

Buprenorphine Initiation in the Age of Fentanyl

Elizabeth Salisbury-Afshar,
MD, MPH

Great Lakes ATTC

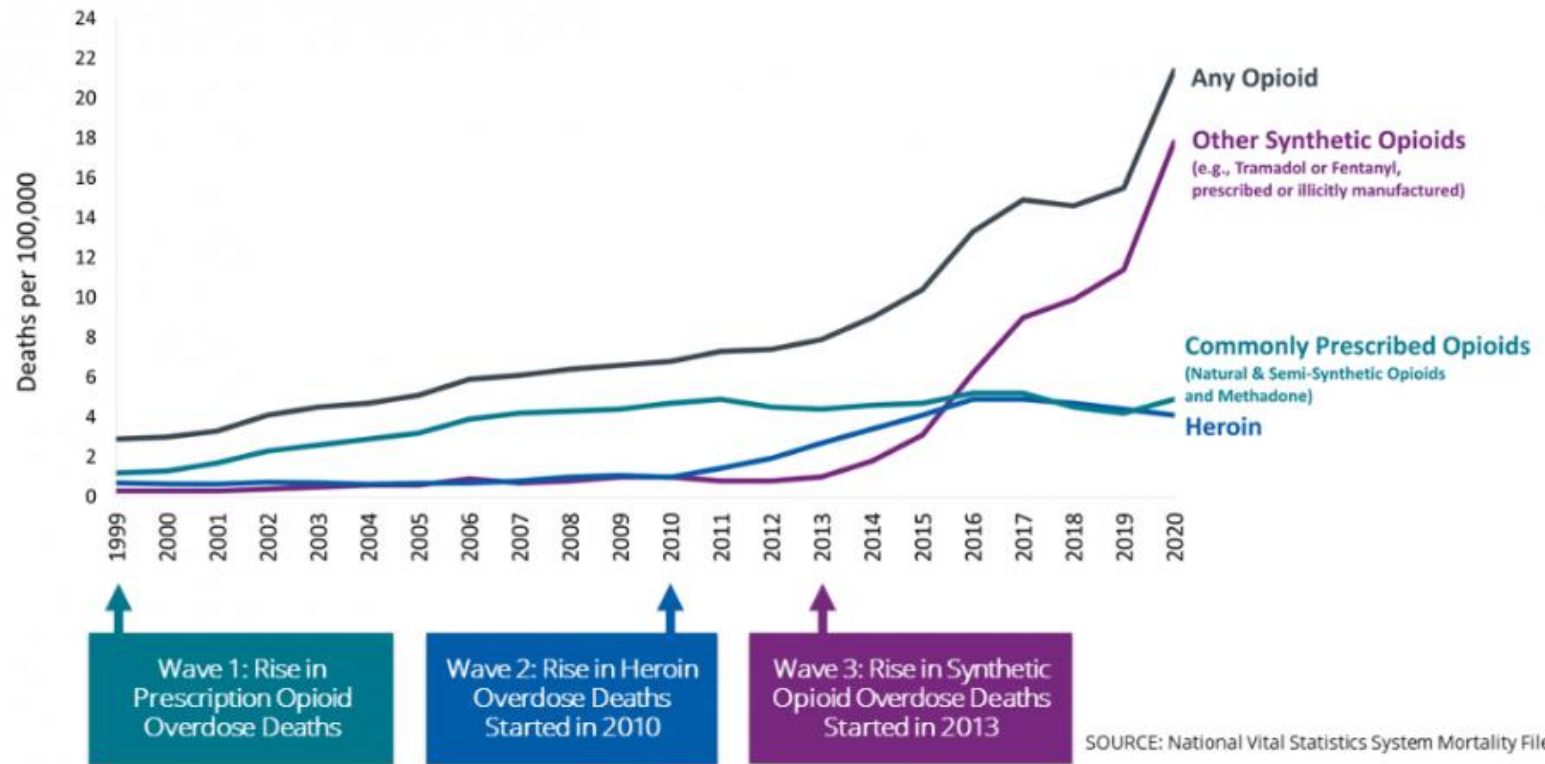
April 2023



Learning Objectives

- Describe the evolving non-pharmaceutical opioid supply
- Describe the challenges of buprenorphine initiation in the fentanyl era
- Name three potential approaches to buprenorphine initiation
- Counsel on reducing fentanyl-related harms

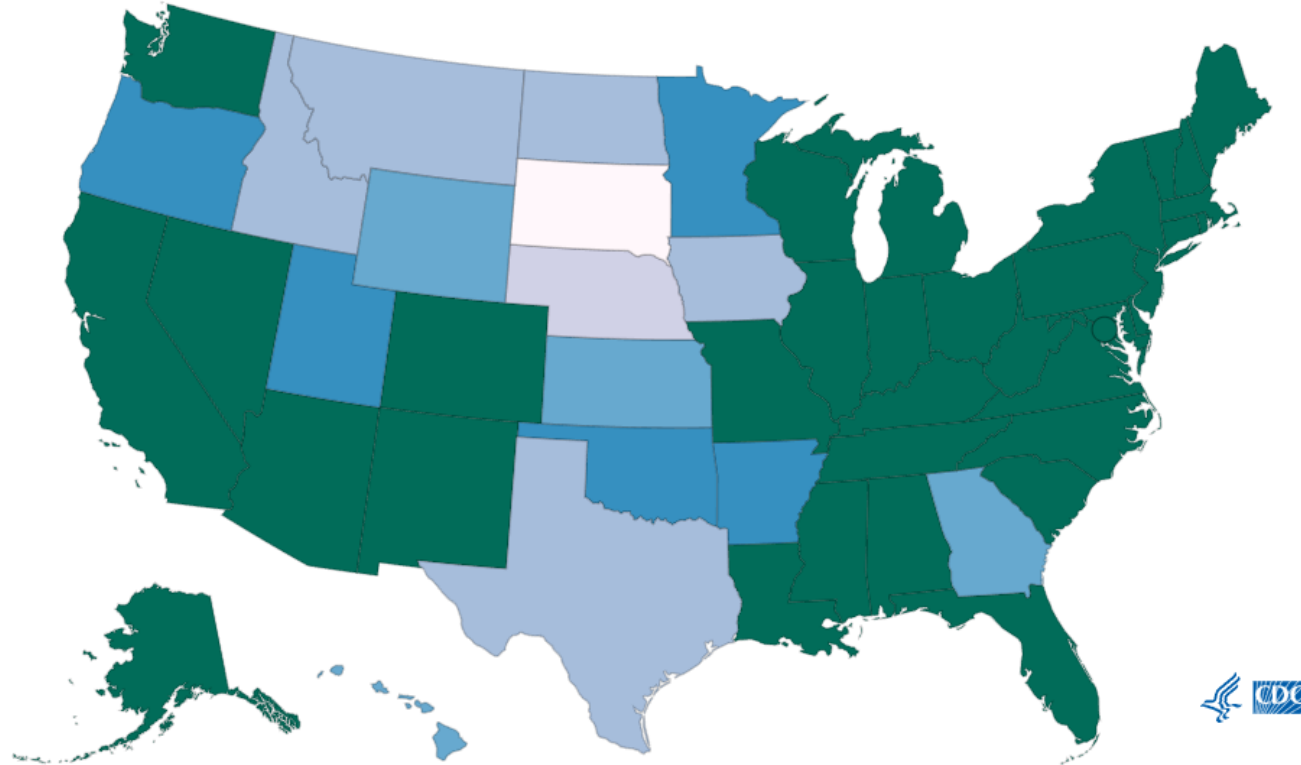
Three Waves of Opioid Overdose Deaths



From 1999–2020, more than 564,000 people died from an overdose involving any opioid, including prescription and illicit opioids¹.

Overdose Death Rates, 2020

Number and Age-adjusted Rates of Drug Overdose Deaths by State, US 2020



Range Category

- | | |
|----------------|----------------|
| ○ 6.9 to 11.0 | ○ 11.1 to 13.5 |
| ○ 13.6 to 16.0 | ○ 16.1 to 18.5 |
| ○ 18.6 to 21.0 | ○ 21.1 to 82.0 |

Drivers of Fentanyl Supply

- Increasing restrictions on prescription opioids
- Availability
 - Internet e-commerce (dark web)
 - Increasing number of labs in China
 - Easy to ship (smaller volume)
- Profitability
 - Per 2016 DEA reports, wholesale price is \$2,000-\$4000 per kilo and street value is \$5M-20M

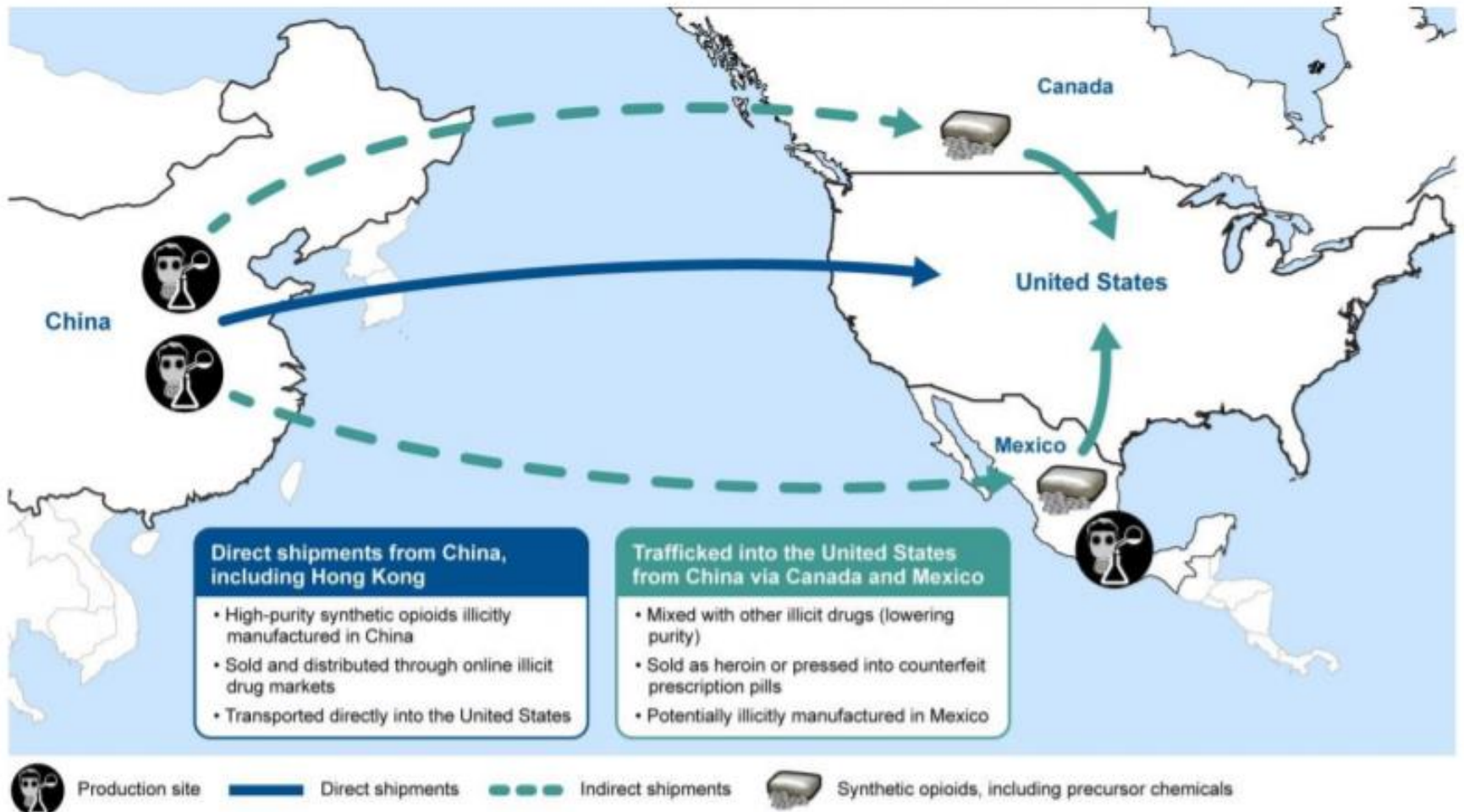


Figure 1 Illicit Synthetic Opioid Flows Originating from China⁶

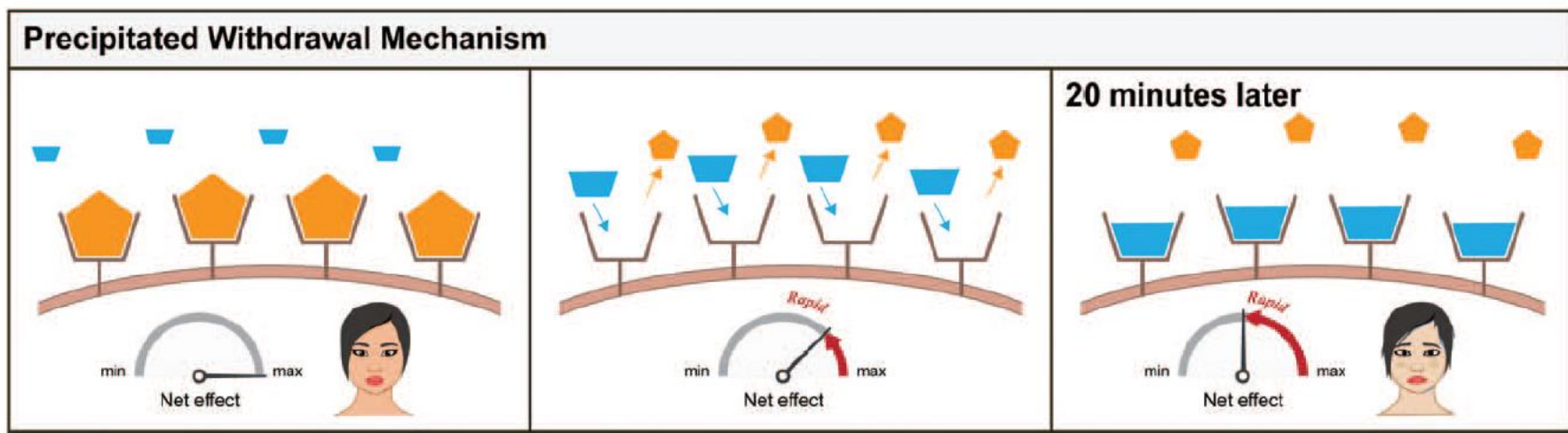
Fentanyl Pharmacology

- 100 x analgesic potency of heroin
 - Respiratory depression can last longer than analgesic effect
- Lipophilicity → high volume of distribution
 - Rapid crossing of blood brain barrier
 - Rapidly distributed to adipose tissue/muscles, slowly released
- Pharmacokinetics
 - Transformed in liver with high first pass clearance (CYP3A4)
 - Distribution time 1.7 min, redistribution 13 min
 - Elimination half life: 3-5 hours
 - Short half life after bolus, long half life after ongoing administration (slowly leaving fat stores)
- Utox pos for norfentanyl for a mean of 13.3 days in treatment program
 - One participant continued to test positive for 26 days after last use

Buprenorphine Initiation Barriers

- Increased precipitated withdrawal
 - Not everyone though!
- Increased tolerance

Precipitated Withdrawal



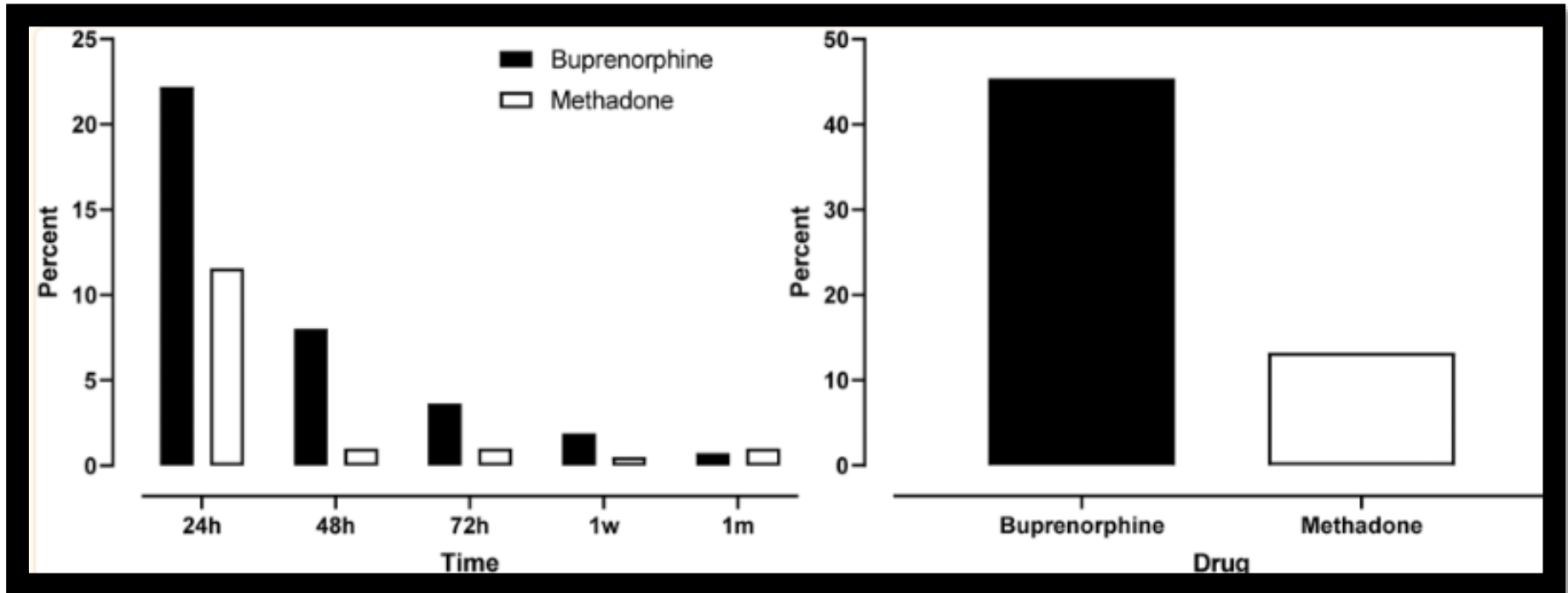
Precipitated Withdrawal: How Common Is It?

- Difficult to say and likely depends on:
 - How we define withdrawal (subjective experience, objective measurement, etc)
 - Time since last use
 - Prevalence of fentanyl in local drug supply
 - Duration of fentanyl use
 - ?? Severity of current withdrawal state
 - Other factors we don't know/understand!

Precipitated Withdrawal: How Common Is It?

- 1679 individuals seeking treatment for OUD in 49 addiction treatment centers in the United States
- Self-report data on opioid withdrawal symptoms after buprenorphine use and after methadone use
 - **22%** (n=152/685) of patients reporting fentanyl use who took buprenorphine within 24 hours of fentanyl reported experiencing severe opioid withdrawal
 - **8%** (55/685) among those who waited less than 48 hours
 - **12%** (n=23/199) of patients reporting fentanyl use took methadone within 24 hours of fentanyl reported experiencing severe withdrawal
 - **1%** (2/199) among those who waited less than 48 hours

Precipitated Withdrawal: How Common Is It?



Longer wait = Less precipitated withdrawal

Precipitated Withdrawal: How Common Is It?

- ER studies have reported lower rates of precipitated withdrawal
 - Retrospective study in ER in Alameda, CA
 - 366 encounters where buprenorphine was initiated
 - 1% (5 cases) experienced precipitated w/d after buprenorphine 4-8mg SL
 - RCT in 28 EDs across the country comparing SL bup and XR-Bup
 - 800 individuals enrolled
 - 1% experienced precipitated withdrawal
 - Among those with precipitated withdrawal, mean time since last fentanyl use was 16 hours

Herring AA, et al. JAMA Netw Open. 2021. PMID: 34264326

D'Onofrio G, Perrone J, Herring AA, et al. Low incidence of precipitated withdrawal in emergency department-initiated buprenorphine, despite high prevalence of fentanyl use. *Acad Emerg Med*. 2022;29(S1):83-87. doi:[10.1111/acem.14511](https://doi.org/10.1111/acem.14511)



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

- Many report fear related to traditional buprenorphine initiation approaches
- New approaches are needed

“Whether attempting novel or conventional initiations with buprenorphine, patient autonomy and patient input are critical to successful initiations and ongoing collaborations.”

How can we support patients?

1. Provide “comfort meds” early during withdrawal
2. Offer adapted buprenorphine initiation schedule
3. Treat precipitated opioid withdrawal

1. Provide Comfort Meds

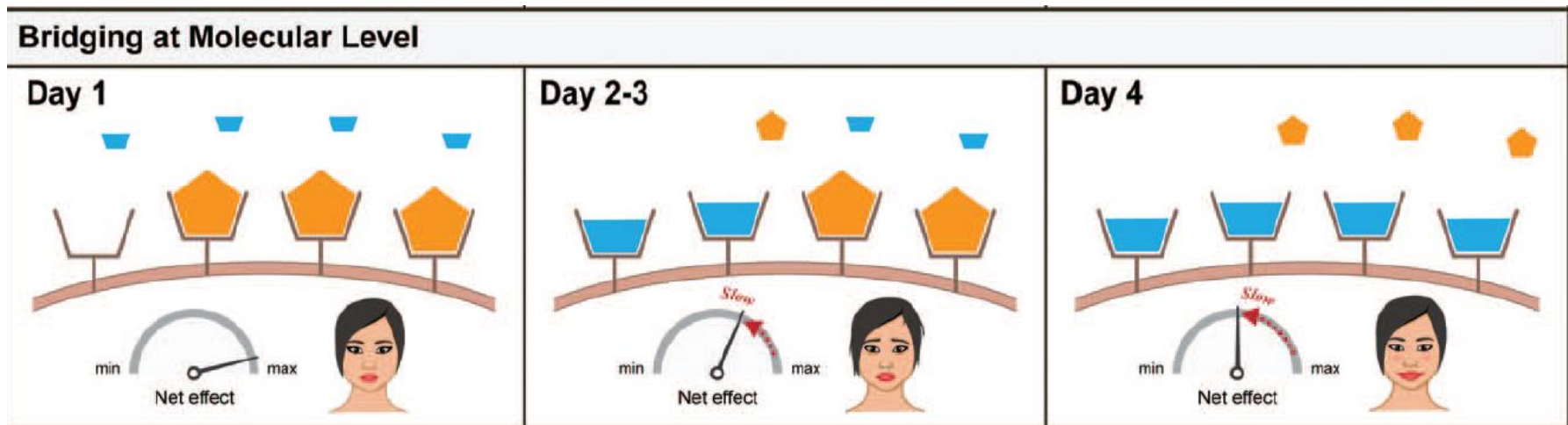
- Consider cost to patient and which symptoms are most bothersome to patient
 - *Lofexidine (0.54mg q6h) or Clonidine (0.1mg q6-8h)*
 - *Ondansetron (4-8mg q6-8h)*
 - *Loperamide (2-4mg q6-12h)*
 - *Others: dicyclomine, acetaminophen, NSAIDs*

2. Adapt Buprenorphine Initiation Approach

	Traditional Dosing	Cross-tapering/ Low Dose Initiation	Rapid Start/ High Dose Initiation
Dosing	4mg SL Bup x 1 Repeat every 1-2 hours Max of 12-16mg on Day 1	Typically starts at 0.5mg-1 mg SL Bup and increase to 16mg over 3-7 days	Initial dose \geq 8mg Second dose 8-24mg Max of 32mg on Day 1
Is withdrawal required?	Yes COWS \geq 8-12	No withdrawal is required (full opioid agonist continues to be administered)	Yes COWS \geq 8-12
When to use it	Low concern for precipitated withdrawal	High concern for precipitated withdrawal; In hospital in cases of severe acute pain	Typically used in ED or inpatient settings as a way to quickly maximize dose (outpatient protocols exist)
Where has it been studied?	Multiple settings	Inpatient settings (Cohort studies) Outpatient settings (Case reports)	Studied in ED (outpatient protocols exist)
Sample Protocol:	https://cabridge.org/resource/guidance-for-patients-starting-buprenorphine-outside-of-hospitals-or-clinics/	https://cabridge.org/resource/starting-buprenorphine-with-microdosing-and-cross-tapering/	https://cabridge.org/tools/on-shift/ https://cabridge.org/resource/rapid-guidance-for-patients-starting-buprenorphine-outside-of-hospitals-or-clinics/

Cross-Tapering/ Low Dose Initiation (AKA “Microdosing”)

- Continue opioid of choice vs inpatient prescribed full opioid agonists
- Small sublingual doses ($\leq 0.5\text{mg}$)
 - Patch or IV small doses can be used in hospital settings
- Often used for methadone conversion
- 3-8 day duration



Cross Taper Schedules



3-day Sublingual Cross Taper Start

Prescribe 2 mg buprenorphine films #6, 8 mg buprenorphine films #4 for 3 day supply)⁴

- Day 1: 0.5 mg (1/4 of 2mg strip) SL buprenorphine q3 hours (4 mg total daily dose), continue full opioid agonists
- Day 2: 1 mg (1/2 of 2 mg strip) SL buprenorphine q3 hours (8 mg total daily dose), continue full opioid agonists
- Day 3: 8-16 mg (1-2 8 mg strips) SL buprenorphine once daily and 4 mg SL q6h prn withdrawal (max 32 mg total daily dose), wean or stop full opioid agonists

7-day Sublingual Cross Taper Start

Prescribe 2 mg buprenorphine SL strips # 15, 8 mg buprenorphine SL strips #4 for 7 day supply

- Day 1: 0.5 mg (1/4 of 2 mg strip) buprenorphine SL daily (0.5 mg total daily dose), continue full opioid agonist
- Day 2: 0.5 mg (1/4 of 2 mg strip) buprenorphine SL BID (1 mg total daily dose), continue full opioid agonist
- Day 3: 1 mg (1/2 of 2 mg strip) buprenorphine SL BID (2 mg total daily dose), continue full opioid agonist
- Day 4: 2 mg buprenorphine SL BID (4 mg total daily dose), continue full opioid agonist
- Day 5: 3 mg (1+1/2 of 2 mg strip) buprenorphine SL BID (6 mg total daily dose), continue full opioid agonist
- Day 6: 4 mg (2 of 2 mg strip) buprenorphine SL BID (8 mg total daily dose), continue full opioid agonist
- Day 7: 6 mg (3 of 2 mg strip) buprenorphine SL BID (12 mg total daily dose), continue full opioid agonist
- Day 8: 16 mg (2 of 8 mg strip) buprenorphine qday and 4mg (1/2 of 8 mg strip) q6h prn withdrawal (max 32 mg total daily dose), wean or stop full opioid agonists

High Dose Initiation/Rapid Start (AKA “Macrodosing”)

- Primarily studied in ED settings
- Requires adequate withdrawal (COWS ≥ 8)
 - Initial dose of 4-8mg with re-assessment in one hour
 - Second dose of 8-24mg (max of 32mg on day 1)
- Post-overdose reversal in ED
 - COWS >4
 - 16mg SL buprenorphine in single or divided doses over 1-2 hours

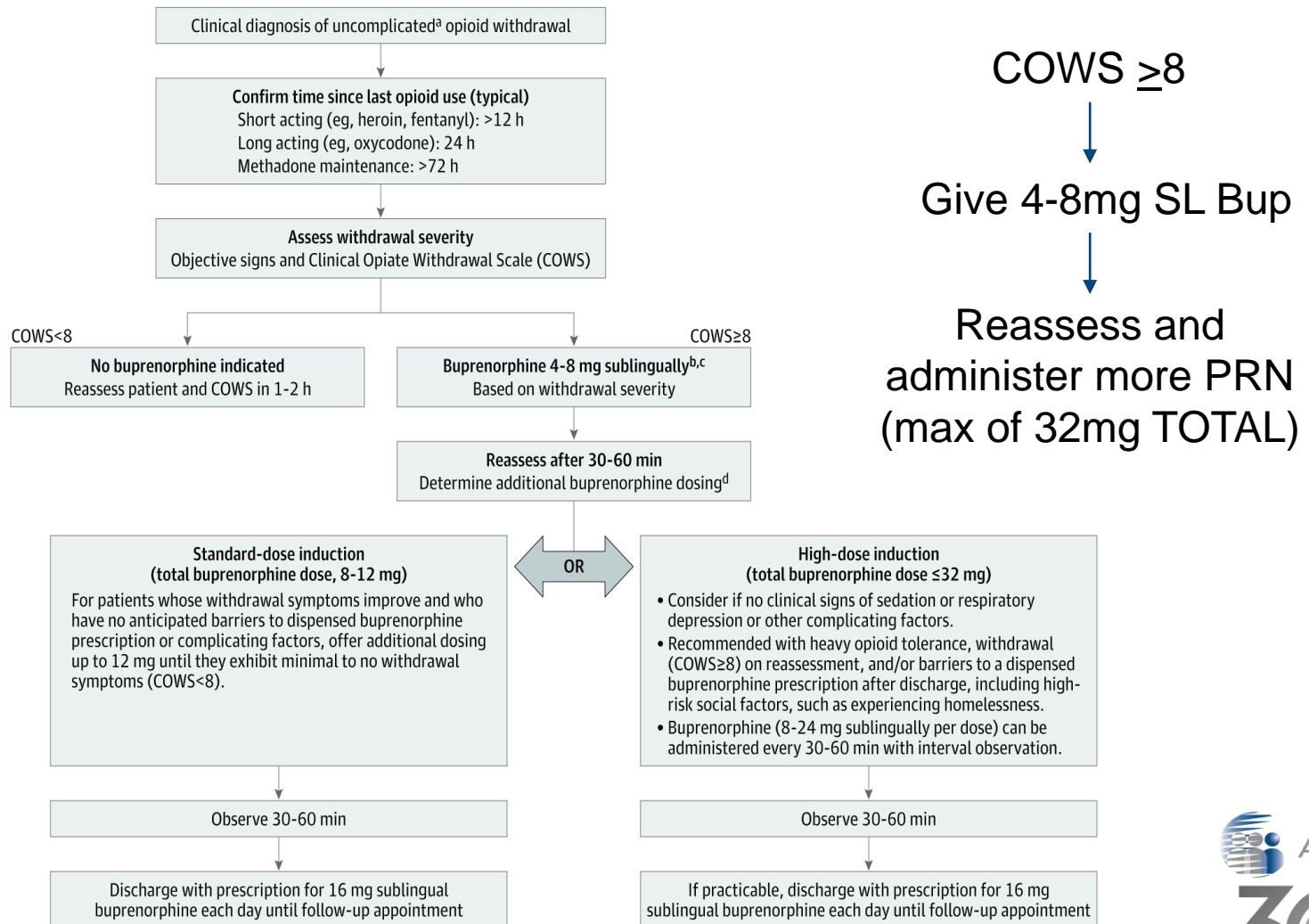
<https://cabridge.org/tools/on-shift/>

<https://cabridge.org/resource/starting-buprenorphine-immediately-after-reversal-of-opioid-overdose-with-naloxone/>

Herring AA, et al. JAMA Netw Open. 2021. PMID: 34264326



From: **High-Dose Buprenorphine Induction in the Emergency Department for Treatment of Opioid Use Disorder**



High Dose Buprenorphine Initiation Case Series

Retrospective Case Series at Highland Hospital (Alameda CA)

- Considered “high dose” if patient received ≥ 12 mg during ED stay
- 366 “high dose” encounters
 - 138 (38%) doses ≥ 28 mg during ED stay

Precipitated withdrawal

- 5 cases (1%) of precipitated w/d
 - 4/5 cases occurred after 8mg bup
 - Additional bup treated precipitated w/d

Adverse Events

- 2-6% experienced nausea or vomiting
 - Not dose dependent
- No cases of respiratory depression or sedation

3. Treat precipitated withdrawal

- How to treat opioid withdrawal?
 - Give more buprenorphine
 - Very little evidence, but case reports and expert guidance suggests this might help
 - Unlikely to make it worse; might reduce the length of withdrawal
 - Alternative: Hold buprenorphine initiation for 24 hours and treat opioid withdrawal using full-agonist opioids
 - Use non-opioid adjuvants liberally
 - Recent research has described ketamine, benzodiazepines, and other non-traditional pharmacotherapy

Cases and discussion

Outpatient Case Study: Mr. M

- Mr. M is a 51 yo man who presents to clinic requesting to start buprenorphine for treatment of OUD.
- He has a 30-year history of heroin use (via injection previously, currently only via insufflation), with only prolonged periods of abstinence being associated with incarceration and after one residential stay 9 years ago.
 - Remote history of methadone treatment (max dose of 90mg daily).
 - His only past buprenorphine use was from friends while withdrawing and has felt that the buprenorphine made his symptoms worse.
- He is very concerned about experiencing withdrawal again.
- All MOUD discussed, and he feels strongly he does not want methadone or XR naltrexone.

Case Study: Mr. M (continued)












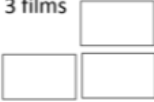



- He works most days of the week (labor job and paid under the table) and reports he will not be able to tolerate any opioid withdrawal
- He is currently experiencing homelessness and is sleeping in his car
- He is interested in buprenorphine using low dose initiation because he:
 - Wants to avoid any withdrawal
 - Has experienced precipitated w/d in past when using buprenorphine
 - “I want to get sober; I want to enjoy the days I have left. I am tired of this.”
 - He is also interested in residential treatment but is hesitant to discuss with his PO at this time (currently does not have funding to pay for room and board).

How would you approach
his initiation?

Low Dose Initiation Instruction

2-0.5mg Buprenorphine-naloxone film



	Date	Morning 	Evening 	Total Dose
Day 1		1/2 film 		1mg
Day 2		1/2 film 	1/2 film 	2 mg
Day 3		1 film 	1 film 	4mg
Day 4		1 1/2 film 	1 1/2 film 	6mg
Day 5		2 films 	2 films 	8mg
Day 6		3 films 	3 films 	12mg (Try to <u>stop</u> other opioid use)
Day 7		3-4 films 	3-4 films 	12-16mg (Try to <u>stop</u> other opioid use)

Created by E. Salisbury-Afshar
Last updated April 2021

Case Study: Mr. M (continued)

- He had intermittent follow up for many months
 - Toxicology intermittently positive for buprenorphine
 - Toxicology consistently positive for other opioids
 - History, toxicology, and remaining film count never aligned
- Interested in residential, but probation status complicated this
- Eventually was lost to care

Questions and Discussion from Mr. M's Case

Low Dose Initiation in Outpatient Setting: Lessons learned

- Many patients who use fentanyl are still tolerating traditional starts and/or prefer rapid start- patient preference is important!
- Ideal if we can offer frequent visits (phone or in-person) when using low dose initiation
- Some patients have a hard time managing this many films and following dosing instructions (handout with pictures may be helpful)
- Reserving this for special circumstances:
 - Recent history of precipitated withdrawal even with adequate withdrawal
 - Patient inability to tolerate moderate withdrawal (COWS ≥ 12)
 - Patient confidence in ability to manage medication

When to avoid 7 day low dose initiation

- Patient doesn't want to continue using heroin/fentanyl during initiation
- Patient is already in significant withdrawal
- Patient prefers rapid start
- Difficulties with health literacy or medication adherence
- Patients unable to self-administer doses or unable to dose sufficiently (sober living home, other place where meds will be held/not available)

Alternative: 3 day cross-taper

- 3 day sublingual cross-taper
 - Day 1: 0.5mg SL buprenorphine Q3 hours (total 4mg on first day); continue full agonist
 - Day 2: 1mg SL buprenorphine Q4 hours (total of 8mg on second day); continue full agonist
 - Day 3: 8mg SL buprenorphine BID (total of 16mg on third day); wean or stop full agonist

Alternative: Rapid Start

- Wait until you feel sick
- Start with 8mg dose; take another 8mg after 1 hour
- Other supportive care (depending on patient preference and reported symptoms):
 - Clonidine 0.1 mg QID
 - Ondansetron 4mg PO QID
 - Dicyclomine 20mg PO QID
 - Immodium 2mg QID



Rapid Self-Start

Guidance for patients starting buprenorphine outside of hospitals or clinics

For people with **HIGHER opioid tolerance**, experience with withdrawal, or experience with buprenorphine

- 1 Plan to take a day off and have a place to rest.
- 2 Stop using and wait until you feel sick from withdrawals (at least 12 hours is best).
- 3 Dose an 8mg tablet or strip **UNDER** your tongue.
- 4 Repeat dose (another 8mg) in an hour to feel well.
- 5 Start 16mg per day the next day.

If you have started Bup before:

- If it went well, that's great! Just do that again.
- If it was difficult, talk with your care team to figure what happened and find ways to make it better this time.

If you have never started Bup before:

- Gather your support team and if possible take a "day off."
- You are going to want space to rest. Don't drive.
- Using cocaine, meth, alcohol or pills actually makes starting Bup harder, but that is up to you. Be safe.



Place dose under your tongue (sublingual).

If you have a light habit: (For example, 5 "Norco 10's" a day)

- Consider a low dose: start with 4mg and stop at 8mg total.
- **WARNING:** Not enough Bup won't treat your withdrawals.

If you have a heavy habit: (For example, injecting 2g heroin a day)

- Consider a high dose: start with first dose of 16mg.
- The effects of Bup max out at around 24-32mg.
- **WARNING:** Too much Bup can make you feel sick and sleepy.

Not going well? Have questions?

Contact your Substance Use Navigator for help! It's our job.

Call or text your Substance Use Navigator for help at _____

Impact of Fentanyl Use on Buprenorphine Treatment Retention and Opioid Abstinence

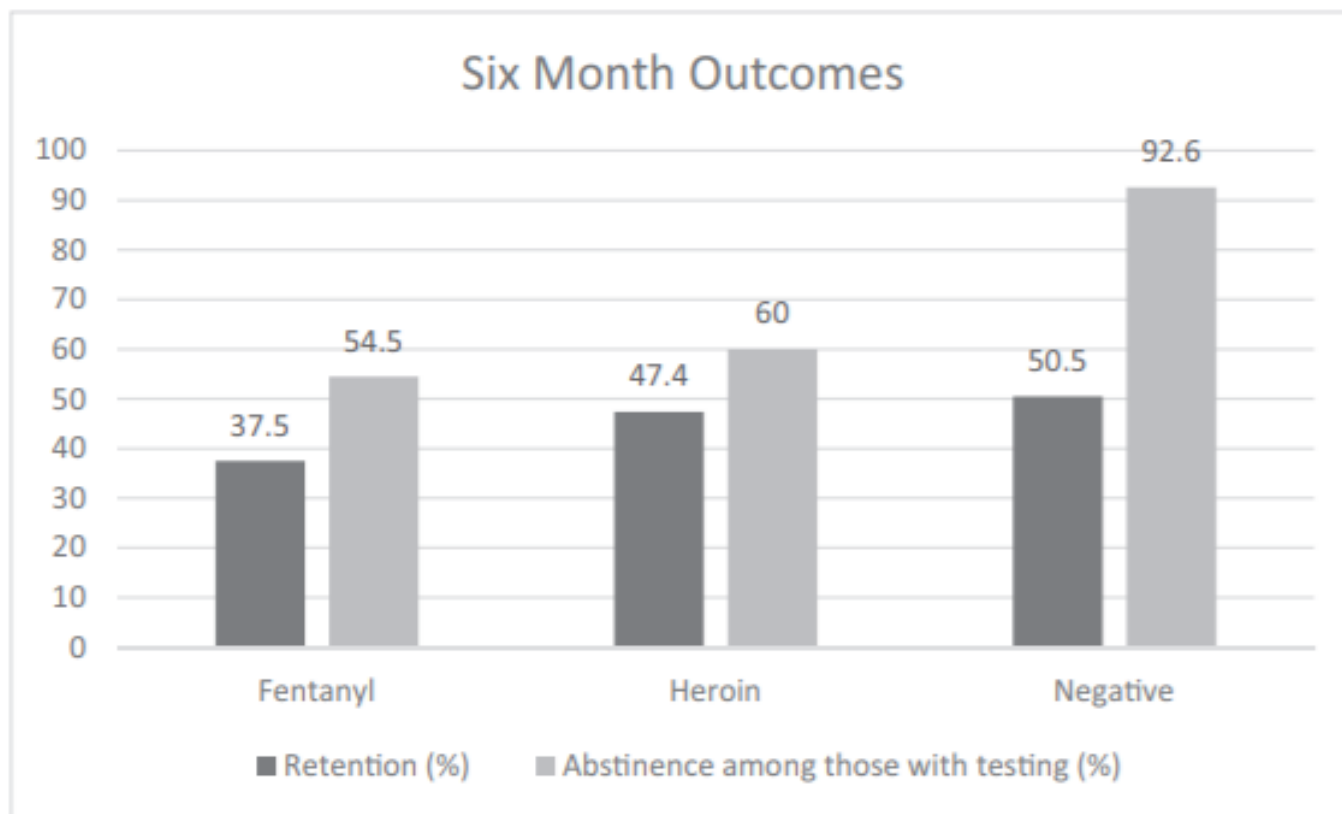


FIGURE 1. Retention and opioid abstinence among those retained at six-month follow-up.

Buprenorphine Best Practices

- Evidence

- To achieve blockade, need <20% mu opioid receptor available (at least 16 mg)
- For higher opioid doses, higher opioid potency, may need higher bup doses
- Preliminary data shows higher retention on 32 mg
- Preliminary data shows less apnea on higher doses

- Anecdote

- 24 mg and higher
- Subcutaneous buprenorphine (after SL start)

Harm Reduction Tips:

- Try not to use alone
- Always carry naloxone
- Assume all opioids are fentanyl
- Pressed pills may contain fentanyl, even if they look like “real” oxy, Xanax, etc.
- Consider using fentanyl test strips (FTS) on pills, cocaine, methamphetamine
 - Dilution matters! Make sure to follow instructions
 - In Madison, fentanyl test strips are available at Vivent
 - WI legislators removed FTS from paraphernalia law-
awaiting Governor’s signature

Drug Supply Awareness: Fentanyl Test Strips (FTS)

- Using FTS & having a positive result is associated with a positive change in overdose risk behaviors
- 4% false negative rate and 10% false positive rate
- Guide for using FTS:
<https://sites.google.com/anypositivechange.org/fentanylteststrips/home>



Image used with permission from Suzanne Carlberg-Racich

Peiper et al. (2018). International Journal of Drug Policy. doi.org/10.1016/j.drugpo.2018.08.007

Park et al. (2021). International Journal of Drug Policy. doi.org/10.1016/j.drugpo.2021.103196

Kreiger et al. (2018). International Journal of Drug Policy. doi.org/10.1016/j.drugpo.2018.09.009

Green et al. (2020). International Journal of Drug Policy. doi.org/10.1016/j.drugpo.2020.102661

Key Takeaways

- Fentanyl is increasingly the primary opioid involved in overdoses in the Midwest and nationally.
- Likely because of its lipophilicity, there may be increased risk of precipitated withdrawal with buprenorphine initiation.
- There are multiple buprenorphine initiation approaches that can be used:
 - Low dose initiation/cross-tapering (3- and 7-day protocols exist)
 - High-dose/rapid start
 - Traditional initiation
- Fentanyl test strips provide information on fentanyl presence and allow people to adjust behaviors
- Naloxone reverses fentanyl overdoses and should be prescribed every time

Questions and Discussion

Inpatient Case Study: Mr. J

- Mr. J is a 32 yo man admitted with a septic joint and severe OUD
- He received 30mg of oxycodone in the emergency department and is currently reporting 10/10 pain
- He reports daily heroin/fentanyl use by injection (estimates 1-2 grams per day), with last use immediately prior to coming to the hospital
 - He feels that if his pain isn't better managed, he will have to leave prematurely because he doesn't think he can handle the pain
 - He denies current withdrawal symptoms
 - He has used buprenorphine in the past- never in a formal treatment program but has found it helpful when trying to self-manage withdrawal symptoms

Case Study: Mr. J (continued)

- OUD diagnosis made
- OUD treatment options are discussed, and he is interested in initiating buprenorphine, but his primary concern is regarding adequate pain management
- Ortho team feels that he will be in the hospital for at least 14 days for administration of IV antibiotics

What would you do/recommend?

Inpatient Buprenorphine Considerations

	Low/No Pain		High Pain	
	COWS <8	COWS $\geq 8^*$	COWS <8	COWS $\geq 8^*$
Short length of stay (<6 days)	Low dose initiation (rapid titration)	Traditional dosing OR Rapid start/High dose initiation	Low-dose initiation via rapid titration (with adjunct full opioid agonists [FOA])	Traditional dosing (+ adjunct FOA) OR Low-dose initiation with rapid titration (+ adjunct FOA)
Long length of stay (≥ 6 days)	Low dose initiation (rapid titration)	Traditional dosing or Rapid start/High dose initiation	Low dose initiation (with adjunct FOA)	Traditional dosing (+ adjunct FOA) OR Low-dose initiation (+ adjunct FOA)

*In settings of chronic fentanyl use, recommend waiting until COWS ≥ 12

Case Study: Mr. J (continued)

- Discussed potential treatment options with Mr. J who preferred low dose initiation because:
 - Concern about adequate pain management
 - Anticipated longer duration of stay
 - Not currently in withdrawal
 - He is aware that low dose buprenorphine can be used in combination with full agonist treatment to maximize pain control and prevent need for withdrawal

Case Study: Mr. J (continued)

	Buprenorphine Dose	Full Agonist
Day 1	1mg buprenorphine	Hydromorphone- IV or PO*
Day 2	1mg buprenorphine BID (2mg total)	Hydromorphone- IV or PO*
Day 3	2mg buprenorphine BID (4mg total)	Hydromorphone- IV or PO*
Day 4	2mg buprenorphine TID (6mg total)	Hydromorphone- IV or PO*
Day 5	2mg buprenorphine Q6 hours (8mg total)	Hydromorphone- IV or PO*
Day 6	4mg buprenorphine TID (12mg total)	Hydromorphone- aim to reduce total daily HM dose given buprenorphine at 12mg daily
Day 7	Re-assess; can go to 4mg buprenorphine Q6 hours (16mg total) IF adequate or near-adequate pain control	Hydromorphone- aim to continue to reduce dose as buprenorphine doses increase
Day 8+	Re-assess; can go to 8mg buprenorphine TID (24mg total) IF adequate or near-adequate pain control	Aim to minimize/stop additional full opioid agonist by time of discharge

* Dose based on patient's level of pain, hold for sedation

Case Study: Mr. J's Pain management (continued)

- Expect patients with chronic opioid daily use will have high opioid tolerance.
- Maximize non-opioid pain medications:
 - SCHEDULED APAP, SCHEDULED NSAIDS, gabapentin as clinically appropriate
 - Consider APS consult/ketamine if clinically appropriate
- Dose opioids based on patient's reported pain; hold for over-sedation or reduced respiratory rate.
 - Calculate total MME of full opioid agonists daily, esp if opioids being used are changing (or IV to PO transition)
- Expect minimal analgesia from buprenorphine <12mg total daily dose
 - Buprenorphine has high binding affinity, so at doses ≥ 12 mg total daily dose, full agonists with lower binding affinity (i.e. oxycodone) will have minimal analgesic effect
 - Split buprenorphine dose across day to optimize analgesic properties

Questions and Discussion for Mr. J's case

Inpatient Case Study: Ms. A

- Ms. A is a 25 yo woman with history of opioid and methamphetamine use admitted to the hospital after an MVC.
 - She experienced splenic injury and pulmonary contusion.
 - Addiction medicine consult team is consulted on hospital day 2
 - Day 1- oxycodone 15mg, fentanyl 150mcg, and hydromorphone 0.8mg on day 1
 - Day 2 (so far)- oxycodone 30mg

Inpatient Case Study: Ms. A (cont)

- Diagnoses- OUD, severe; Meth use disorder, severe
- Patient is open to the idea of starting buprenorphine “later” because she is concerned about precipitated withdrawal and uncontrolled pain.
- She would prefer to continue on full agonist opioids for now.

What questions would you have?

Inpatient Case Study: Ms. A (cont)

- Primary team notes that she is stable and should be able to discharge today.
- Primary team says they will not be discharging her on any opioids.
- She has an assigned PCP but has never met them.
- COWS score is 5 (she had just received oxycodone).
- She is terrified of experiencing withdrawal.

What would you do?

Inpatient Case Study: Ms. J (cont)

- 1mg Q2 hours for up to a total of 8 doses (8 mg)
- Supportive medications ordered for overnight (clonidine, ondansetron, etc)
- Patient reported mild sweats and chills, but otherwise did well.

- Went home on 4mg TID-QID
- Follow up in 6 days- advised to bring any remaining films to appointment
- Naloxone Rx

- Stabilized at 8mg BID

Sample Rapid Low-Dose Initiation Schedule

TABLE 2. Titration schedule for Case 2

	Buprenorphine/Naloxone*		Hydromorphone	
	Dosing	Total Daily Dose	Dosing	Total Daily Dose
Day 0	N/A		3 mg PO q4h regular 2-4 mg PO q4h PRN	24 mg
Day 1	0.5 mg SL q3h	2.5 mg	3 mg PO q4h regular 2-4 mg PO q4h PRN	26 mg
Day 2	1 mg SL q3h	8 mg	3 mg PO q4h regular 2-4 mg PO q4h PRN	24 mg
Day 3	12 mg SL daily	12 mg	Discontinued	

*Expressed as milligrams of buprenorphine in buprenorphine/naloxone sublingual tablet.

Questions and Discussion for Ms. A's case