

# Fentanyl Updates

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# Disclosures

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No conflicts of interest to disclose

# Disclaimer

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# Data Considerations

*Data in this presentation offer a limited perspective of how systemic, social, and economic factors impact health. We recognize that racism, not race, creates and perpetuates health disparities.*



To Learn More:

<https://www.cdc.gov/minorityhealth/racism-disparities>

# Agenda

1. Overview and pharmacology
2. Fentanyl-involved overdose
3. Implications for OUD treatment strategies
4. Areas for further research

- I use “fentanyl” as short-hand for fentanyl, fentanyl analogues, and other highly-potent synthetic opioids (HPSO)
- I want to acknowledge that the fentanyl overdose crisis is often syndemic with HIV and other conditions such as homelessness, mental health disorders, cycles of trauma, etc.

# Fentanyl

- Synthetic opioid active at mu opioid receptor
  - Not detected on routine urine toxicology screens
- Smoked, snorted, injected, taken orally
- Relatively easy to synthesize and traffic, hugely profitable to drug dealers
- Nearly universally present in U.S. drug markets
  - Sold as pressed pills (“blues”), powder
  - Found in heroin, methamphetamine, cocaine - assume anything illicit contains fentanyl
  - Amount and strength vary unpredictably
  - Look, smell, taste will not tell you if substance contains fentanyl

# Why is fentanyl so deadly?

- 80-100 x more potent than morphine
  - Greater ability to activate receptor, less of drug is required for effect
  - Smaller margin of error for toxicity and overdose
  - Greater down-regulation of opioid receptors
  - Profound and more rapid tolerance, dependence, and withdrawal
- Rapid, profound, prolonged effects on respiratory drive
- Pronounced noradrenergic toxicity (“wooden chest” and laryngospasm)
- High lipophilicity

**WARNING**

**FENTANYL HAS BEEN FOUND IN BLACK TAR**

Recent overdose deaths involved **fentanyl** in black tar. This is new in King County.



**Fentanyl** continues to be most common in **pills**, primarily M30s. It can also be found in **white powders**.



**Reduce overdose risk**

- **Avoid using alone.** If you must use alone, have someone check on you often or use a service like [neverusealone.com](http://neverusealone.com).
- **Have naloxone (Narcan) ready** to reverse an overdose. Find it near you at [stopoverdose.org](http://stopoverdose.org).
- **Recognize signs of overdose:** abnormal breathing (slow or no breath, gurgling, snoring), not responding, grey or blue skin.
- **Call 911** right away if you suspect an overdose.

**WARNING**

**FENTANYL IS KILLING KING COUNTY RESIDENTS**

“Oxycodone” and “Percocet” pills sold on the street or online are **FAKE** and likely contain **fentanyl**.



**Fentanyl** can also be found in **white powders**.



**HOW TO PREVENT OVERDOSE**

- Don't use pills/powders from the street or online
- Don't mix drugs
- Don't use alone
- Have Naloxone (Narcan) ready Find it near you at [stopoverdose.org](http://stopoverdose.org)
- Call 911 if someone overdoses

# Fentanyl is highly lipophilic

- Faster onset of effects: euphoria *and* respiratory suppression
- Short duration of action → frequent use
- Redistribution to fatty tissues → prolonged metabolite elimination
- Less predictable onset of withdrawal
- Blood levels may continue to climb with cumulative dosing as people use frequently and concentrations increase in fatty tissue

**What's up with fentanyl?**

**Strong**  
Fentanyl is a very strong opioid, **50x stronger** than heroin.

**Fast**  
Overdose can happen in **seconds or minutes**.

**Higher Risk**  
Most overdose deaths in WA State now involve **fentanyl**.

**What does it look like?**  
In WA State, most fentanyl has been in blue pills with a "M30" stamp. It's sometimes in drugs that look like powder, or a rock like crack cocaine.  
Fentanyl could be in any drug you buy on the street or online. What fentanyl looks like will continue to change.

**What's the risk?**  
The amount and strength of fentanyl can vary a lot. One pill might have a deadly amount. Another pill might have very little, if any, fentanyl.

**Naloxone works on fentanyl.**  
Carry naloxone. Tell people you have it and how to use it. Because fentanyl is so strong, it may take more than one dose to work. Keep extra kits around.

**Meth does not protect from OD.**  
Using meth along with fentanyl actually **increases the chance of overdose**. If you use both meth and fentanyl, use one at a time, and pace yourself slowly with small amounts.

**Mythbusting Facts**

- 1 You can overdose on fentanyl however you use it: if you smoke, swallow, snort, or inject.
- 2 It's safe to respond to a fentanyl overdose! You can't overdose just by touching fentanyl or drugs that contain fentanyl.

Logos for ADAI, Center for Community-Engaged Education, Research and Research, University of Washington, and StopOverdose.org.

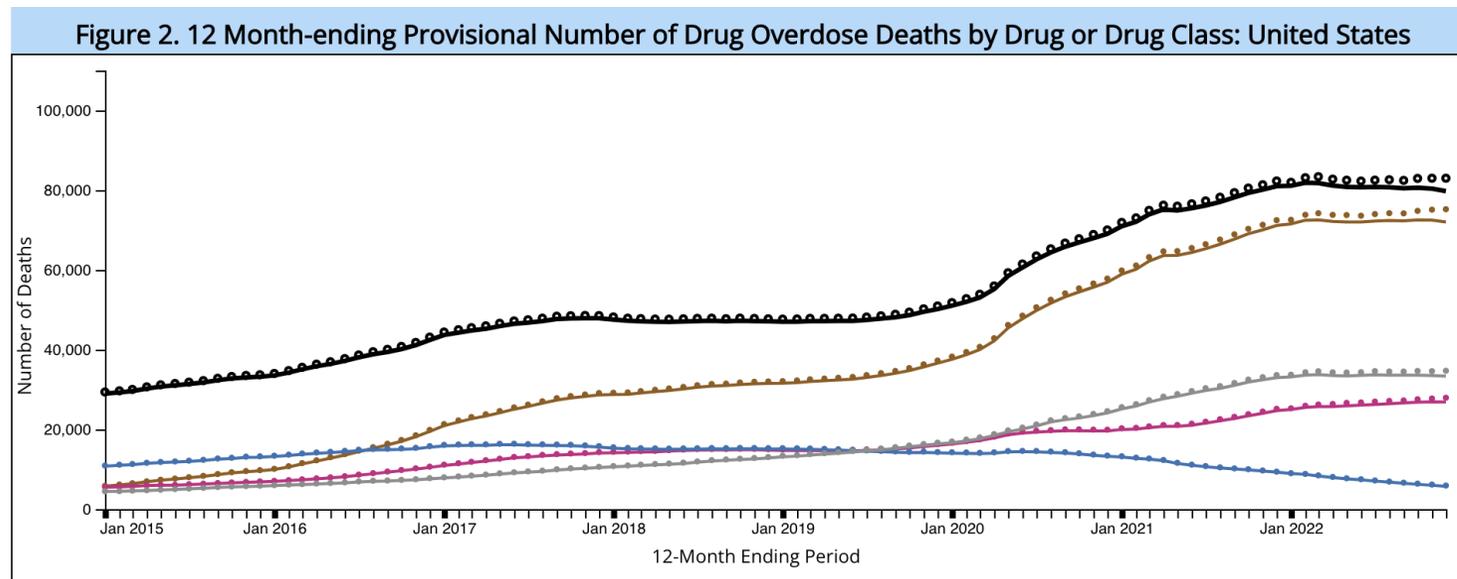
# Withdrawal may be harder to tolerate

- Occurs with cessation or reduction in use
  - Physiological and psychological
  - **Subjective sense of withdrawal**
  - Anxiety, restlessness, insomnia
  - Nausea, vomiting, diarrhea
  - Chills, sweats, body aches
  - Rhinorrhea, tearing, yawning
  - Pupillary dilation, piloerection
- **Many people use continuously to avoid withdrawal symptoms**



# Overdose death crisis

- Year ending December 2022: 109,680 overdose deaths in U.S. of which 82,998 (76%) involved an opioid
- 82% of opioid-involved overdose deaths in 2020 involved fentanyl/HPSO



Any opioid

Fentanyl/HPSO

Legend for Drug or Drug Class

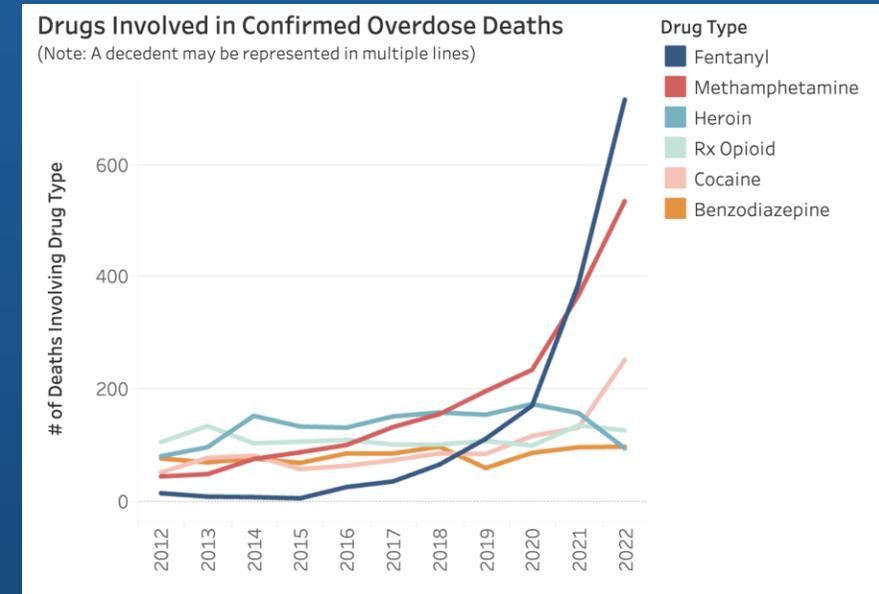
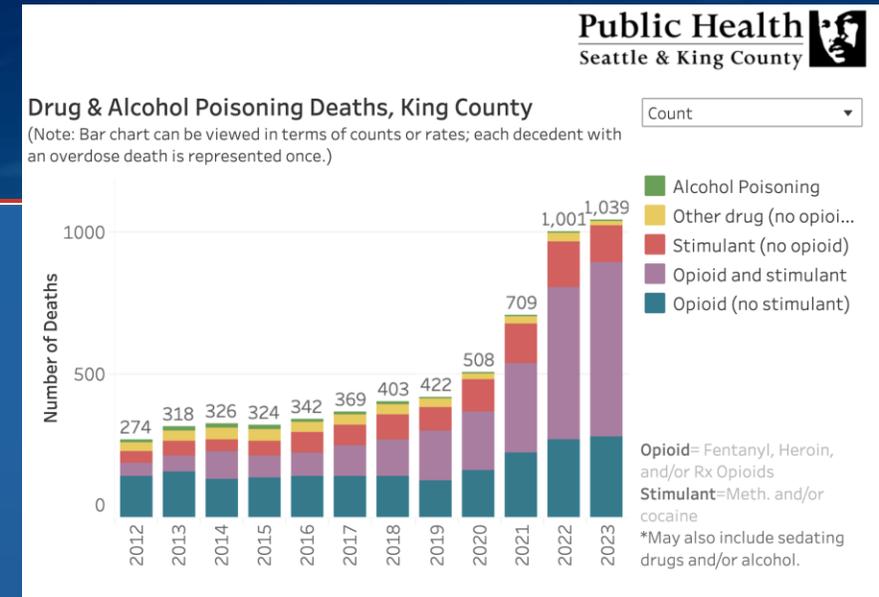
Cocaine (T40.5)
Heroin (T40.1)
Opioids (T40.0-T40.4, T40.6)
Psychostimulants with abuse potential (T43.6)
Synthetic opioids, excl. methadone (T40.4)

--- Reported Value

○ Predicted Value

# King County overdose deaths

- Fentanyl involved in 81% overdose deaths in 2023 thus far
- Dramatic increase in stimulant + opioid-related deaths
- Disproportionate impacts:
  - Those experiencing homelessness or in temporary/supportive housing
  - AI/AN residents
  - Black residents
  - Seattle
  - South King County



# Psychostimulants + opioids: 4<sup>th</sup> wave of opioid epidemic

- Why use both?
  - Synergistic/enhanced high
  - Balance out negative effects, mitigate withdrawal, detox, mitigate harm from opioid use
- Depressant + stimulant drugs → immense pressure on CNS and cardiopulmonary system → increased risk of death
- Unintentional use of fentanyl in those using stimulants - high lethality in those without opioid tolerance

# Fentanyl overdose

- Blue/gray lips or nails, pale/ashy skin, trouble waking up, slow or no breathing
- Chest wall rigidity, laryngospasm may further interfere with breathing
- Multiple doses naloxone often needed (short half-life relative to that of fentanyl, especially in those with chronic use)
- Polysubstance overdose - other medications to stimulate respiration/oxygenation are needed

# Overdose response

- Carry naloxone, ideally >1
- Call 911 before administering naloxone
- Give second dose of naloxone if not responding after 3 minutes
- Provide rescue breaths
- Stay until responders arrive

Image: Washington State Department of Health

## Use Naloxone for a Drug Overdose

You should give naloxone to anyone who has taken drugs and may be overdosing. Someone who is overdosing may stop breathing or their breathing may be slow and labored. **Act fast! An overdose is life threatening.**

Give naloxone even if you do not know what kind of drugs a person took. Naloxone will only work on opioids, but there is no harm if they took a different kind of drug.

**Washington's Good Samaritan Law provides some protection when calling 9-1-1 to save a life – even if drugs are at the scene. (RCW 69.50.315)**

### 1. Check for a response

- Try to wake them up. Shake them and shout their name.
- Rub your knuckles hard on the center of their chest.
- Hold your ear close to their nose, listen and feel for signs of breathing.
- Look at their lips and fingernails – pale, blue, or gray color is a sign of overdose.

### 2. Call 9-1-1

- Tell the operator your exact location.
- Say you are with a person who is not breathing. You do not have to say anything about drugs or medicines at the scene.
- Tell the operator you are going to give the person naloxone.
- Follow any instructions you get from the operator.

### 3. Give naloxone

- There are two common types of naloxone. Follow the "How to Use" instructions on the right.

### 4. Start rescue breathing

- Someone who has overdosed needs oxygen. Naloxone may take a few minutes to start working. Check again to see if they are breathing.
- If you can't hear them breathe or their breath sounds shallow, provide rescue breaths. (See the other side of this sheet.)
- Follow instructions of 9-1-1 operator until help arrives.

### 5. Give a second dose of naloxone

- Wait about 3 minutes for naloxone to take effect.  
**If the person has not responded after 3 minutes, give a second dose.**

### 6. Post care for overdose

- Stay with the person until help arrives. Remember, the Good Samaritan Law offers protections when you call 9-1-1 for an overdose.
- If the person starts breathing on their own, but they do not wake up, roll them on their side to a recovery position. (See the other side of this sheet.)
- When the person wakes up, they may have opioid withdrawal symptoms such as chills, nausea, and muscle aches.
- They may not remember what happened. They may be scared, nervous, or restless. Keep them calm until help arrives. Try to stop them from taking more drugs.

## How to Use

**Nasal spray** – Needs no assembly. **Do not test the device.** Each device only works once. You may need both devices.

- 1 Peel** back the package to remove the device.



- 2 Place** and hold the tip of the nozzle in either nostril.



- 3 Press** the plunger firmly to release the dose into nose.



OR

**Injectable** – This requires assembly.

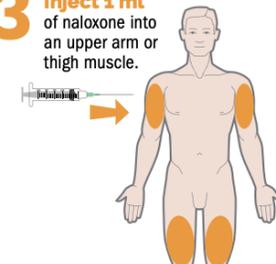
- 1 Remove cap** from naloxone vial and uncover the needle.



- 2 Insert needle** through rubber plug with vial upside down. Pull back on plunger and take up 1 ml.

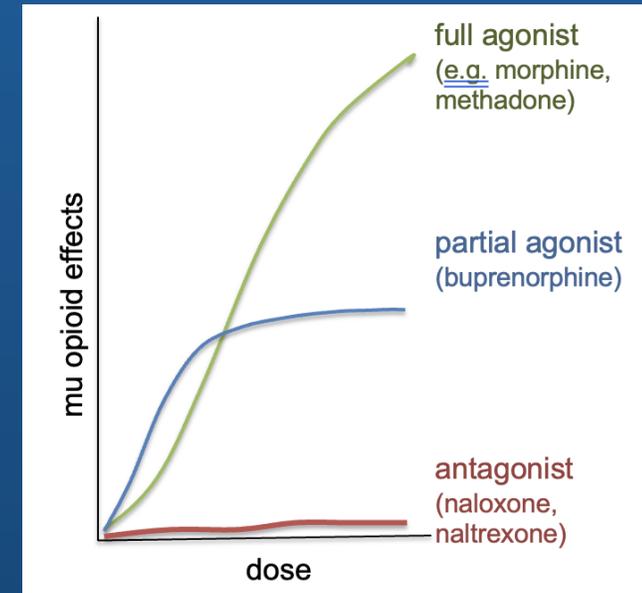
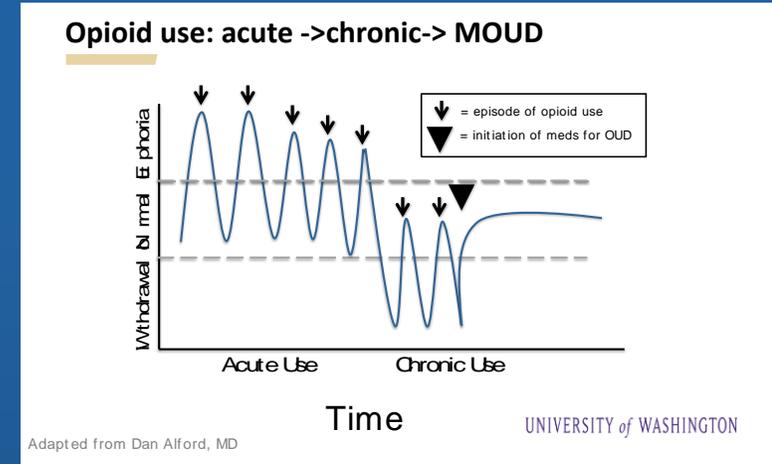


- 3 Inject 1 ml** of naloxone into an upper arm or thigh muscle.



# OUD is a treatable, chronic medical condition

- **Buprenorphine and methadone** – medications for opioid use disorder (MOUD) – are the standard of care and **SAVE LIVES**
- MOUD address cravings and withdrawal symptoms and allow people to engage in other domains of recovery
- Opioid tolerance is protective against overdose



# Anecdotal reports of challenges in treating fentanyl OUD

- More difficult to tolerate withdrawal
  - Higher risk (and less predictable) precipitated withdrawal
  - Difficulty initiating buprenorphine
  - Decreased retention in buprenorphine treatment
  - Higher doses buprenorphine and methadone required to suppress cravings and withdrawal
- **Practice changes preceding rigorous research, driven by scale of overdose death**

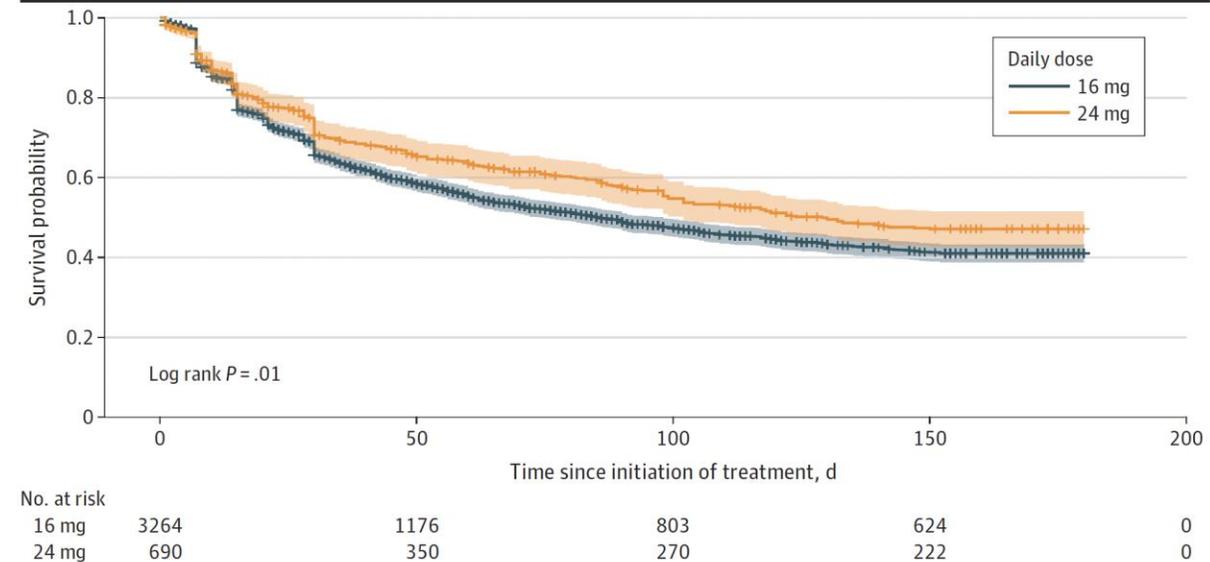
# Methadone via OTPs

- Traditional protocols at opioid treatment programs (OTPs) are conservative, focused on preventing diversion and limiting risk of overdose
  - E.g., 30 mg on day 1 and 5-10 mg/day increases every 3-5 days
  - Takes months to get to treatment dose
- Anecdotal reports of needing higher doses
- Calls for rapid titration protocols for those with high volume fentanyl use and without significant medical comorbidities or use of alcohol/BZD

# Buprenorphine

- Traditional initiation and dosing guidelines based on people using heroin
- Effect of fentanyl use on retention unclear
  - Wakeman et al found no difference at 6 mos between those with fentanyl + vs. heroin + urines, but study was small and fentanyl + was thought to be contamination rather than intended use
- Some data that higher bupe dose at initiation of treatment is associated with improved retention (Chambers et al)

Figure 2. Time to Buprenorphine Treatment Discontinuation in the 180 Days After Initiation, by Daily Dose Starting on Day 0 (Primary Analysis)



# Low-dose initiation of buprenorphine

- Titrated over 3-14 days beginning with very low doses of buprenorphine, while full opioid agonist is continued
- Patient does not have to go through withdrawal
- Full agonist is stopped after 1-2 weeks of overlap
- Well-tolerated, even among people on methadone
- More successful when driven by patients rather than medical team (e.g. placement concerns)
- Complicated instructions, easier in inpatient setting or with structured support (e.g., OTP)

# Rapid low-dose initiation

## Harborview protocol

Day 1 (first 24 hours): Bupe-naloxone 2-0.5 mg film, 0.25 film every 3 hours (**4 mg bupe** total)

Day 2 (next 24 hours): Bupe-naloxone 2-0.5 mg film, 0.5 film every 3 hours (**8 mg bupe** total)

Day 3 (next 24 hours): Bupe-naloxone 8-2 mg tablet, 1 tablet twice daily (**16 mg bupe** total)

- Sokolski et al reported on outcomes among 24 hospitalized patients who underwent rapid low-dose initiation; 79% completed it; no precipitated withdrawal
  - Only 5 had used fentanyl within 48 hours; of these 3 completed initiation

TABLE 1. Rapid Low-dose Buprenorphine Initiation Protocol

	Buprenorphine Schedule	Total Daily Dose	Full-Agonist Opioid
Day 1	Buprenorphine 20 µg/h patch	~0.48 mg	Continue*
Day 2†	1 mg SL TID	3 mg	Continue*
Day 3†	1 mg SL q3h (8 AM–11 PM)	6 mg	Continue*
Day 4	1 mg SL at 6 AM, followed by 8 mg SL at 9 AM	9 mg + additional doses if needed	Continue as needed

\*Continue high-dose full-agonist opioids for acute pain and/or withdrawal. Once initiation is complete and the patient is on a treatment dose of buprenorphine, discontinue full-agonist for withdrawal indication.

†On days 2 and 3, providers reviewed the medication administration record to ensure there were no missed doses. If patients missed 1 or more 1 mg doses on days 2–3, then that day was repeated to reduce the risk for precipitated withdrawal.

SL indicates sublingual; TID, 3 times a day; q3h, every 3 hours.

# High-dose initiation for people using fentanyl

- ER studies with differing definitions of “high dose” demonstrated safety, low risk precipitated withdrawal
- Accumulating clinical experience
- Wait 24+ hours and until onset of moderate withdrawal symptoms (COWS >12)
- Options include higher starting doses (8-16 mg), higher total dose in first day (up to 32 mg)

## HIGH DOSE BUPRENORPHINE INITIATION

THE CURB  
SIDERS  
ADDICTION  
MEDICINE

### EXAMPLE PROTOCOL

- **Step 1:** Stop all opioids
- **Step 2:** Wait at least 48 hours from last HPSO use and until signs of opioid withdrawal (at least 1 objective sign)
- **Step 3:** Give buprenorphine 8-16mg
- **Step 4:** Repeat buprenorphine every 2 hours until improvement of withdrawal symptoms (max dose 24-32 mg on Day 1)

# Important research questions relating to fentanyl

- Risks and benefits of more rapid induction protocols for methadone
- Comparative benefit of methadone vs buprenorphine
- Where is ceiling effect on dose of buprenorphine in era of fentanyl? What is optimal buprenorphine dose?
- Comparative benefit of sub-lingual vs long-acting injectable buprenorphine
- Optimal buprenorphine initiation strategies
  - Canadian randomized controlled trial of rapid low-dose vs standard initiation among hospitalized patients underway
- Risk/benefit of buprenorphine and ER naltrexone for people with other SUD who are exposed to fentanyl
- Adjunctive overdose management for people with polysubstance overdose

# Conclusions

- The scale of the fentanyl crisis is unprecedented and closely connected to its unique pharmacologic properties
- OUD remains a highly treatable condition for which methadone and buprenorphine are life-saving and standard of care
- Guidelines continue to recommend standard initiation protocols for methadone buprenorphine based on widespread clinical experience and available evidence; however, emerging strategies are rooted in the same pharmacologic principles and need further study

**Comments or questions?**

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