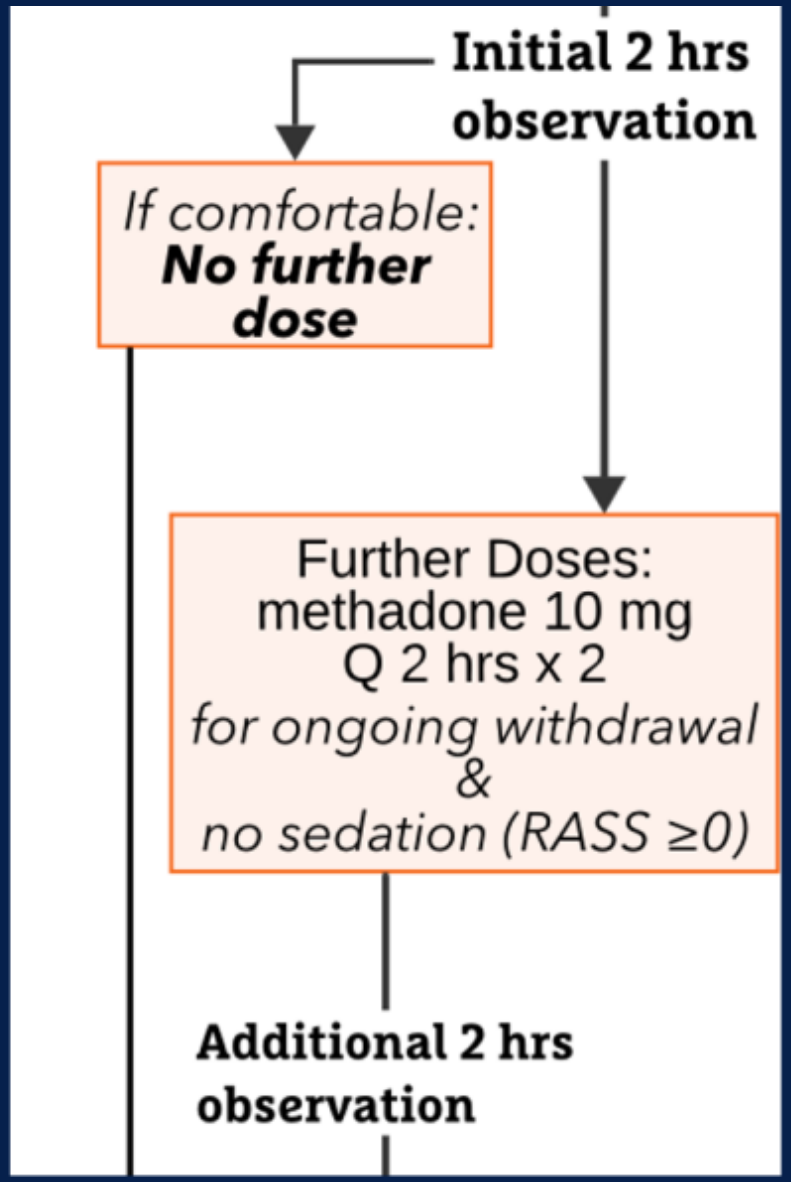
Rapid Methadone Titration for suspected high tolerance



- ☑ Fentanyl user
- ☑ In withdrawal
- ☑ In the ED

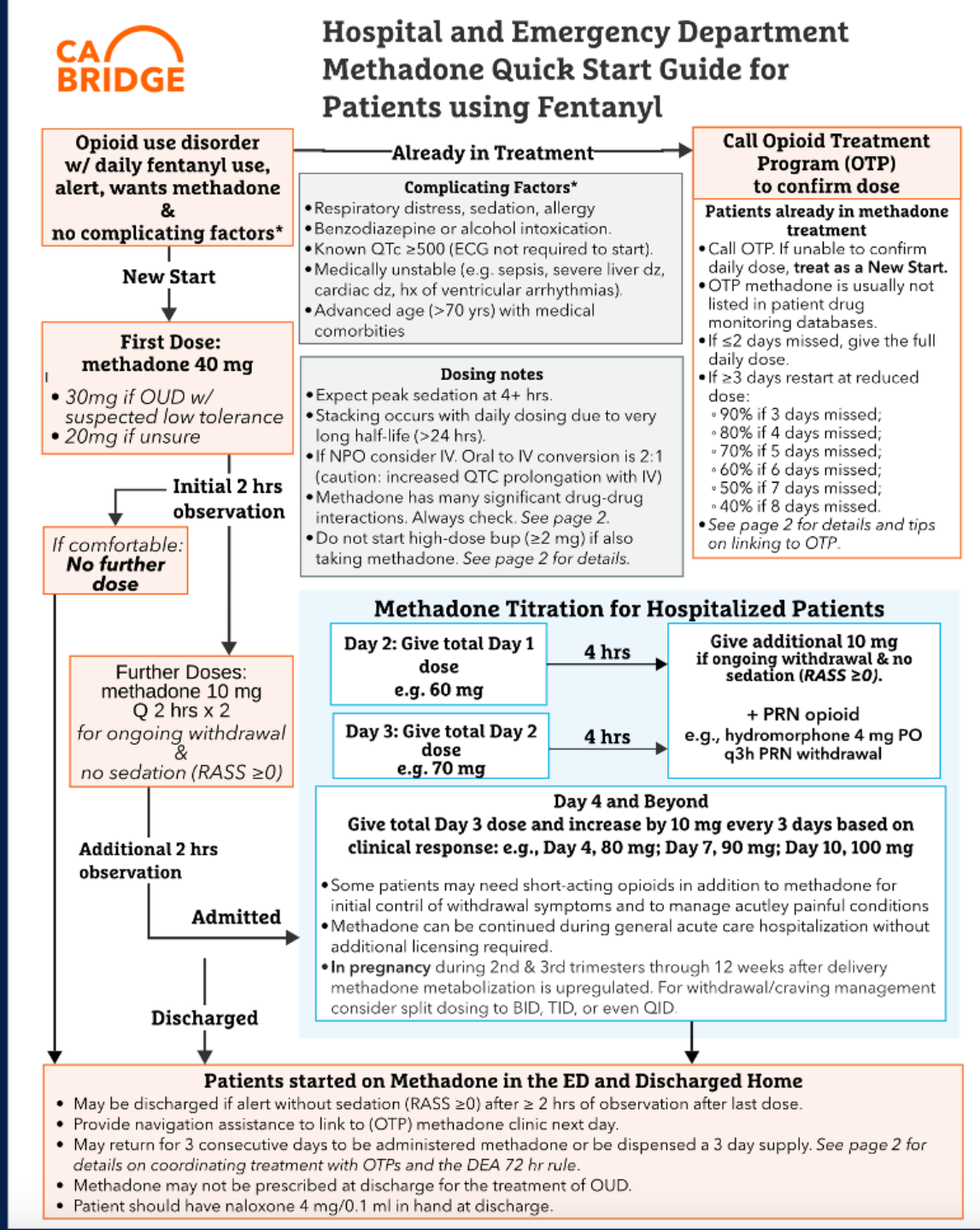
Treatment and ED Course:

Total 60 mg in ED on day one



- ☑ Fentanyl user
- ☑ In withdrawal
- ☑ In the ED

Emergency Department case Putting it all together

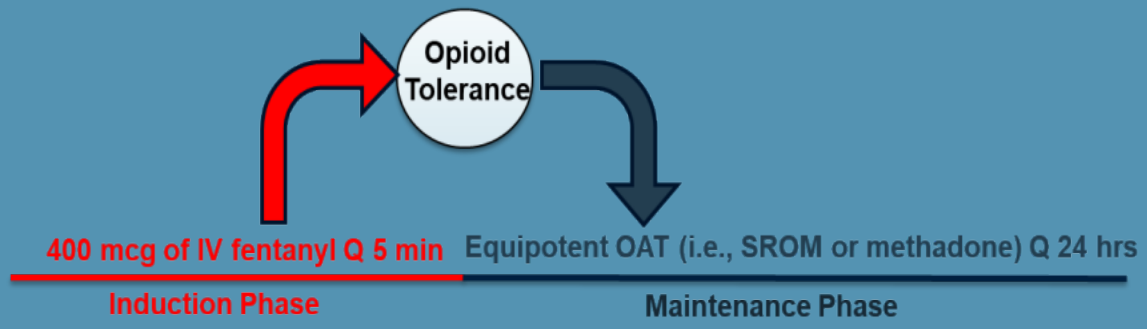


AMERICAN SOCIETY OF ADDICTION MEDICINE FOUNDED 1954 ASAM

Symptom-Inhibited Fentanyl Induction (SIFI)

Purpose: Rapidly assess opioid tolerance and initiate an equipotent OAT dose

Patients using fentanyl



Azar et al. Addiction Science & Clinical Practice (2025) 20:58
https://doi.org/10.1186/s13722-025-00586-7

Addiction Science & Clinical Practice

STUDY PROTOCOL Open Access

Rapid intravenous symptom-inhibiting fentanyl induction (SIFI) to optimize rotation onto oral opioid agonist therapy among individuals who use unregulated fentanyl: protocol for an open-label, single arm clinical trial

Pouya Azar[1,2], Martha J. Ignaszewski[1,2,3], Marianne Harris[4,5*], Zoran Barazanci[4], Ruth Davison[4], James S. H. Wong[1,2], Anil Maharaj[6], Nickie Mathew[2,7], David Hall[4], Silvia A. Guillemi[4,5], Julie Foreman[4], Rolando Barrios[4,8] and Julio S. G. Montaner[4,9]

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DOI: 10.1111/ajad.70011

THE AMERICAN JOURNAL ON ADDICTIONS

CASE SERIES

Case series: Symptom-inhibited fentanyl induction (SIFI) onto treatment-dose opioid agonist therapy in a community setting

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[7]Bridge, Public Health Institute, Oakland, California, USA
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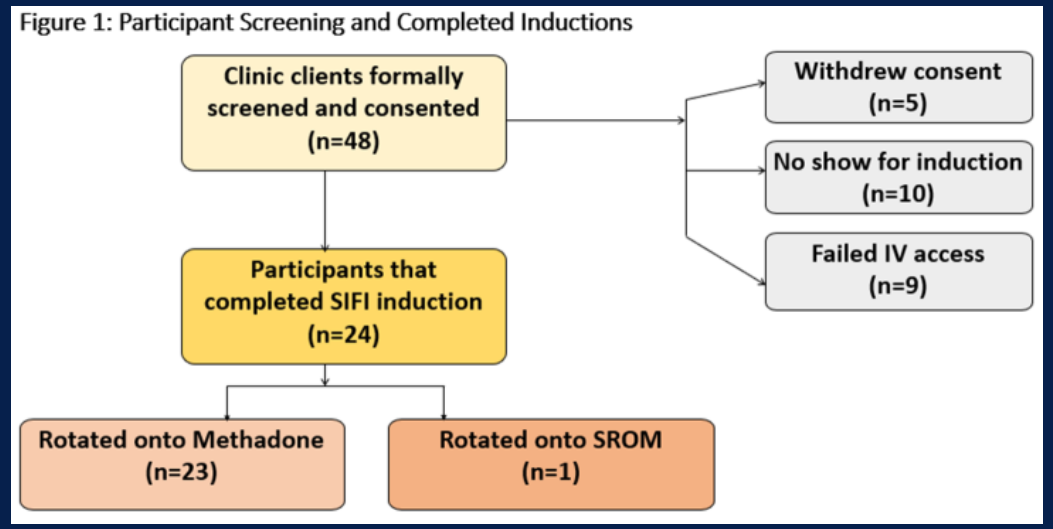
Symptom-Inhibited Fentanyl Induction (SIFI) Clinical Trial: Preliminary Results



Average fentanyl induction dose 4,050mcg (min 800mcg, max 9600mcg)

Average methadone starting dose: 166mg (min 45mg, max 200mg)

- 13 participants started on 200mg of methadone
- 1 participant started on 2000mg of SROM

0 adverse events during induction or through the 7-day follow-up

More results to be shared/published!

Azar P, Kim JJ, Davison R, et al. Case series: symptom-inhibited fentanyl induction (SIFI) onto treatment-dose opioid agonist therapy in a community setting. *Am J Addict.* 2025;34:355-360. doi:10.1111/ajad.70011

Azar P, Ignaszewski MJ, Harris M, et al. Rapid intravenous symptom-inhibiting fentanyl induction (SIFI) to optimize rotation onto oral opioid agonist therapy among individuals who use unregulated fentanyl: protocol for an open-label, single arm clinical trial. *Addict Sci Clin Pract.* 2025;20:58. doi:10.1186/s13722-025-00586-7

Case: ICU management of Opioid Withdrawal

- 31 yo female, severe OUD
- 4th presentation to the hospital for left lower extremity wound with full thickness necrosis
- BMI is 15
- Xylazine level >100,000
- Multiple premature discharges from the ED while waiting for bed
- Last ED presentation had tried Q1 hour IV fentanyl 150mcg + methadone 60mg + valium without tolerance

Methadone – Day 1

- Patient placed on medical hold
- BP 90/40, HR 140, COWS 20-25, wide awake, vomiting
- Bacteremia
- IV fluids
- Fentanyl 100mcg/hr gtt started and titrated to Richmond Agitation-Sedation Scale (RASS) 0 to -1
- Methadone 20mg IV + 10mg IV
- Olanzapine 5-10mg IV
- Ondansetron IV PRN
- Patient in severe lower extremity pain, COWS 15-20, HR 130

Day 2

- Methadone 30mg IV
- Dexmedetomidine gtt started
- Increased Fentanyl gtt to 150mcg/hr
- Added ketamine 0.3mg/kg-0.4mg/kg
- Added IV PRN fentanyl boluses Q1hr 100mcg
- Patient remaining awake, vomiting, has not slept
- Severe pain
- QTc 490ms

Day 3

- Methadone 70mg
- Fentanyl TD patch 100mcg
- Continued ketamine gtt
- Continued Dexmedetomidine gtt
- Olanzepine 5mg BID

Day 4-9

- Methadone escalated each day by 10-15mg to total dose 100mg
- Close monitoring QTc
- Fentanyl gtt and boluses continued
- Fentanyl TD patch 100mcg
- Dexmedetomidine gtt transitioned to PO clonidine taper
- Ketamine gtt continued
- PO hydromorphone 4-6mg Q3H

Day 10

- Continue ketamine infusion through day 12
- Discontinue fentanyl gtt
- Methadone 110mg
- Oral hydromorphone 6-8mg PO Q3H PRN
- 100mcg fentanyl patch
- Clonidine taper
- Acetaminophen, ketorolac
- *Amputation on day 21 of hospitalization – received nerve blocks*

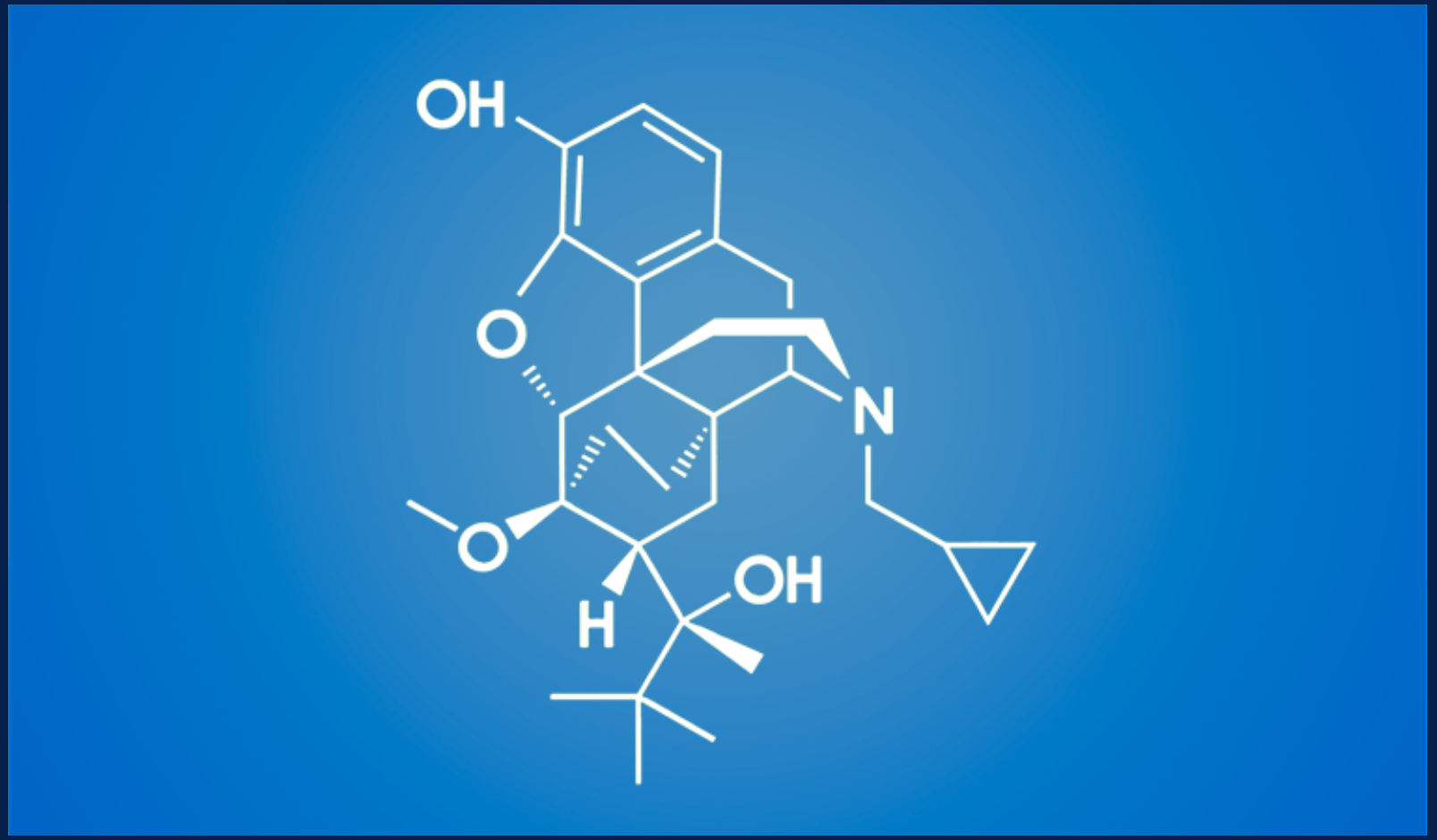
Day 36

- Discharged home with methadone 170mg

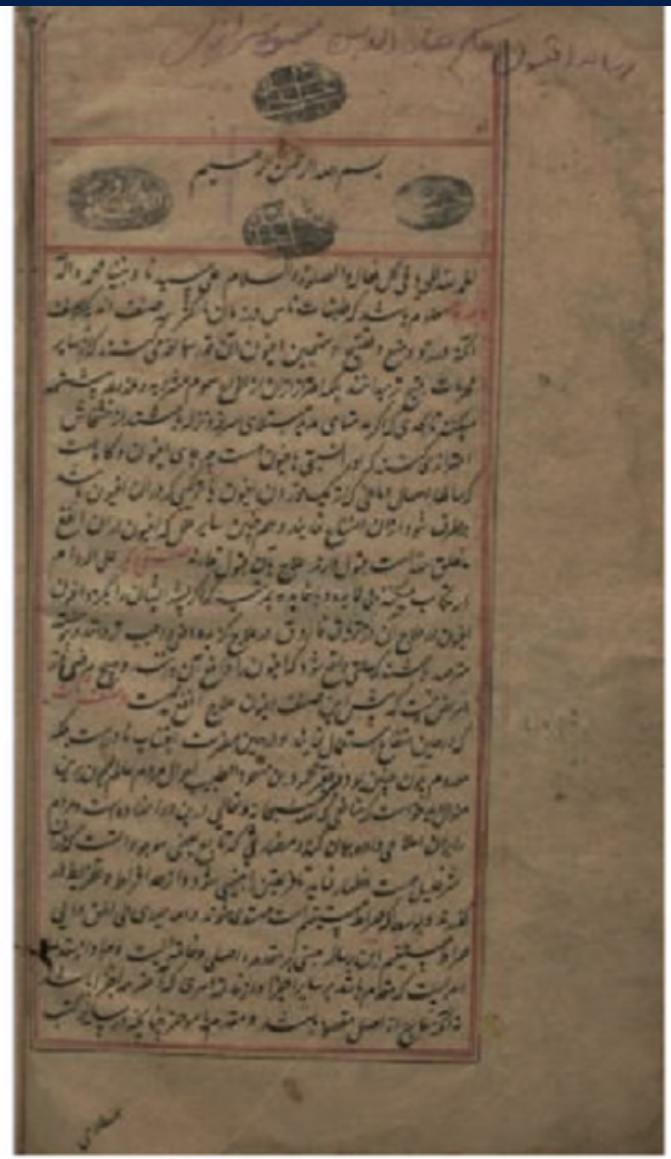
Case Takeaways

- Use of fentanyl gtt and other fentanyl agents in addition to methadone titration to address profound opioid tolerance
- Use of multiple layering adjuncts to address opioid withdrawal and alpha agonist withdrawal
  - Methadone, fentanyl, dexmedetomidine, ketamine, olanzapine, hydromorphone
- Balance of opioid tolerance and sedation, utilize RAS
- Complex ICU-level opioid withdrawal can take several days to resolve and is an essential start to recovery process

Buprenorphine Initiations



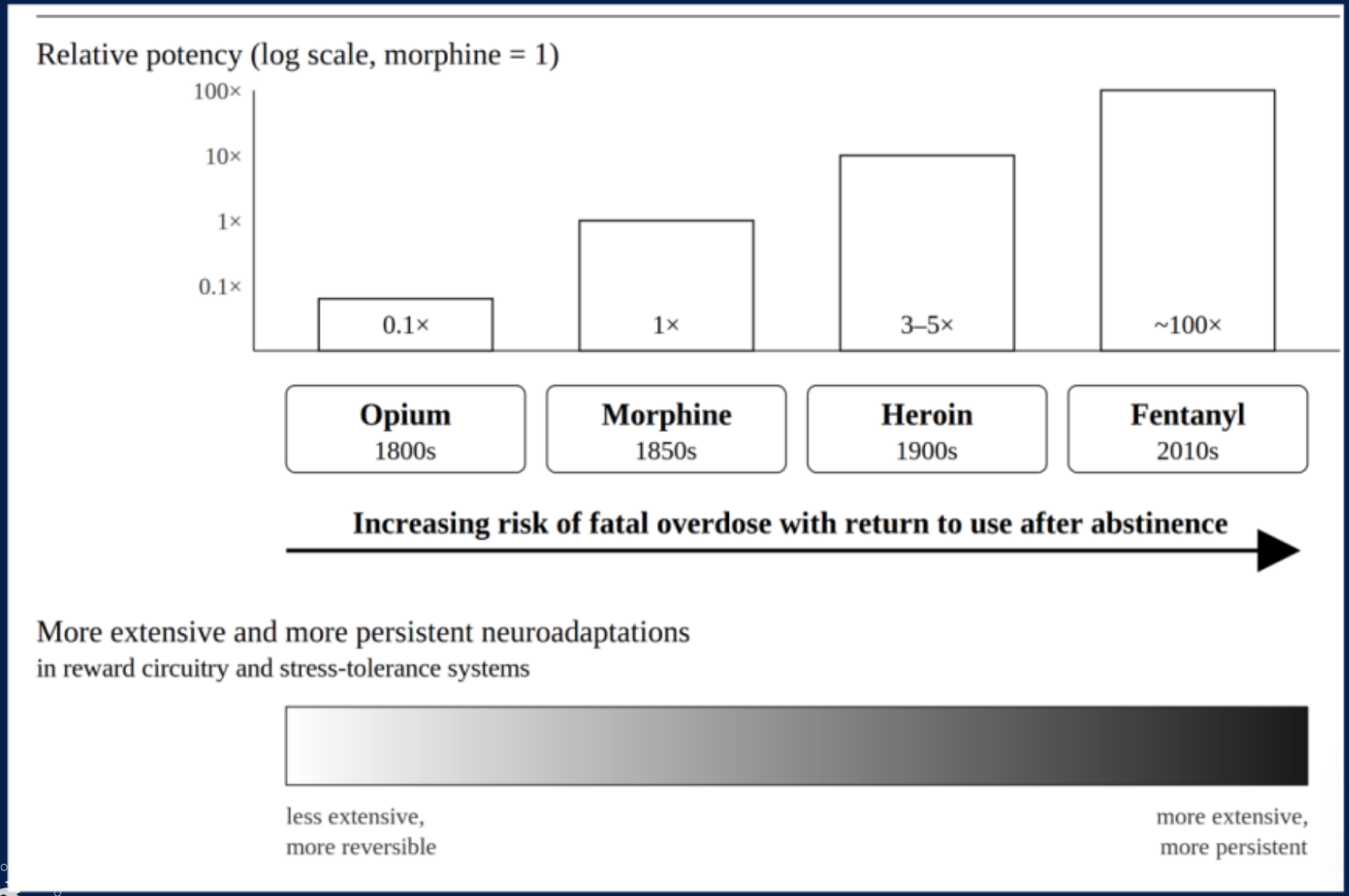
Afyunieh ~ 1500



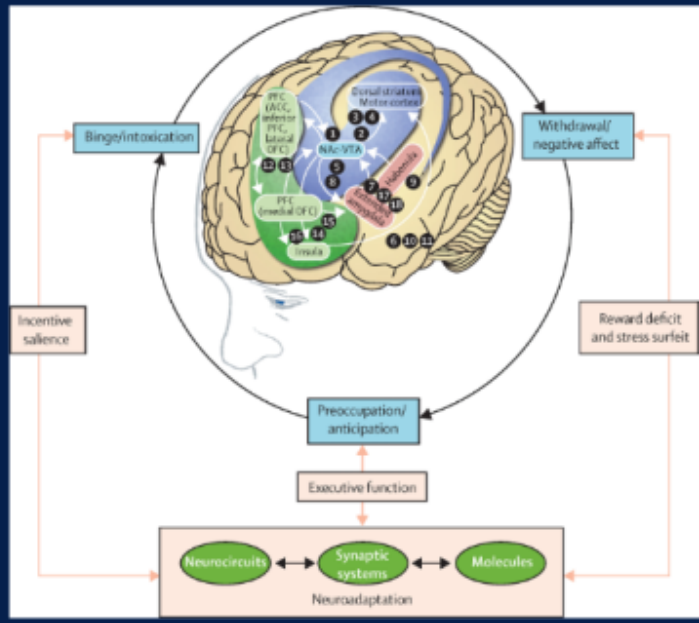
Afyunieh ~ 1500

Method	script	Description
Increasing the time between doses	تعویق	Progressively spacing doses farther apart
Regular dose reduction	تقلیل	Gradually lowering the amount of opium used
Substitution, then taper	تعویض	Replacing opium with another agent, then tapering that substitute

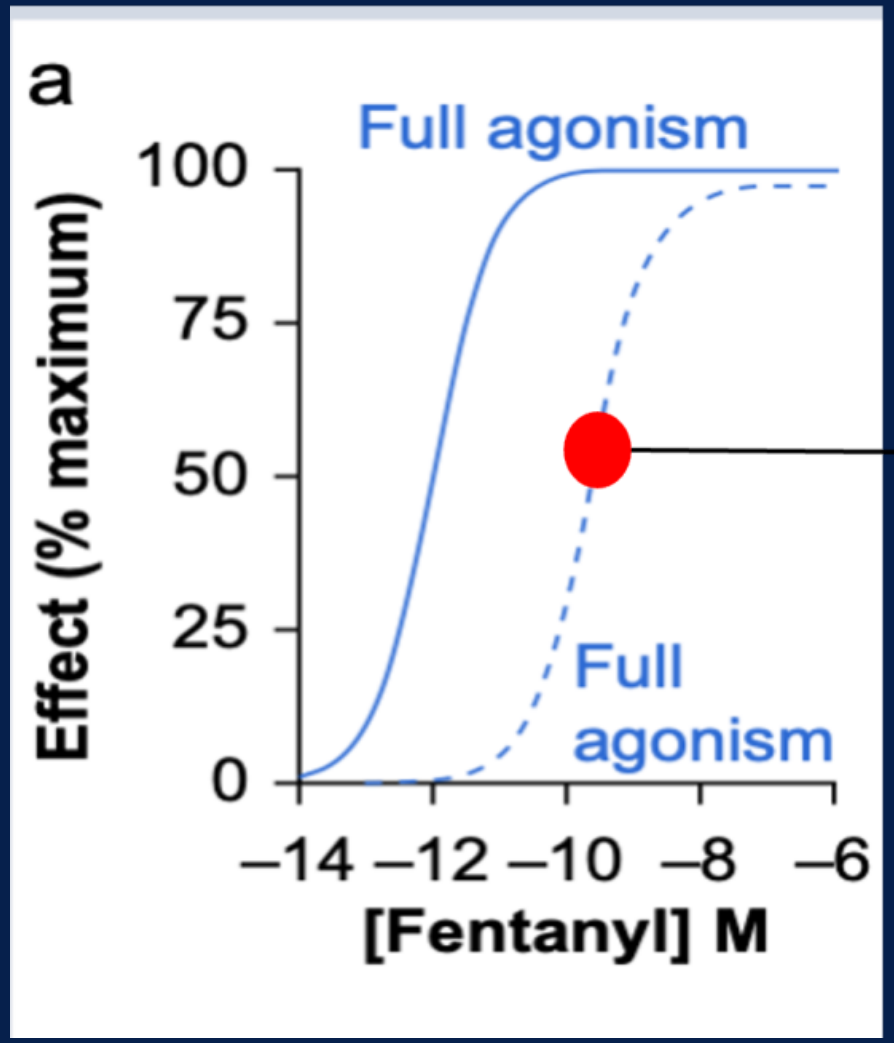
Increasing opioid potency = larger neuroadaptive hurdle



- Duration and magnitude of exposure drive adaption

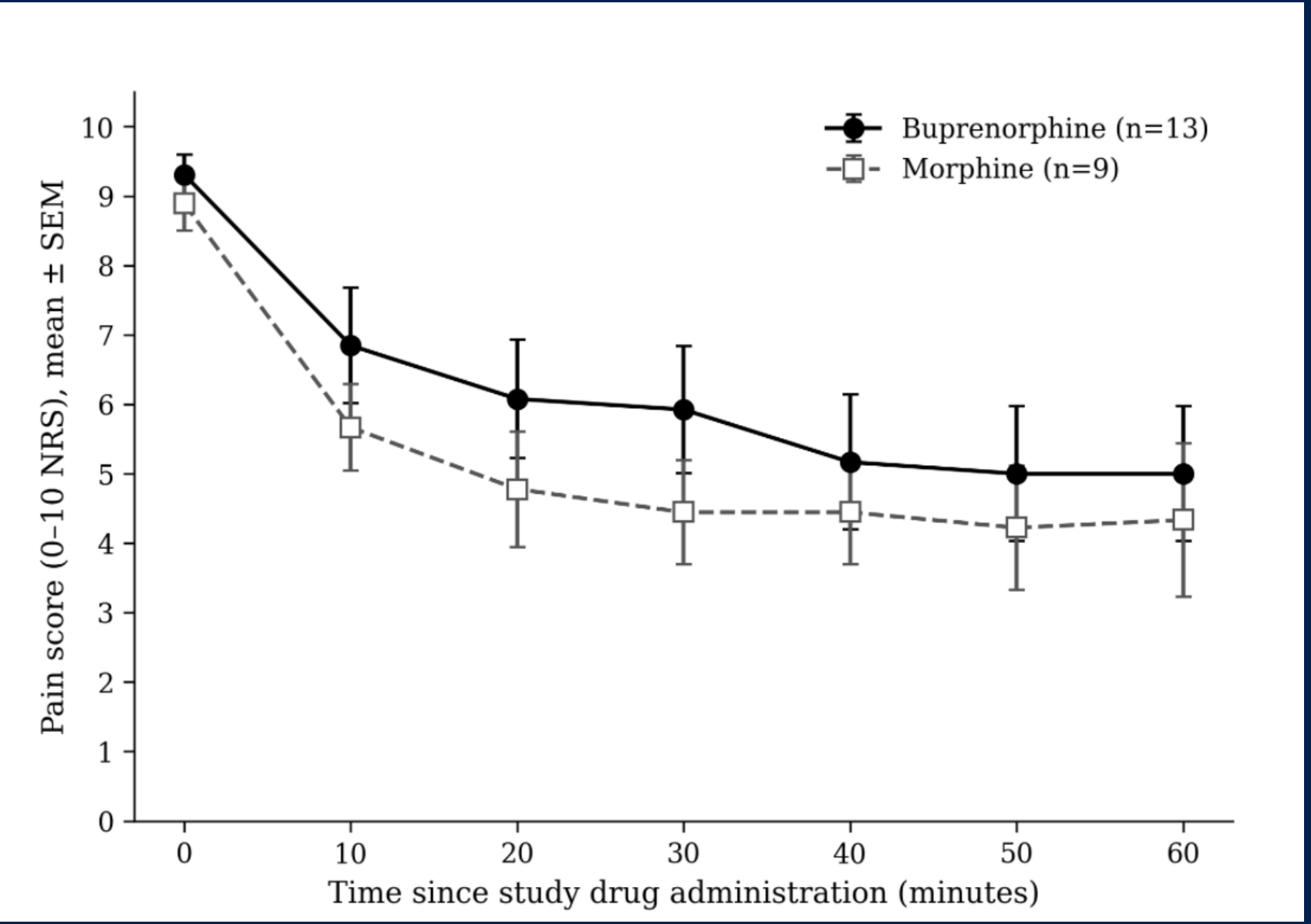


Full agonist

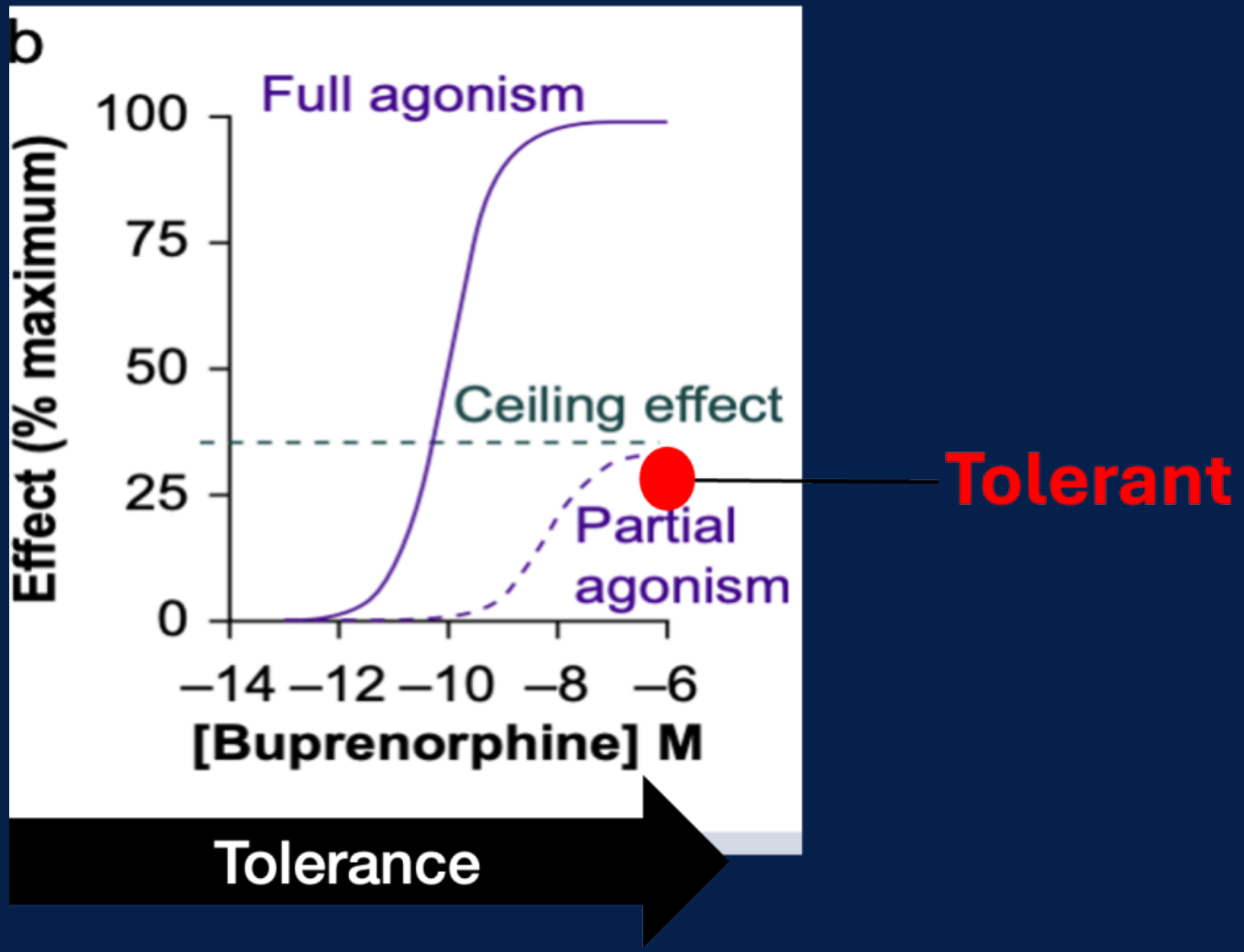


Samways, Damien SK. "Clarifying intrinsic efficacy, partial agonism, and full agonism: the case of buprenorphine." *British Journal of Anaesthesia* 132.2 (2024): 431-432

Buprenorphine: Normal Opioid Sensitivity



Buprenorphine in setting of tolerance



Interventions to recover opioid sensitivity

1. Abstinence + time
2. Partial agonist + full agonist
3. **Antagonists**
4. Potentiators that accelerate tolerance recovery

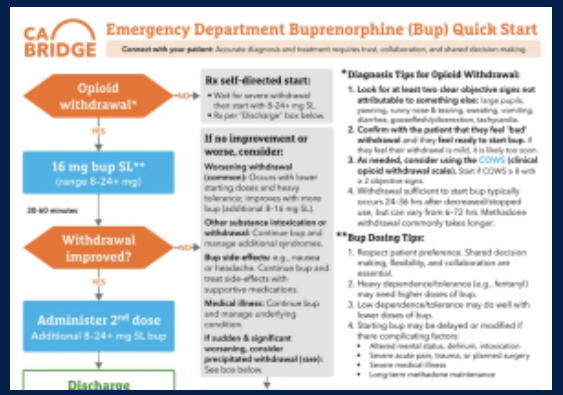
Interventions to recover tolerance

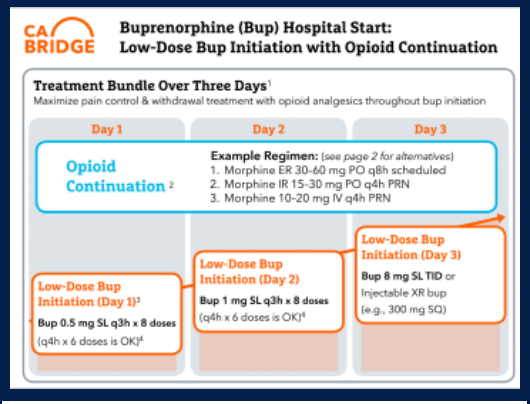
Abstinence + time

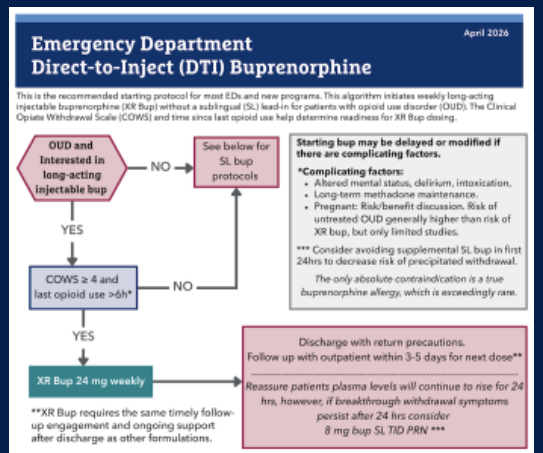
Partial agonist & full agonist

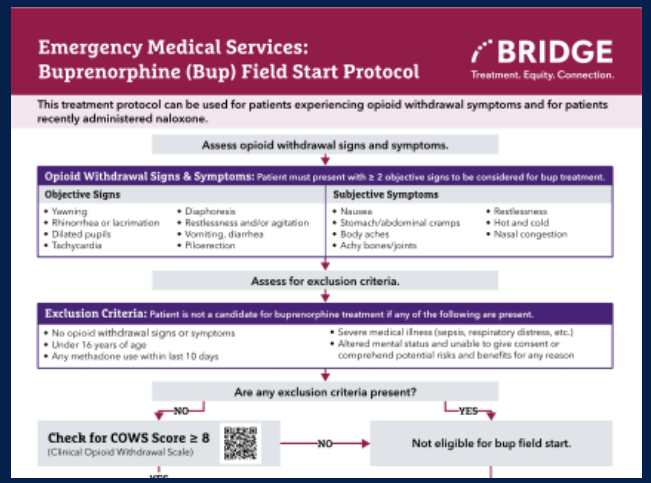
Antagonists (naloxone)

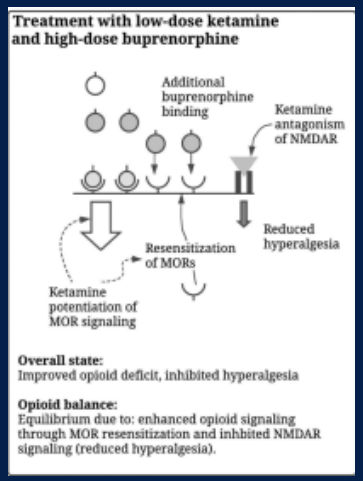
Potentiators (ketamine)

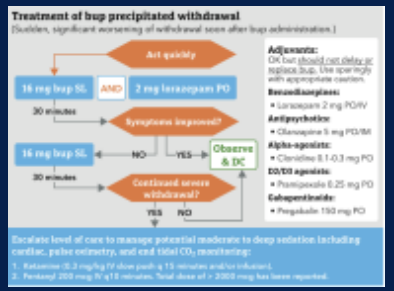












BUPRENORPHINE

(bupe, subs)

WHAT CAN BUPE DO FOR ME?

- **Reduces cravings and withdrawal**
- **Protects against opioid overdose**
- **Treats pain and stabilizes energy**

You can pick buprenorphine up at a pharmacy like **any other medication.**

Buprenorphine can be tablets, films, or injections

SO YOU WANT TO TRY BUPE?

Would you consider an INJECTION?

YES

Direct to inject

Once you're in mild withdrawal, you can start a weekly injection. After that first week, you can stay with injections or switch to films or tablets if you prefer.

NO

How much WITHDRAWAL can you handle?

VERY LITTLE

LOW dose tabs or films

Start bupe 1 week before stopping other opioids, either:

- **7 day:** take bupe 2 times a day most days
- **4 day:** take bupe 4 times a day

I CAN TOUGH IT OUT

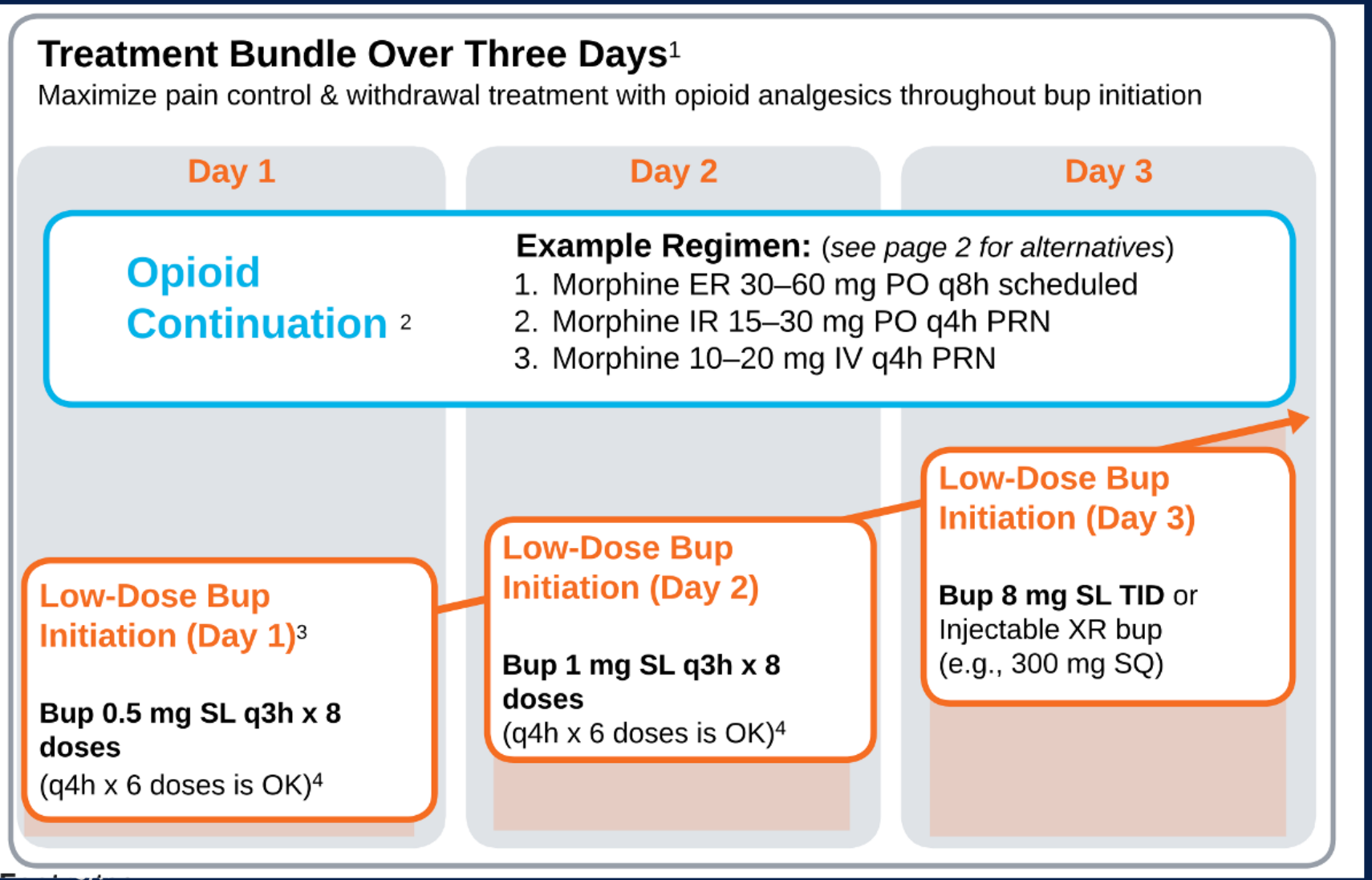
HIGH dose tabs or films

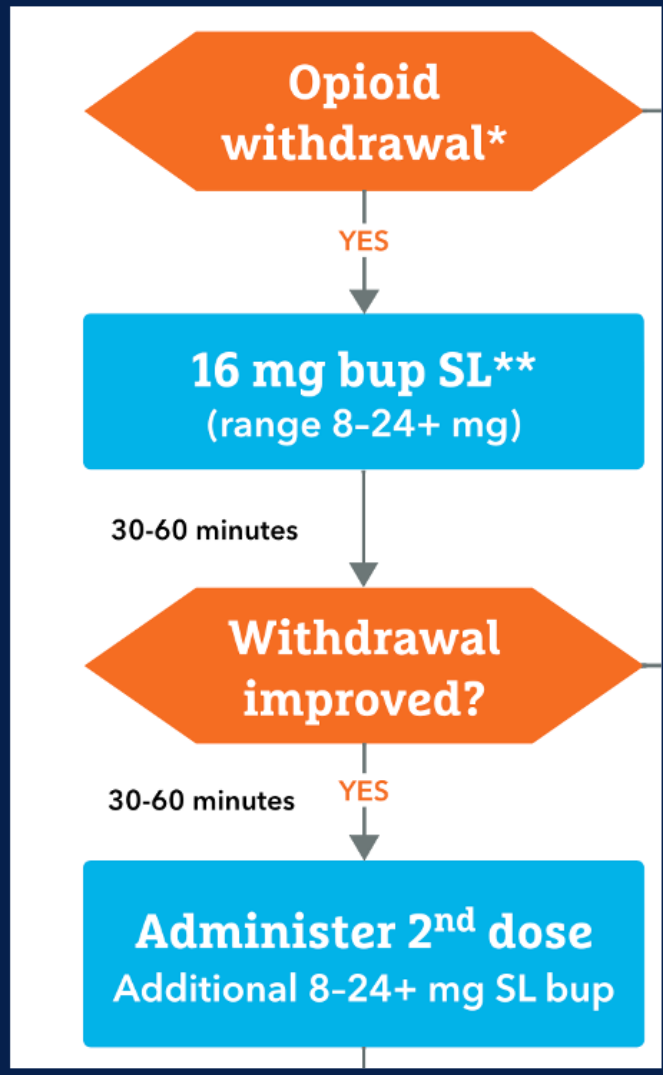
Stop opioids, then when withdrawal gets severe, start bupe and increase dose over 1-2 days.

Withdrawal (e.g., runny nose, body aches, nausea, etc.) is treatable. Make a plan with your provider.

SOURCE(S): Coffin, P., & San Francisco Department of Public Health., n.d.

High Dose is the only option





Antagonists

Naloxone → Bup

Antagonists

Why does naltrexone/naloxone precipitated withdrawal differ from buprenorphine precipitated withdrawal?

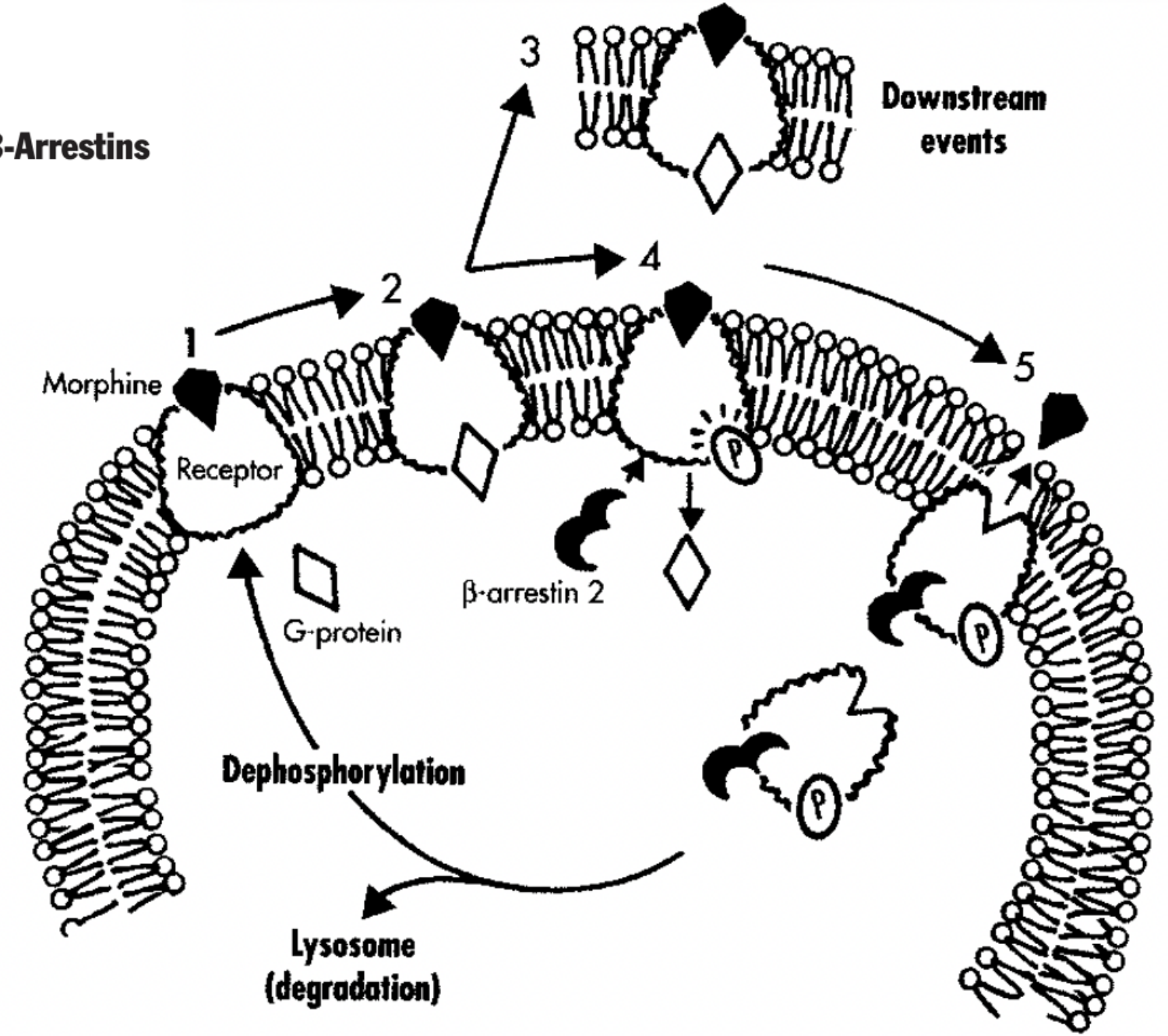
MEDICAL INTELLIGENCE

The Role of Opioid Receptor Internalization and β-Arrestins in the Development of Opioid Tolerance

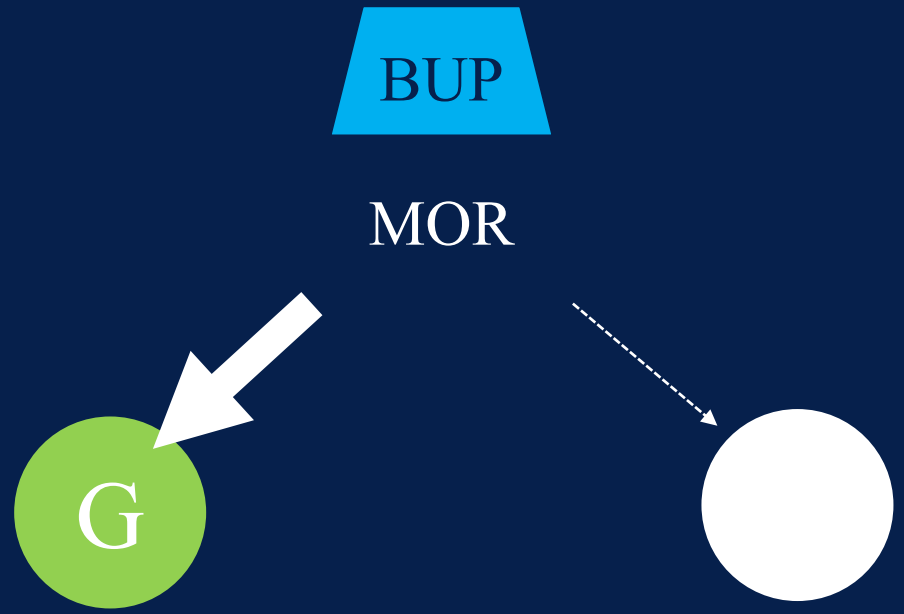
Zhiyi Zuo, MD, PhD

Department of Anesthesiology, University of Virginia, Charlottesville, Virginia

Zuo, Zhiyi MD, PhD. The Role of Opioid Receptor Internalization and β-Arrestins in the Development of Opioid Tolerance. Anesthesia & Analgesia 101(3):p 728-734, September 2005.



Buprenorphine has partial Beta-arrestin activity

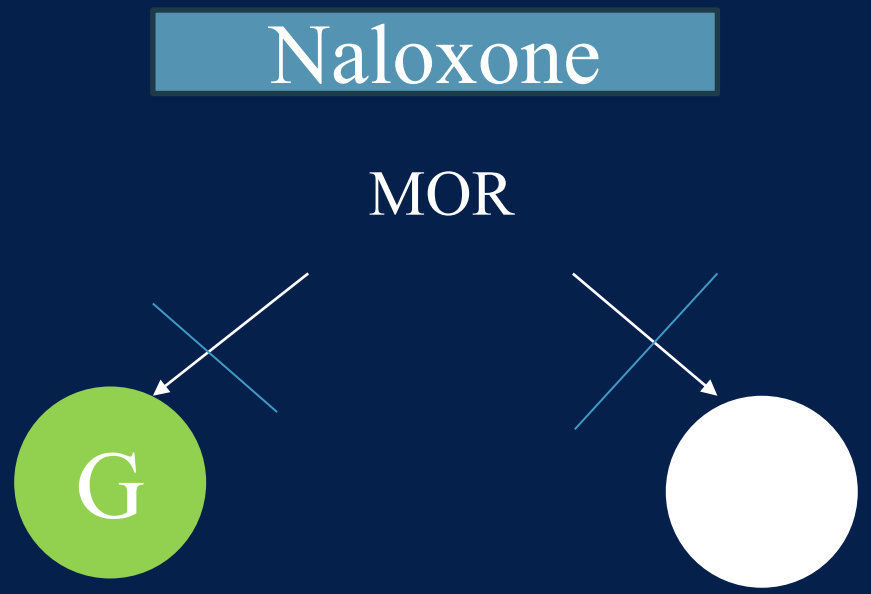


Analgesia
Mood elevation

Tolerance
Hyperalgesia
Respiratory depression

Virk MS, Arttamangkul S, Birdsong WT, Williams JT. Buprenorphine is a weak partial agonist that inhibits opioid receptor desensitization. J Neurosci. 2009 Jun 3;29(22)

Naloxone completely blocks Beta arrestin



Blockade of beta arrestin activity triggers more rapid Mu receptor traffic to membrane surface

Díaz, A., et al. "Regulation of μ-opioid receptors, G-protein-coupled receptor kinases and β-arrestin 2 in the rat brain after chronic opioid receptor antagonism." *Neuroscience* 112.2 (2002): 345-353.
Bohn, Laura M., et al. "μ-Opioid receptor desensitization by β-arrestin-2 determines morphine tolerance but not dependence." *Nature* 408.6813 (2000): 720-723.

Naloxone Reset

- *Rapid MOR dephosphorylation and recruitment of MORs to cell surface*
- *Halts the desensitization/internalization cycle*
- *Rapidly leads to c recovery of tolerance*

Buprenorphine leads to incomplete recovery of tolerance.
Withdrawal severity may exceed the degree of recovery of tolerance.

Huang P, Liu-Chen LY. Detection of the endogenous mu opioid receptor (mopr) in brain. Front Biosci (Elite Ed). 2009 Jun 1;1(1):220-7. doi: 10.2741/E21. PMID: 19482639

Buprenorphine Post-Overdose Case

1 OVERDOSE & REVERSAL

Pre-arrival

- Just discharged from inpatient methadone withdrawal program
- IV fentanyl 0.5 mg → opioid overdose
- 12 mg IN naloxone by bystanders
- Respirations and mentation restored

2 PRECIPITATED WITHDRAWAL

1315 — SUD observation unit

- N/V, headache, abdominal pain
- HR 102, BP 140/76
- Undecided on preferred MOUD

3 SYMPTOMATIC MANAGEMENT

1358 – 1528

- Acetaminophen + clonidine + dicyclomine
- Lorazepam 2 mg PO for residual anxiety
- GI symptoms improve; patient elects buprenorphine

4 BUPRENORPHINE & RESOLUTION

1629 – 1900

- SL bup/nx 16/4 mg — tolerated well
- Extended-release SQ buprenorphine 300 mg
- Symptoms fully resolved by 1900
- Vitals normalized (BP 108/57, HR 85)

Taylor JL et al. Subst Use Addict J. 2024;45(4):771–776.

Overdose to 30 day BUP

- Post-naloxone withdrawal is a clinical window for extended release BUP
- Same-day XR-buprenorphine provides ~30 days of coverage
- EMS partnerships with low-barrier programs can expand access

DTI Buprenorphine from Methadone

- *Off label, case series submitted*

DTI Buprenorphine from Methadone - Case

- 37 yo female w decades severe OUD in remission on 70 mg methadone
- Tapered from 120 to 58 in past with return to opioid use
- Dose increased to 70, one time fentanyl use 4 weeks prior, declines further dose optimization
- Tired of OTP, daily medication, attributes wt gain to MTD, false positive tox was demoralizing/lost take-homes
- Does not want to experience opioid withdrawal, but about to “walk off” clinic
- Hates the taste of SL bup

- Goal: transition off MTD to buprenorphine with “the shot”

Methadone to Buprenorphine transition

- Why?
  - High desire by pts to taper off methadone for variety of reasons
    - High barrier structure of OTP
    - Inappropriate or misguided management or dosing
    - Symptoms/ side effects
    - Safety concerns or lack of access/discrimination

- How?
  - First see if above can be addressed/remedied
    - Increase take homes, split dose, check and treat testosterone deficiency
    - Legal Action Center | Addressing Discrimination in Health Care…
  - Educate, empower, partner
  - Ensure patients have evidence base/meet with medical provider to make an informed decision

DTI Buprenorphine from Methadone: Sample shared decision-making documentation and dose guidance

MGH Substance Use Disorder Bridge Clinic

OUD: Patient requesting transition from methadone to extended-release buprenorphine. Patient counseled around methadone being one of our gold standard treatments for OUD. We reviewed and attempted to address any barriers to staying on methadone.

Despite counseling, patient elects to transition to extended-release buprenorphine. We discussed evidence for direct-to-inject buprenorphine is strongest for people with untreated OUD actively using non-prescribed opioids, and especially for individuals with at least a COWS of 4. Patient is not interested in staying on methadone or getting to COWS of 4, therefore we discussed the experimental option of methadone to weekly BUP-XR protocols that we have been piloting in the Bridge Clinic.

We reviewed that on the first night some people have mild to moderate symptoms, but rarely have we seen actual precipitated withdrawal. Anticipatory anxiety may be the worst symptom, thus we provided reassurance and discussed management strategies.

DTI Buprenorphine from Methadone: early experience

Direct-to-Inject Buprenorphine from Methadone: MGH Protocol

Basal Methadone ≥ 80mg

Day	Methadone	Buprenorphine	Non-opioid
-1	Full dose	SL bup 0.5mg BID	
0	Full dose	SL bup 0.5mg QID	
1	Full dose	SC bup 8mg	clonidine 0.1mg TID PRN + clonazepam 1mg qhs or gabapentin 600mg TID
2	Full dose	SC bup 16mg	Clonidine 0.1mg TID PRN
3		SC bup 128mg or 300mg (prefer latter)	

Basal Methadone < 80mg

Day	Methadone	Buprenorphine	Non-opioid
1	Full dose	SC bup 8mg	clonidine 0.1mg TID PRN + clonazepam 1mg qhs or gabapentin 600mg TID
2	Full dose	SC bup 16mg	Clonidine 0.1mg TID PRN
3		SC bup 128mg or 300mg	

- n= 17
- Setting: low barrier bridge clinic, primary care
- OUD in remission, >1 mo continuous methadone
- Methadone dose: 24-120 mg
- Median length of methadone: 2 yr (2 mo -13 years)
- 94% (16/17) completed protocol
  - (15/16 received 2nd monthly)
  - 1/17 returned to MTD

Slow increase in weekly LAI BUP levels (peak 24 hr) facilitates gradual build up and reducing risk of POW vs. SL bup (quick serum peak 1 hr)

Table courtesy Daniel Liauw, MD

Evolving Outpatient Real World Experience: Lessons Learned

- Despite steps to lower barriers to methadone/optimize care in OTPs
  - many patients still wish to transition off and suffer
- Our practice has evolved by partnering with patients
  - Patients are terrified of withdrawal
  - SL Low dose buprenorphine-opioid continuation (LDB-OC) is complicated
  - Comfort meds *make a difference*
  - Transition better tolerated on lower methadone doses
  - More to learn...
- We need to double down on efforts to reform methadone care and delivery

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