Innovative Strategies for Medication Initiation in Opioid Use Disorder

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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

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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.

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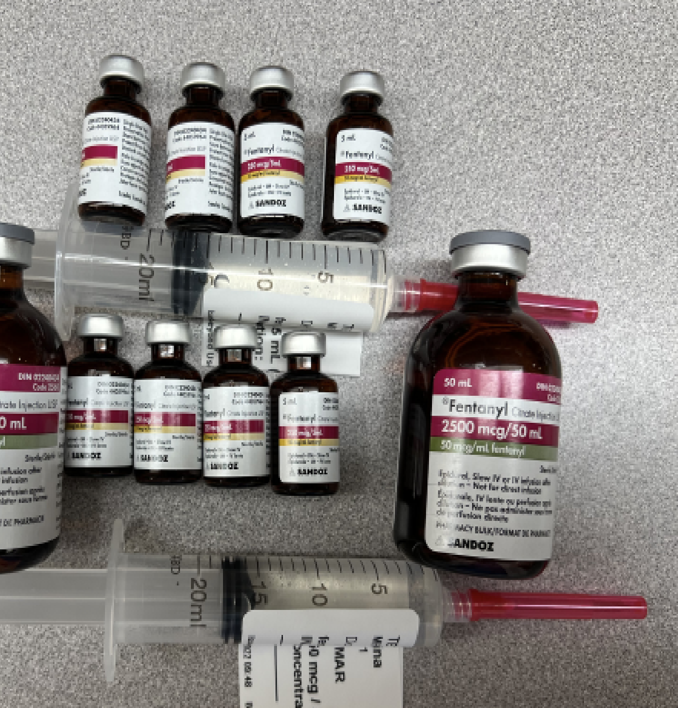

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	Respiratory Rate: 16 br/min	Respiratory Rate: 16 br/min	Respiratory Rate: 17 br/min
	8,000 mcg @0551		8,000 mcg @0603
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	8,000 mcg @0755		8,000 mcg @0752
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	8,000 mcg @1105		8,000 mcg @1045
	Respiratory Rate: 16 br/min		Respiratory Rate: 18 br/min
	8,000 mcg @1315		8,000 mcg @1531
	Respiratory Rate: 16 br/min		Respiratory Rate: 18 br/min

Methadone Initiations

ASAM Guidelines: Methadone Initiation

- Day 1 total dosage: 10-40 mg
- Titration schedule: Increase 10 mg ~ every 5 days

April 26, 2026
Starting Dose 40mg

Dose Titration
~11.5 weeks / 80 days

July 15, 2026
Target Dose: 200mg

Slide References: American Society of Addiction Medicine. The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update. *J Addict Med.* 2020;14(2S Suppl 1):1-91. doi:10.1097/ADM.0000000000000633

Emergency Department case
Putting it all together

Hospital and Emergency Department Methadone Quick Start Guide for Patients using Fentanyl

Opioid use disorder w/ daily fentanyl use, alert, wants methadone & no complicating factors*

→ Already in Treatment → **Call Opioid Treatment Program (OTP) to confirm dose**

Patients already in methadone treatment
- Call OTP. If unable to confirm daily dose, **treat as a New Start.**
- OTP methadone is usually not listed in patient drug monitoring databases.
- If ≤2 days missed, give the full daily dose.
- If ≥3 days restart at reduced dose:
  - 90% if 3 days missed;
  - 80% if 4 days missed;
  - 70% if 5 days missed;
  - 60% if 6 days missed;
  - 50% if 7 days missed;
  - 40% if 8 days missed.
- *See page 2 for details and tips on linking to OTP.*

Complicating Factors*
- Respiratory distress, sedation, allergy
- Benzodiazepine or alcohol intoxication.
- Known QTc ≥500 (ECG not required to start).
- Medically unstable (e.g. sepsis, severe liver dz, cardiac dz, hx of ventricular arrhythmias).
- Advanced age (>70 yrs) with medical comorbities

Dosing notes
- Expect peak sedation at 4+ hrs.
- Stacking occurs with daily dosing due to very long half-life (>24 hrs).
- If NPO consider IV. Oral to IV conversion is 2:1 (caution: increased QTC prolongation with IV)
- Methadone has many significant drug-drug interactions. Always check. *See page 2.*
- Do not start high-dose bup (≥2 mg) if also taking methadone. *See page 2 for details.*

↓ **New Start**

First Dose: methadone 40 mg
- *30mg if OUD w/ suspected low tolerance*
- *20mg if unsure*

↓ **Initial 2 hrs observation**

If comfortable: ***No further dose***

Further Doses: methadone 10 mg Q 2 hrs x 2 *for ongoing withdrawal & no sedation (RASS ≥0)*

↓ **Additional 2 hrs observation**

→ **Admitted**

Methadone Titration for Hospitalized Patients

Day 2: Give total Day 1 dose e.g. 60 mg → **4 hrs** →

Day 3: Give total Day 2 dose e.g. 70 mg → **4 hrs** →

Give additional 10 mg if ongoing withdrawal & no sedation (*RASS ≥0*).

+ PRN opioid e.g., hydromorphone 4 mg PO q3h PRN withdrawal

Day 4 and Beyond

Give total Day 3 dose and increase by 10 mg every 3 days based on clinical response: e.g., Day 4, 80 mg; Day 7, 90 mg; Day 10, 100 mg

- Some patients may need short-acting opioids in addition to methadone for initial contril of withdrawal symptoms and to manage acutley painful conditions
- Methadone can be continued during general acute care hospitalization without additional licensing required.
- **In pregnancy** during 2nd & 3rd trimesters through 12 weeks after delivery methadone metabolization is upregulated. For withdrawal/craving management consider split dosing to BID, TID, or even QID.

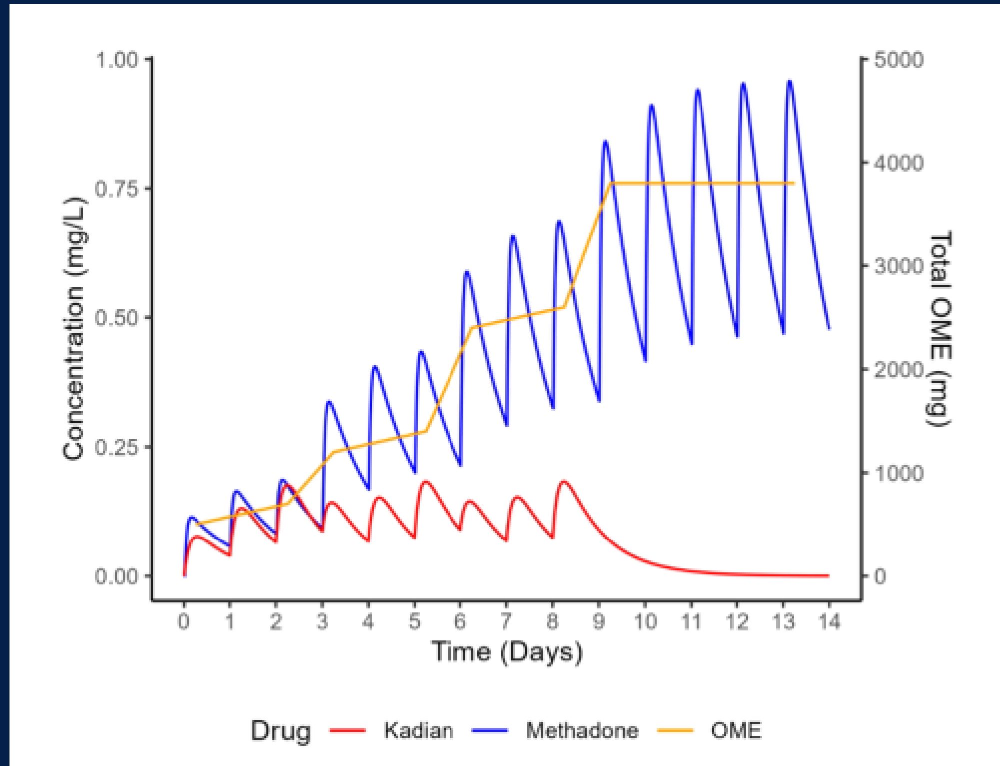
↓ **Discharged**

Patients started on Methadone in the ED and Discharged Home
- May be discharged if alert without sedation (RASS ≥0) after ≥ 2 hrs of observation after last dose.
- Provide navigation assistance to link to (OTP) methadone clinic next day.
- May return for 3 consecutive days to be administered methadone or be dispensed a 3 day supply. *See page 2 for details on coordinating treatment with OTPs and the DEA 72 hr rule.*
- Methadone may not be prescribed at discharge for the treatment of OUD.
- Patient should have naloxone 4 mg/0.1 ml in hand at discharge.

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

Half-Life: ~11-13 hours

Tmax: ~8.5 hours



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

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Rapid Methadone Titration with SROM Bridging - Case

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

- Severe oud
- Unhoused
- schizophrenia
- Declined buprenorphine, past methadone

Substance Use

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

Goal: restart Methadone, abstinence.

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Rapid Methadone Titration with SROM Bridging - Case

Day	Methadone	SROM	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	‘’	400 mg PO daily	Withdrawal ongoing	“
Day 3	“	500 mg PO daily	Withdrawal improving	“
Day 5	100 mg PO daily	300 mg PO daily	“	“
Day 6	“	400 mg PO daily	“	“
Day 7	“	500 mg PO daily	“	“

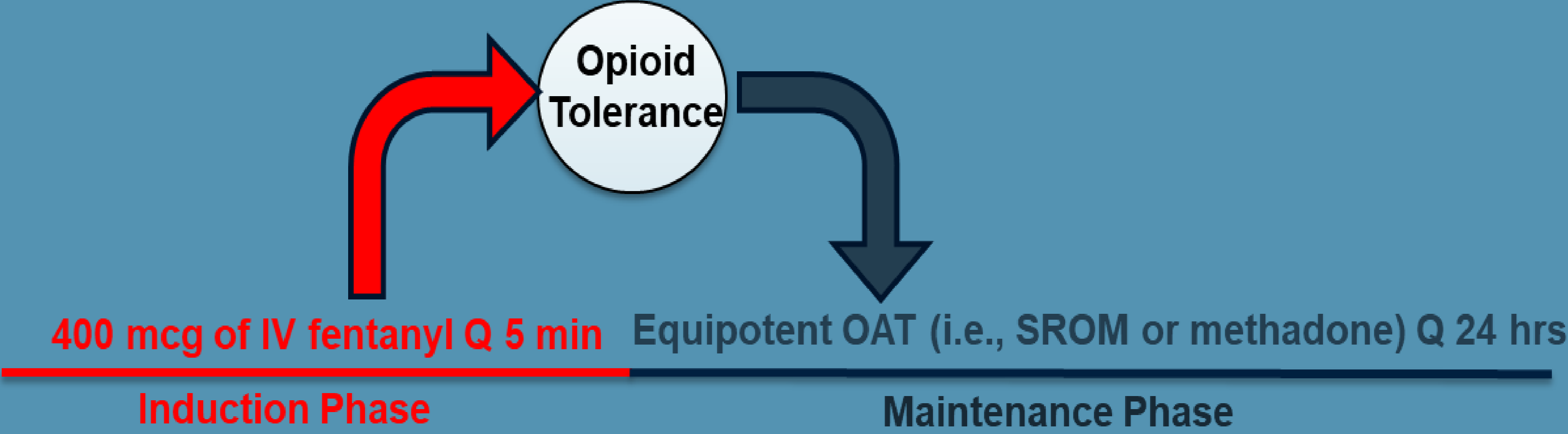
Rapid Methadone Titration with SROM Bridging - Case

Day	Methadone	SROM	UDS	Cravings / Withdrawal	Fentanyl Use
Day 8	150 mg PO daily	300 mg PO daily		Withdrawal improving	reduced
“	“	400 mg PO daily			“
“	“	500 mg PO daily			“
Day 11	200 mg PO daily	Discontinued			“
”	“	“		Cravings largely resolved; mild residual withdrawal	“
“	“	“		No withdrawal; denies cravings	“
Day 18	240 mg PO daily	“		Withdrawal absent; mild cravings persist	“
Day 21	“	“			“
Day 22	“	“	NEG (+ EDDP)		No reported use
Day 46	240 mg PO daily	“	NEG (+ EDDP)	No cravings/No withdrawal	No reported use

Symptom-Inhibited Fentanyl Induction (SIFI)

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

Patients using fentanyl



Symptom-Inhibited Fentanyl Induction (SIFI) Clinical Trial: Preliminary Results

- **24 participants**
- **Average fentanyl induction dose 4,050mcg (800 to 9600mcg)**
- **Average methadone starting dose: 166mg (45 to 200mg)**
- **0 adverse events during induction and the 7-day follow-up**
- **7-day follow-up: 83.3% participants retained**
- **1-month follow-up: 82% participants retained**
- **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

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

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Received: 29 October 2024 | Revised: 31 January 2025 | Accepted: 6 February 2025
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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analytical chemistry

pubs.acs.org/ac Article

Development of a Graphene-Oxide-Deposited Carbon Electrode for the Rapid and Low-Level Detection of Fentanyl and Derivatives

Daniel Jun, Glenn Sammis, Pouya Rezazadeh-Azar, Erwann Ginoux, and Dan Bizzotto*

Symptom-Inhibited Fentanyl Induction (SIFI)

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

Patients using fentanyl

Opioid Tolerance

Equipotent OAT (i.e., SROM or methadone) Q 24 hrs

Maintenance Phase

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

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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

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Day 3

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

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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

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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*

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Day 36

- Discharged home with methadone 170mg

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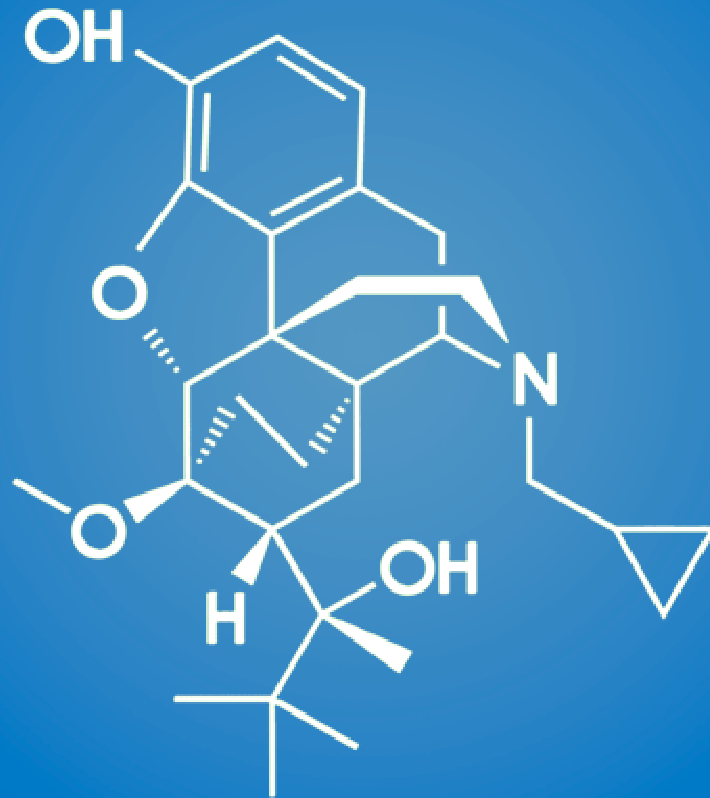
Case Takeaways

- 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



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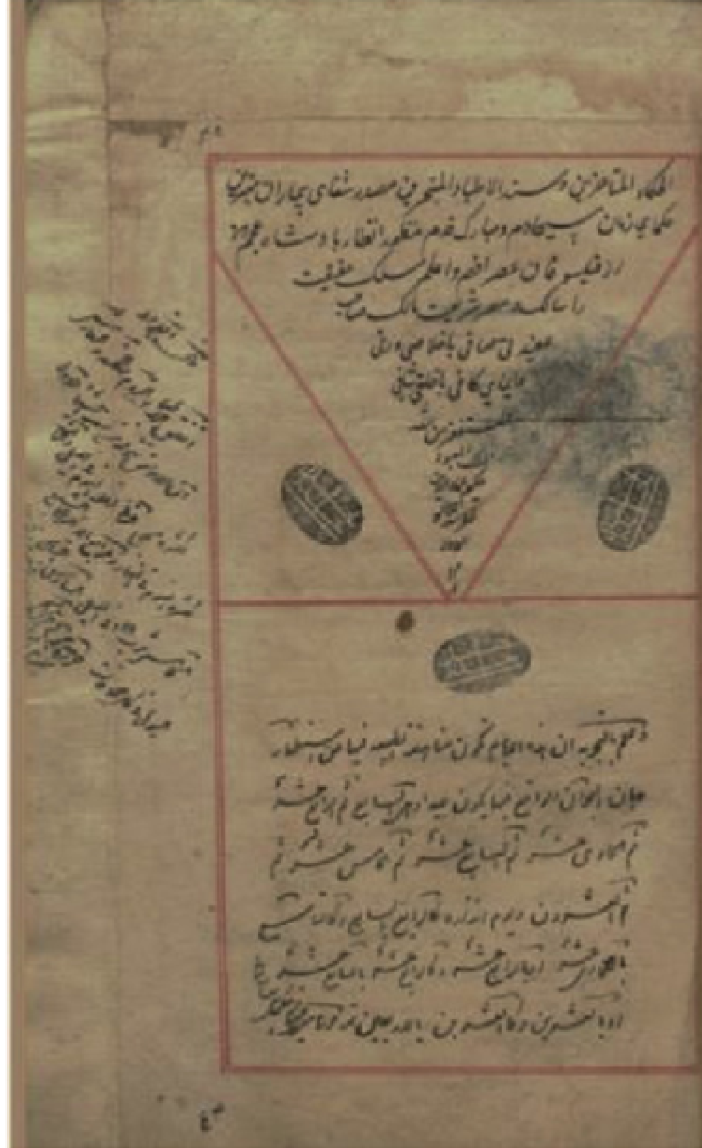
Afyunieh ~ 1500



Afyunieh ~ 1500

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

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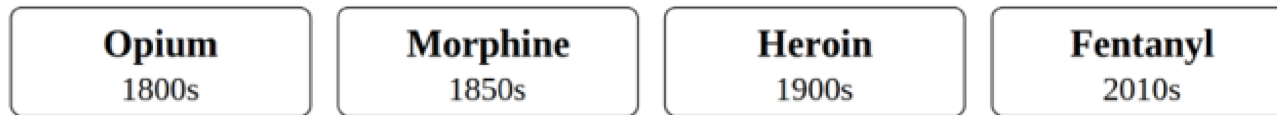
Increasing opioid potency = larger neuroadaptive hurdle

Relative potency (log scale, morphine = 1)



Increasing risk of fatal overdose with return to use after abstinence

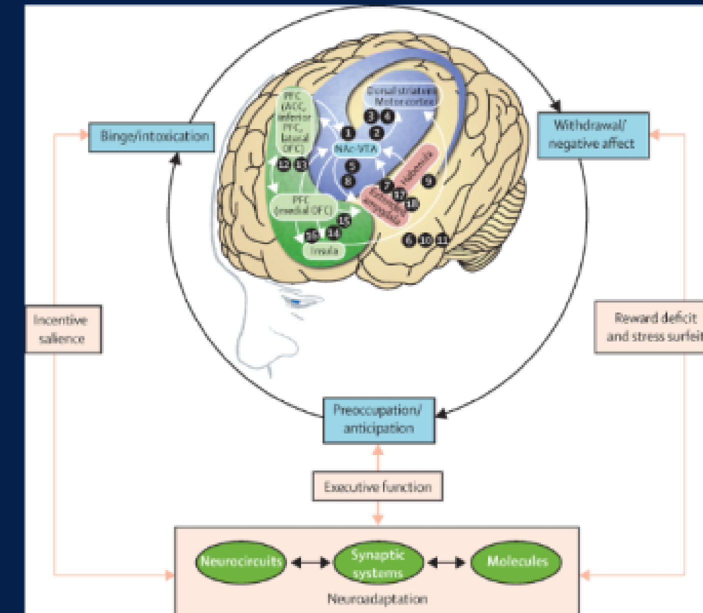
More extensive and more persistent neuroadaptations

in reward circuitry and stress-tolerance systems

less extensive,
more reversible

more extensive,
more persistent

- Duration and magnitude of exposure drive adaption



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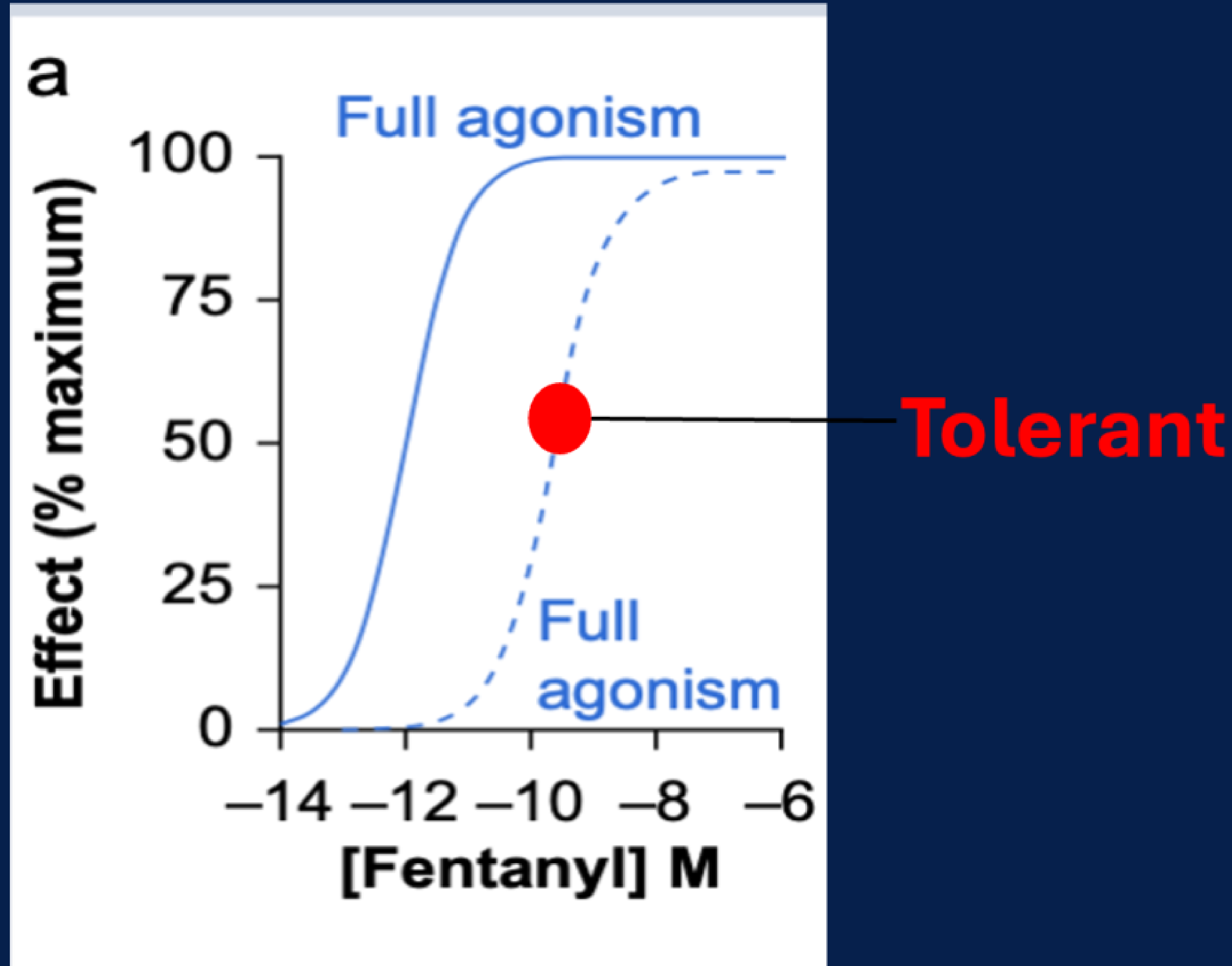
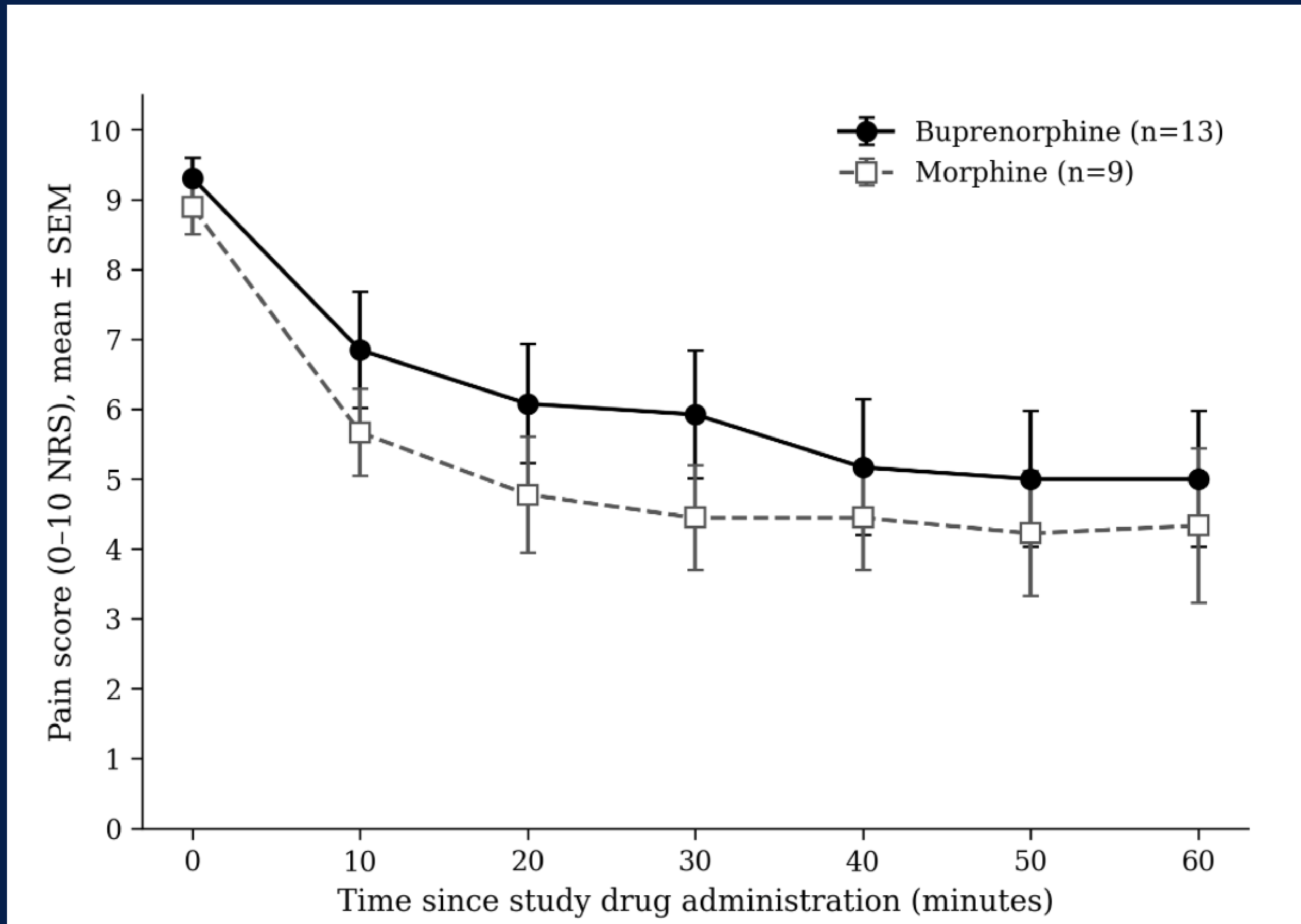
Full agonist

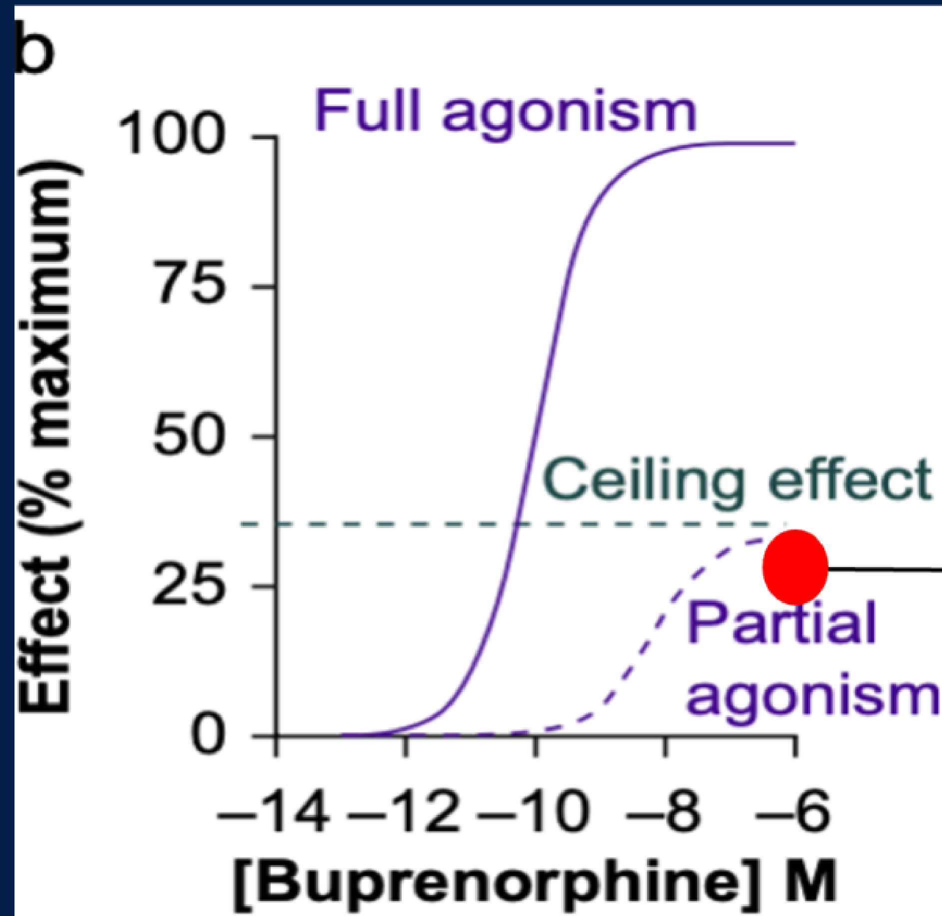


Samways, Damien SK. "Clarifying intrinsic efficacy, partial agonism, and full agonism: the case of buprenorphine." *British Journal of Anaesthesia* 132.2 (2024): 431-432

Buprenorphine: Normal Opioid Sensitivity



Buprenorphine in setting of tolerance



Tolerant

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Interventions to recover opioid sensitivity

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

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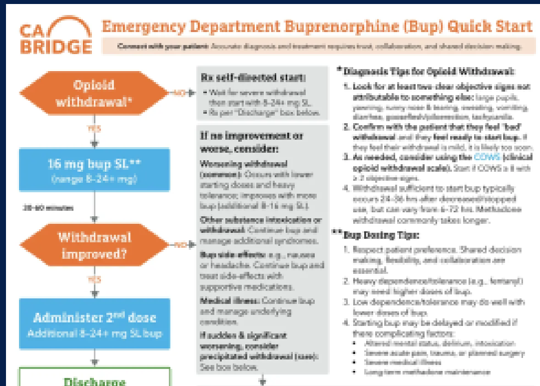
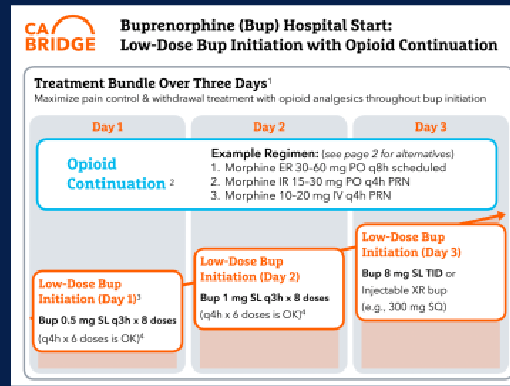
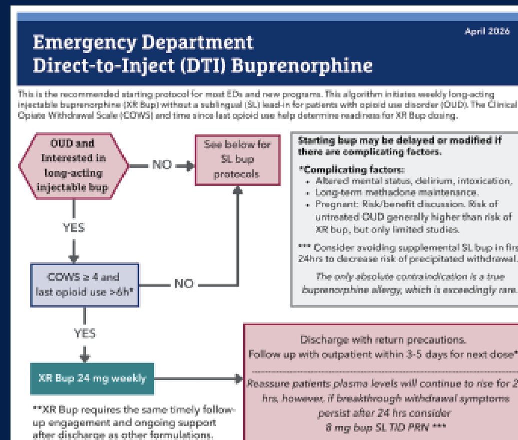
Interventions to recover tolerance

Abstinence + time

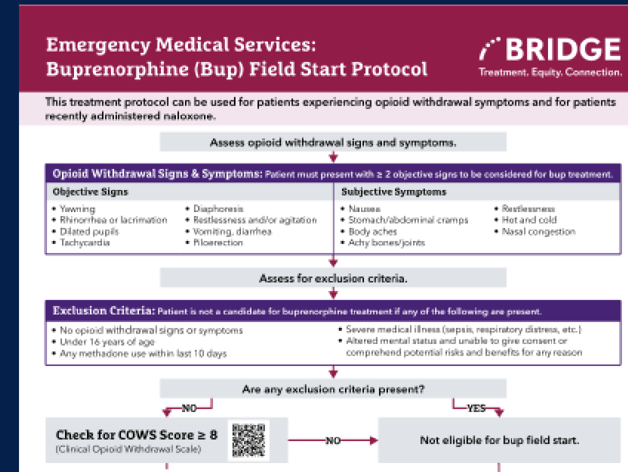


Partial agonist & full agonist

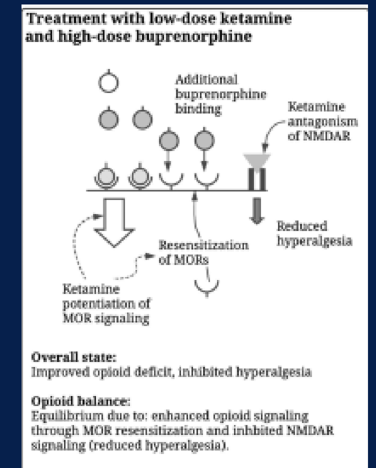


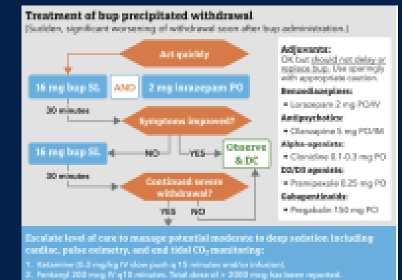


Antagonists (naloxone)



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?

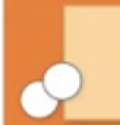
Would you consider an INJECTION?

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.

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High Dose is the only option

Treatment Bundle Over Three Days[1]

Maximize pain control & withdrawal treatment with opioid analgesics throughout bup initiation

Day 1	Day 2	Day 3

Opioid Continuation [2]

Example Regimen: (*see page 2 for alternatives*)

1. Morphine ER 30–60 mg PO q8h scheduled
2. Morphine IR 15–30 mg PO q4h PRN
3. Morphine 10–20 mg IV q4h PRN

Low-Dose Bup Initiation (Day 1)[3]

Bup 0.5 mg SL q3h x 8 doses

(q4h x 6 doses is OK)[4]

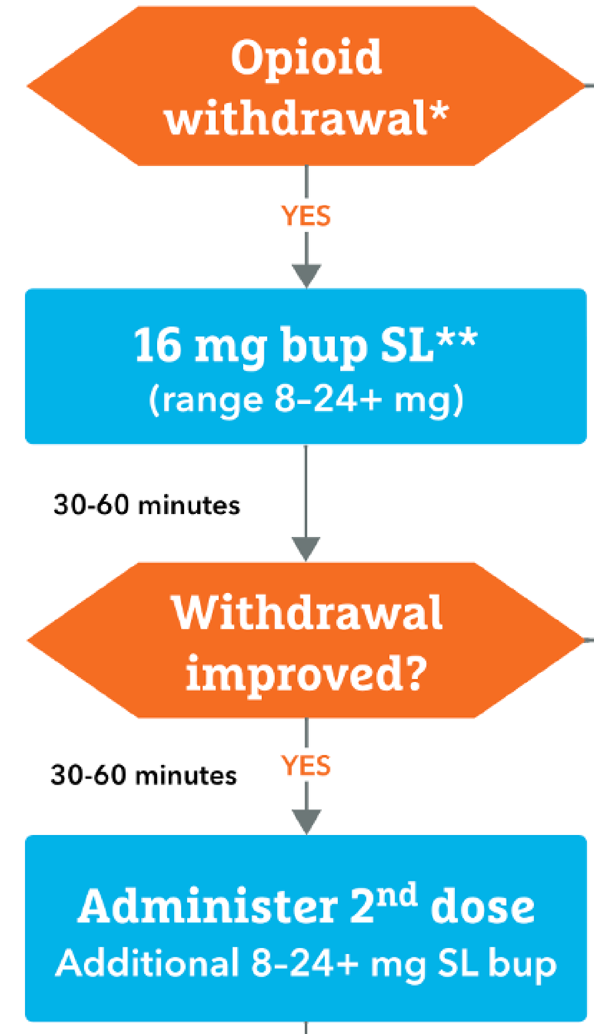
Low-Dose Bup Initiation (Day 2)

Bup 1 mg SL q3h x 8 doses

(q4h x 6 doses is OK)[4]

Low-Dose Bup Initiation (Day 3)

Bup 8 mg SL TID or Injectable XR bup (e.g., 300 mg SQ)



Antagonists

Naloxone → Bup

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Antagonists

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

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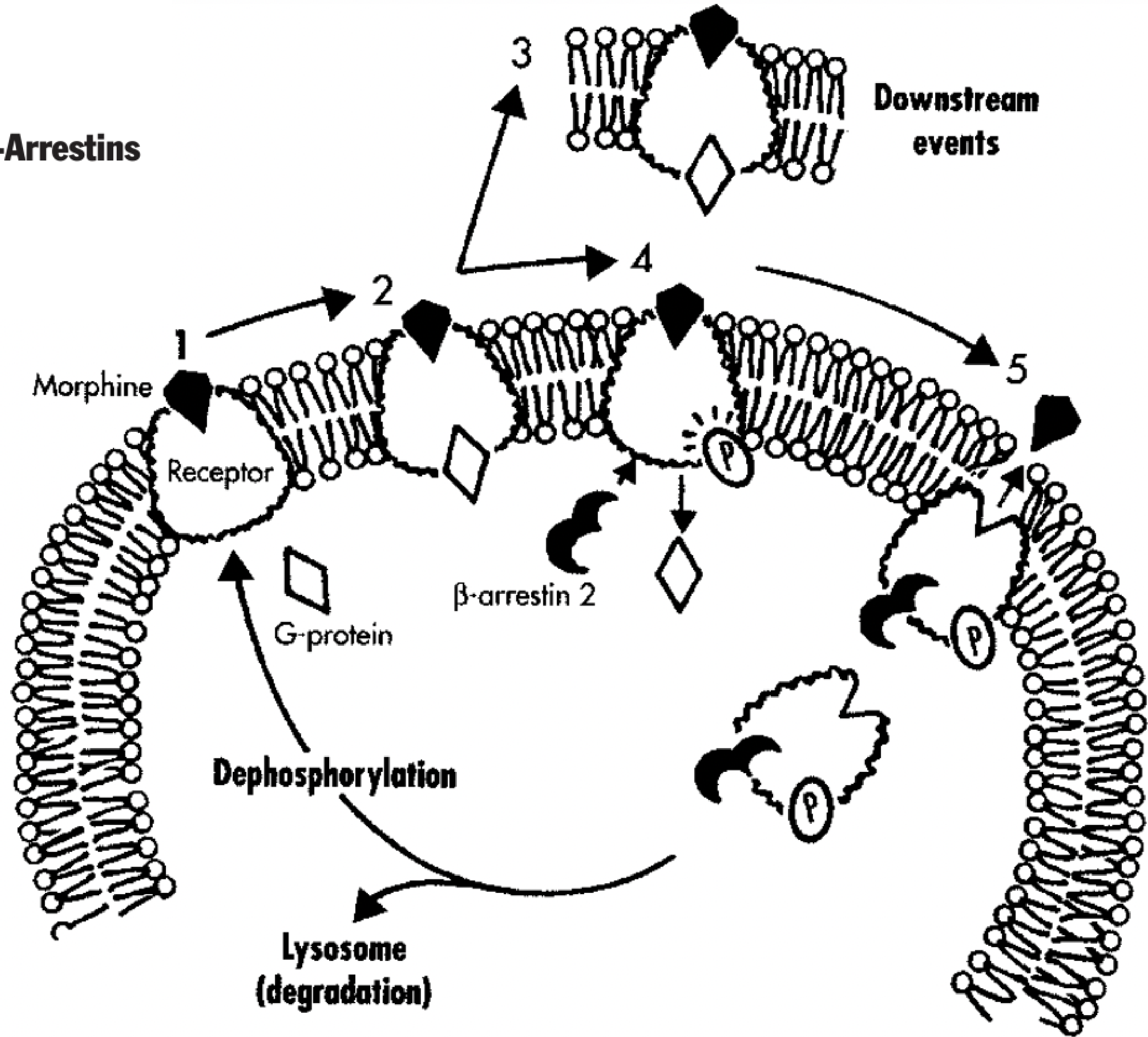
Medical Intelligence

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.



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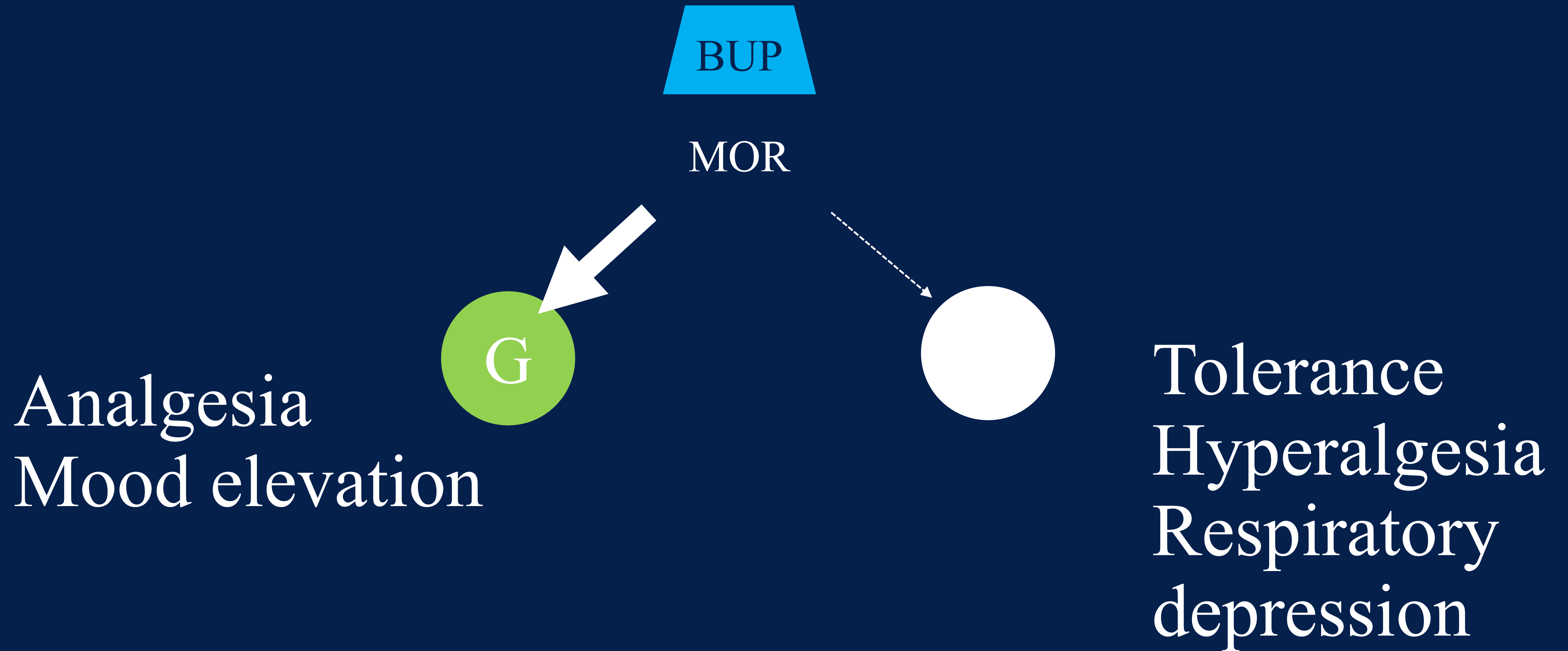
Buprenorphine has partial Beta-arrestin activity



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)

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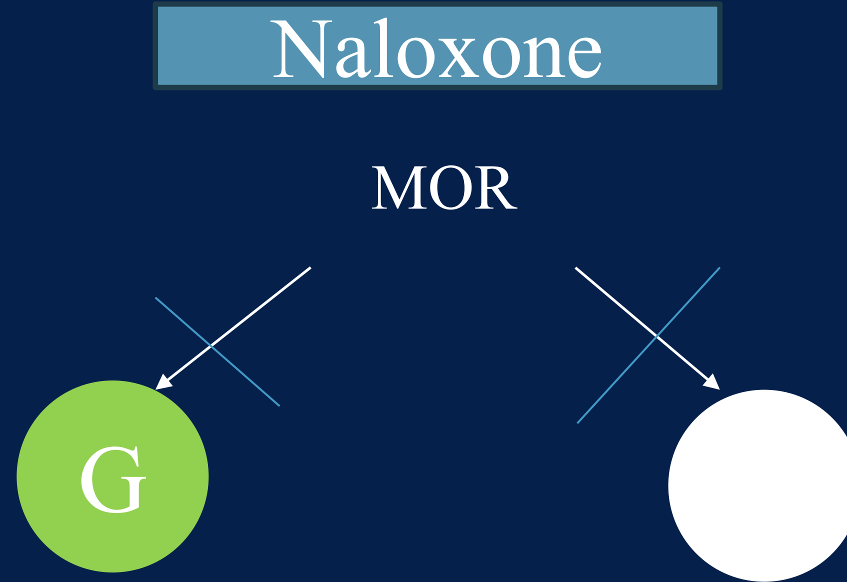
Naloxone completely blocks Beta arrestin



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.

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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

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DTI Buprenorphine from Methadone

- *Off label, case series submitted*

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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”

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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

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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.

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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

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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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The protocols are only useful if they're in your hands when it matters.

10:24

Azar Lab

New Firstline App Updated

Emerging Guidelines

Standard Guidelines

Recently Viewed

Symptom-Inhibited Fentanyl Induction (SIFI)

Medetomidine Objective Withdrawal Scale (MOWS)

See it in action →

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