



# Current Issues in Opioid Use Disorder (OUD): Focus on Fentanyl



**Shannon Robinson, MD**

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## DISCLAIMER

- This session was conducted for members of county-based teams in CA that are working to expand access to **Medications for Addiction Treatment in jails and drug courts**. The project is funded through California's Department of Health Care Services (DHCS) with State Opioid Response funding from SAMHSA. The content is being made available to all interested parties. Please note this content has not been professionally edited and the session was conducted using Zoom.
- In the case of any security issues that may occur, this session will immediately end. A separate email will be sent to all participants with further instruction.
- Any data and information collected through polls and chats will only be used to inform future webinar/learning collaborative topics and to provide DHCS with evaluation results.

Welcome and  
Introductions

Review of  
learning  
objectives

Q & A; wrap  
up and what's  
next

## LEARNING OBJECTIVES

Compare and contrast treatment of overdoses related to fentanyl versus heroin

Distinguish treatment of opioid withdrawal related to fentanyl versus heroin

Discuss how to manage the patient who is not in withdrawal when evaluated

## BACKGROUND FENTANYL

- First synthesized in 1960
- Approved in 1968 for analgesia and anesthetic, and later for break through cancer pain
- Fentanyl found in illicit opioids, stimulants, cannabis, vape products
- Fentanyl found in illicitly manufactured stimulants, benzodiazepines and opioid pills
- Fentanyl in liquid form
  - Eye drops, nasal spray, dropped onto paper
- 99% of oxycodone pills submitted to crime lab contained fentanyl
- Pills look identical to legally manufactured pills

**Sources:**

O'Donnell 2021 MMWR Early Release

<https://skylab.cdph.ca.gov/ODdash/>

Sacramento County Fentanyl Awareness Virtual Town 1.27.22 Hall

<https://drugabusestatistics.org/drug-overdose-deaths/>

<https://www.cdc.gov/drugoverdose/featured-topics/VS-overdose-deaths-illicit-drugs.html>

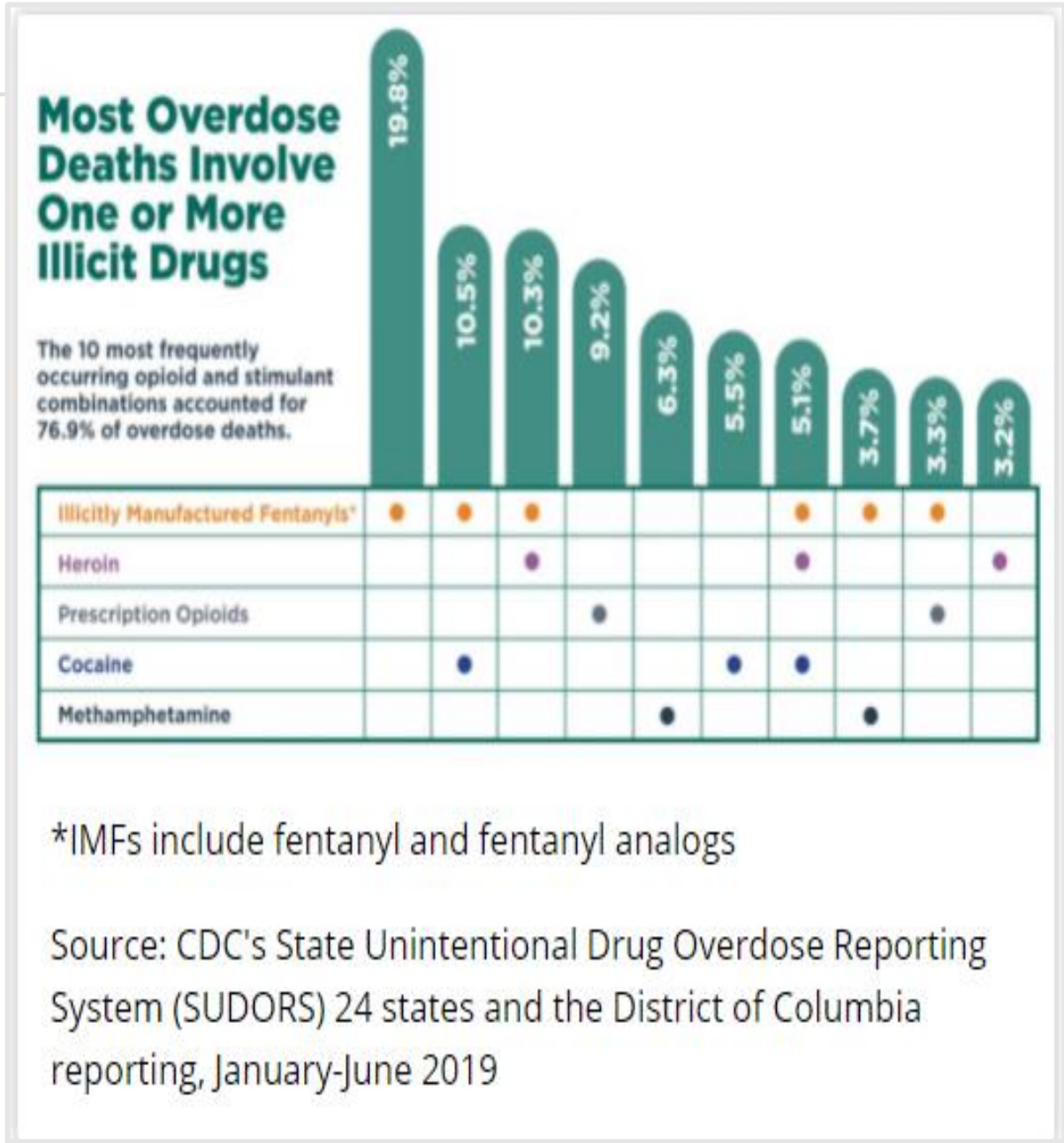
<https://www.cdc.gov/stopoverdose/fentanyl/>

## BACKGROUND FENTANYL

- Involved in 85% of overdoses
  - 2020 40% of fentanyl deaths also involved stimulants
- Drug OD deaths exceeded homicides by 306.7%
- Drug OD deaths exceed motor vehicle accidents and suicides combined

**Sources:**

O'Donnell 2021 MMWR Early Release  
 Sacramento County Fentanyl Awareness Virtual Town 1.27.22 Hall  
<https://drugabusestatistics.org/drug-overdose-deaths/>  
<https://www.cdc.gov/drugoverdose/featured-topics/VS-overdose-deaths-illicit-drugs.html>



# NATIONAL DATA

Based on data available for analysis on:

2/6/2022

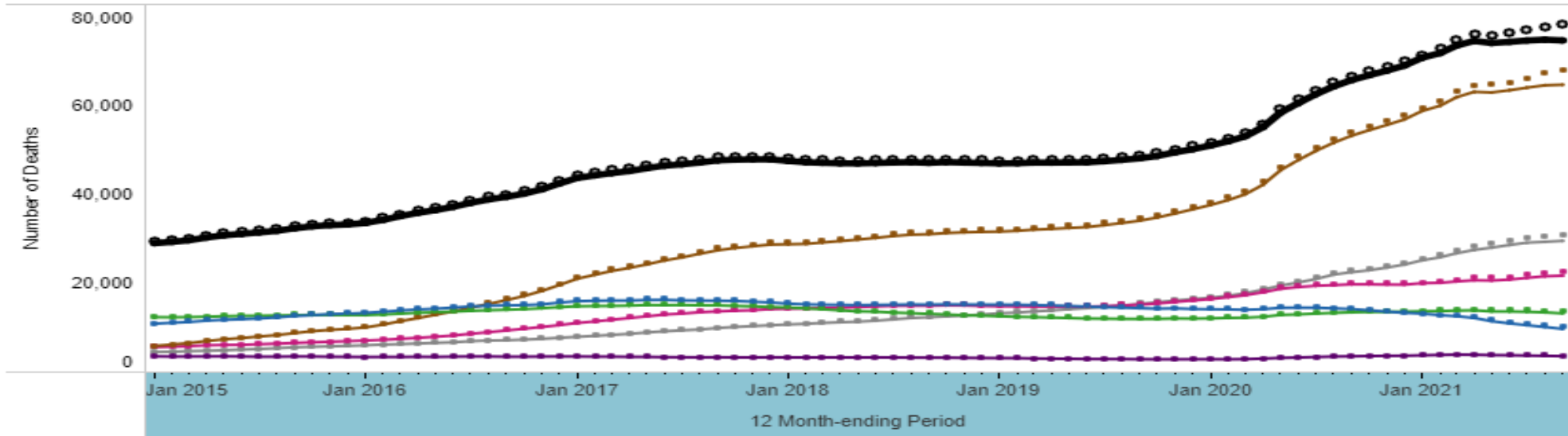
Select Jurisdiction

United States

Select specific drugs or drug classes

(Multiple values)

Figure 2. 12 Month-ending Provisional Number of Drug Overdose Deaths by Drug or Drug Class: United States



Legend for Drug or Drug Class

Opioids (T40.0-T40.4, T40.6)

Heroin (T40.1)

Natural & semi-synthetic opioids (T40.2)

Methadone (T40.3)

Synthetic opioids, excl. methadone (T40.4)

Cocaine (T40.5)

Psychostimulants with abuse potential (T43.6)

--- Reported Value

○ Predicted Value

Sources:

<https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>

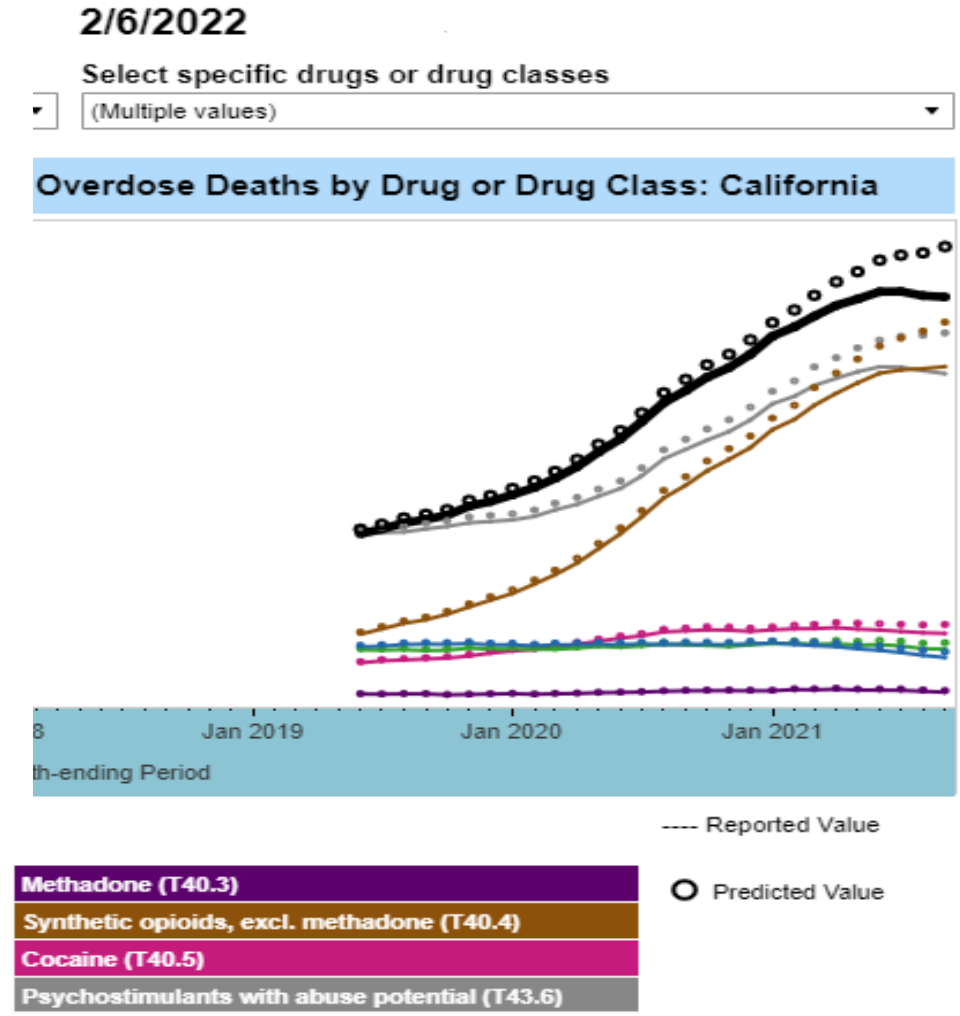
# CALIFORNIA DATA

Many routes of drug use related to fentanyl deaths:

- Injecting 
- Snorting 
- Smoking 
- Ingesting 

Legend for Drug or Drug Class

- Opioids (T40.0-T40.4,T40.6)**
- Heroin (T40.1)**
- Natural & semi-synthetic opioids (T40.2)**



Sources:  
<https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>



## BACKGROUND FENTANYL

- Potency
  - Morphine, heroin, fentanyl, carfentanyl
- Potency within pills and inside pill varies
  - Range from 1mg to 5mg fentanyl in pill
  - Inter pill inconsistencies from different parts of pill
  - DEA's ONE PILL CAN KILL Campaign
    - Harm Reduction
      - Test to see if fentanyl present
      - Use tester doses
      - Never use alone



Comparing the size of lethal doses of heroin, fentanyl, and carfentanyl. The vials here contain an artificial sweetener for illustration. (New Hampshire State Police Forensic Laboratory)

### Sources:

Baumann, 2018

Boas, 1985

Hug, 1981

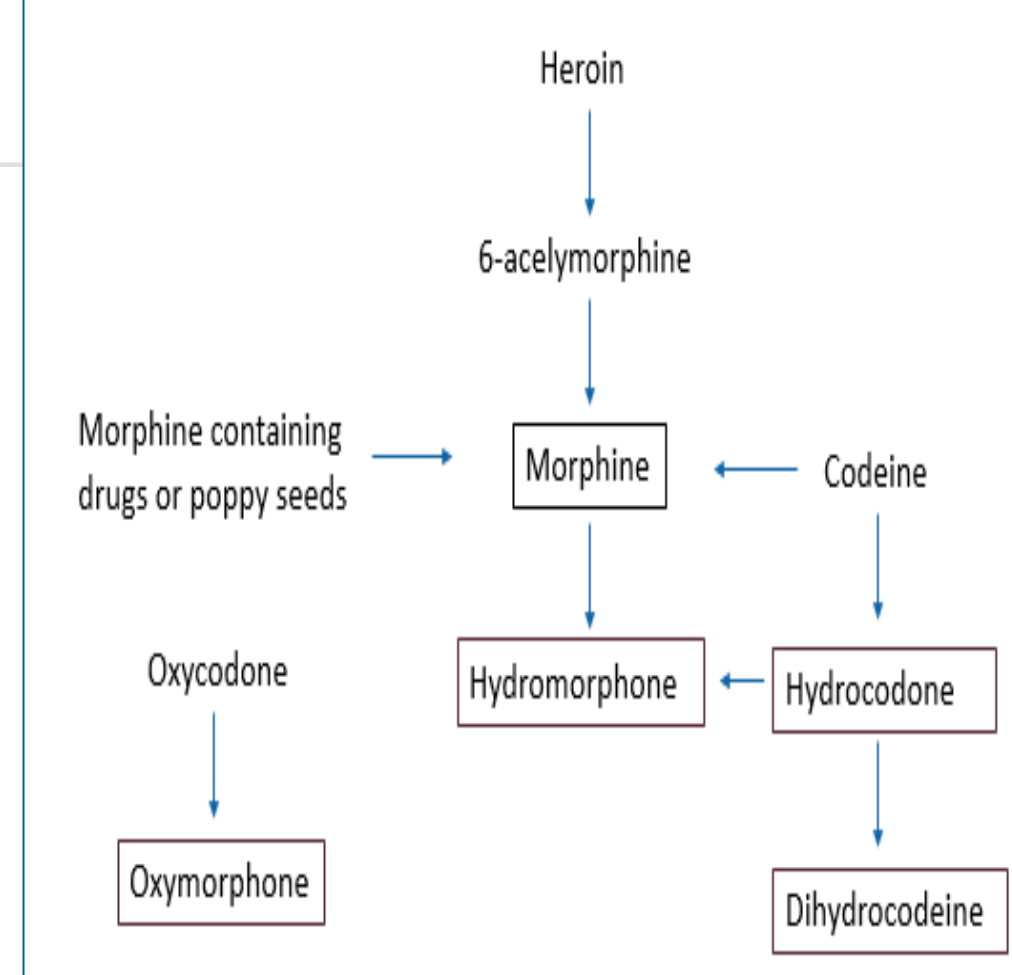
Roy, 1988

Torralva, 2019

[https://www.dea.gov/sites/default/files/2021-12/DEA-OPCK\\_FactSheet\\_December%202021.pdf](https://www.dea.gov/sites/default/files/2021-12/DEA-OPCK_FactSheet_December%202021.pdf)

## BACKGROUND FENTANYL

- Fentanyl is
  - Highly lipophilic
  - Crosses blood brain barrier quickly
  - Redistributes to adipocytes
  - 1000 times more lipid soluble than morphine
    - Morphine, heroin, fentanyl, buprenorphine
- Lipophilicity influences onset of action
  - The more lipophilic the faster the onset of action
  - Morphine 6 minutes, fentanyl 60 seconds
- Take Home Points: Brain Effects
  - Morphine: slow in slow out
  - Fentanyl: fast in fast out
  - Heroin: fast in slow out



Fentanyl → norfentanyl

Sources:

Fairbairn 2017

Torralva, 2019

[https://www.dea.gov/sites/default/files/2021-12/DEA-OPCK\\_FactSheet\\_December%202021.pdf](https://www.dea.gov/sites/default/files/2021-12/DEA-OPCK_FactSheet_December%202021.pdf)

## **| POLLING QUESTION**

**Before we start talking about intervening on overdoses and initiation buprenorphine for persons on fentanyl...**

**Is your organization testing for fentanyl?**

- A. Yes**
- B. No**
- C. I don't know**

# FOLLOW-UP QUESTION

If you are not testing for fentanyl currently, what are barriers to doing this?

Please respond in chat.



# Compare and contrast treatment of overdoses related to fentanyl versus heroin

Near 100% success with reversal of overdoses with naloxone pre-fentanyl era



## NEED FOR NALOXONE & FATALITY WITH FENTANYL

- **Cook County Illinois (4/2005 – 12/2006)**
  - Cook County Medical Examiner Officers Fentanyl Fatality Database: 342 fentanyl related deaths
  - University of Illinois Chicago Emergency Department (ED): Naloxone .4mg to 12mg
    - Incomplete drug testing in ED; can't confirm higher doses of naloxone related to fentanyl
- **California (3/2016)**
  - 18 patients tested positive for fentanyl presented to University California Davis ED
    - 4 required naloxone infusion for 26-39 hours
- **Kentucky (10/2015-9/2016)**
  - Correlated with law enforcement data with toxicology from ED
  - More fentanyl related ODs were reported than fentanyl related ED visits
  - >10 to 1 heroin related ED visits compared to overdoses
  - < 40% of heroin OD ED discharges listed procedure code for drug testing

**Sources:**

Schuman 2008  
Sutter 2017  
Slavova 2017

# NEED FOR NALOXONE & FATALITY WITH FENTANYL

- **Massachusetts (2014-2016)**
  - Interviewed 64 people who had witnessed or experienced overdose (OD) over 12 months
    - 75% witnessed naloxone administration
    - 83% of those reported >2 doses of naloxone were required
    - Incomplete drug testing in ED; can't confirm higher doses of naloxone related to fentanyl
    - However, 3 counties in Massachusetts 125 of 196 opioid overdoses were fentanyl related
- **Allegheny County Pennsylvania (1/2013-12/2016)**
  - No statistical difference on average number of naloxone doses to reverse OD
    - 2013 89%, 2014, 2015 and 2016 93-95% of overdose reversed with  $\leq 2$  doses of naloxone
    - Despite Medical Examiner documented increase in fentanyl contributed opioid overdose deaths from 3.5% to 68.7%
- **Vancouver, Canada (12/2016-4/2017)**
  - Observation of safe injection sites (witnessed overdose rescues) and interviews
    - 4-6 ampoules of naloxone required for fentanyl ODs
- **Atlanta, Georgia (1/2017-6/15/2018)**
  - No statistical difference on average number of naloxone doses to reverse OD between fentanyl only, opiate only and opiate + fentanyl

**Sources:**

Somerville 2017  
Bell 2019  
Mayer 2018

# OVERDOSE FENTANYL – NOT JUST RESPIRATORY DEPRESSION

- Wooden chest syndrome (WCS)
  - Rigidity of the diaphragm & chest wall and upper airway closure (laryngospasm)
  - Narrow therapeutic window; doses as low as 50 micrograms
  - Onset within 2 minutes and duration of 15 minutes
  - Associated with cardiovascular system and decreased perfusion
    - Heart, liver and brain
    - So rapid that many fentanyl ODs don't have norfentanyl present because the blood hasn't circulated through the liver to be metabolized
  - Almost always fatal without expert airway management
  - Mediated via alpha adrenergic and cholinergic
  - Difficult to perform chest compression or ventilation
  - Increased death associated with fentanyl OD compared to other opioids

**Sources:**

Grell, 1970  
Somerville, 2017  
Mayer, 2018  
Torralva, 2019



# OVERDOSE TREATMENT HEROIN VERSUS FENTANYL

Receptor	Physiological Effect	Morphine	Heroin	Fentanyl	Reversed by	Prevented by
Mu opioid	Respiratory depression	+	+	+	naloxone	naltrexone buprenorphine
Alpha 1 adrenergic	Muscle rigidity & laryngospasm	-	-	+	succinylcholine	prazosin succinylcholine
Muscarinic Cholinergic	Cardiovascular system	-	-	+		

**Sources:**

Baumann 2018  
 Fairbairn 2017;  
 Grell, 1970  
 Hill, 2019  
 Jansen Pharmaceuticals, 2017 package insert  
 Rzasa, 2018  
 Schuman, 2008  
 Slavova, 2017  
 Torralva, 2019

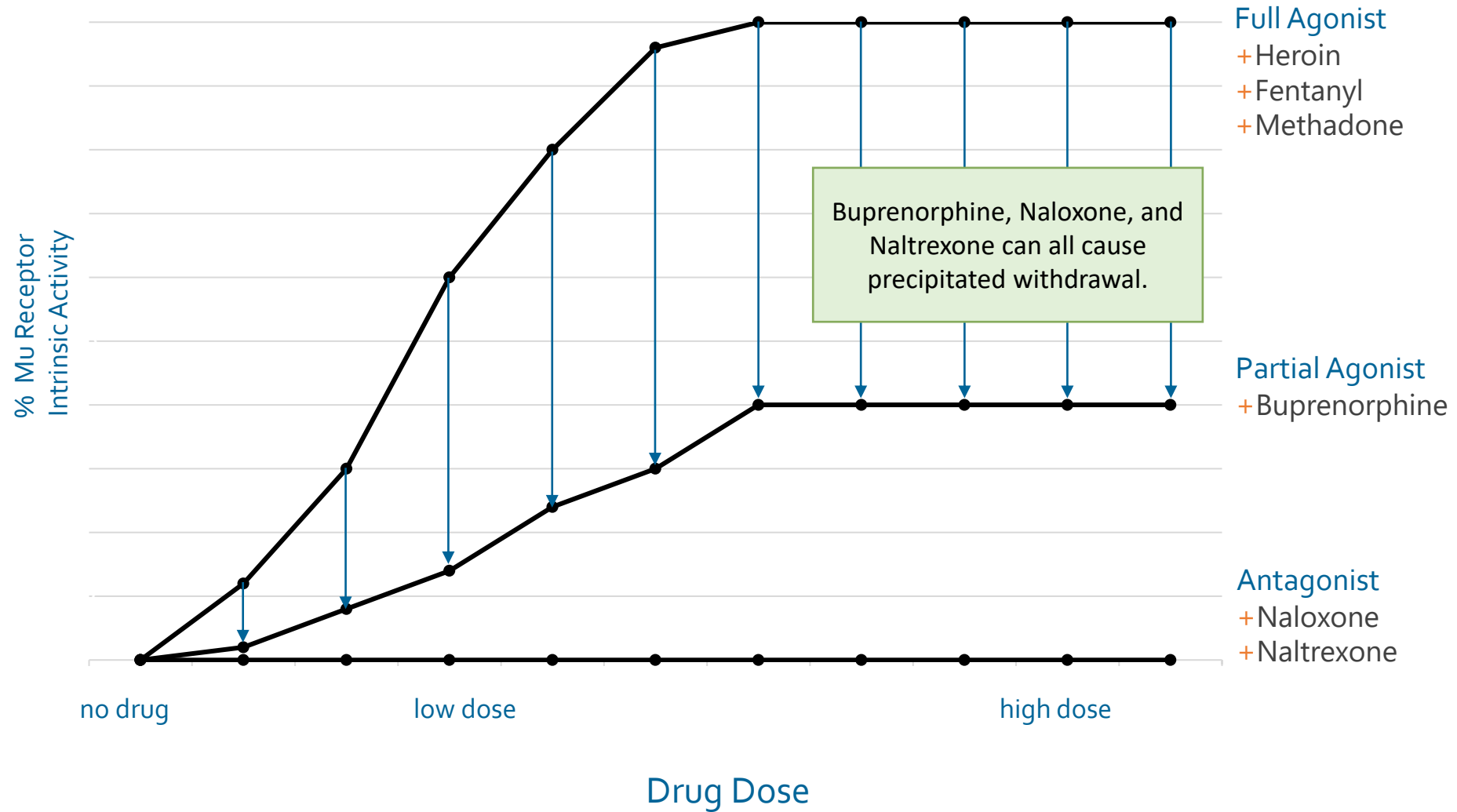
**Some of our California counties and organizations have great data tracking abilities.**

**Do you have data in your community/emergency department, EMS system comparing number of doses of naloxone required for heroin ODs vs fentanyl ODs?**

- A. Yes**
- B. No**
- C. I don't know**

Distinguish  
treatment of opioid withdrawal  
related to fentanyl vs. heroin

# MECHANISM OF ACTION: MU OPIOID RECEPTOR BINDING



# BUPRENORPHINE INITIATION FOR FENTANYL

- Precipitated withdrawal described when trying to initiate buprenorphine after having withdrawal symptoms associated with fentanyl cessation
- Why might this occur?
  - Possible explanation: delayed clearance from body related to fentanyl in the adipose tissue
    - Heroin excretion 2-4 d; fentanyl 7 d and norfentanyl 13 days
- Precipitated withdrawal in 2 patients using their normal protocol
  - Protocol was
    - 24 h after last use; COWS >9
    - 4mg buprenorphine/naloxone; Additional dose optional at 3 h later
  - Withdrawal protocol modified and successful in next 2 patients
    - 48 hours since last use; COWS >13
    - 2mg buprenorphine/naloxone; additional 2mg doses at 60-90 min intervals
    - Patients will benefit from alpha agonist and other symptomatic treatments prior to initiating buprenorphine- see next slide
  - Multi-site trial of ED initiated buprenorphine
    - 1% precipitated withdrawal despite 76% positive being positive for fentanyl

#### Sources:

Silverstein, 2019  
Huhn, 2020  
Antoine, 2022  
D'Onofrio 2022

## MICRO DOSING – 18 PAPERS DESCRIBING 63 PATIENTS

- Various schedules associated with giving small doses of buprenorphine and other opioid
  - Most used 4-8 days
  - Some used much longer transitions
  - Some outpatients and some hospitalized patients
  - .2 to 4mg starting dose of SL buprenorphine or transdermal patch 5 micrograms to 35 micrograms
    - FDA has NOT approved transdermal buprenorphine for OUD
  - Cases describe transitions from hydrocodone, hydromorphone, oxycodone, morphine, heroin, methadone
  - Generally, without generating withdrawal symptoms
  - No randomized controlled trials; no quasi experimental or case control or cohort studies
- NO CONSENSUS REGARDING A SINGLE MICRODOSING APPROACH
- May be considered in those who have failed buprenorphine initiation
- Those with chronic pain; exacerbation of pain during withdrawal may now be unnecessary
- High dose methadone where the standard taper to 30 mg per day is time consuming
- Fentanyl use as precipitated withdrawal is more likely with buprenorphine than when transitioning from other short acting opioids

Sources:  
Ahmed, 2021

## BUPRENORPHINE FOR FENTANYL POST OVERDOSE

- 2 patients successfully initiated on buprenorphine within 30-120minutes **post naloxone** for fentanyl overdose
  - First dose 4-8mg; total 16-24mg given

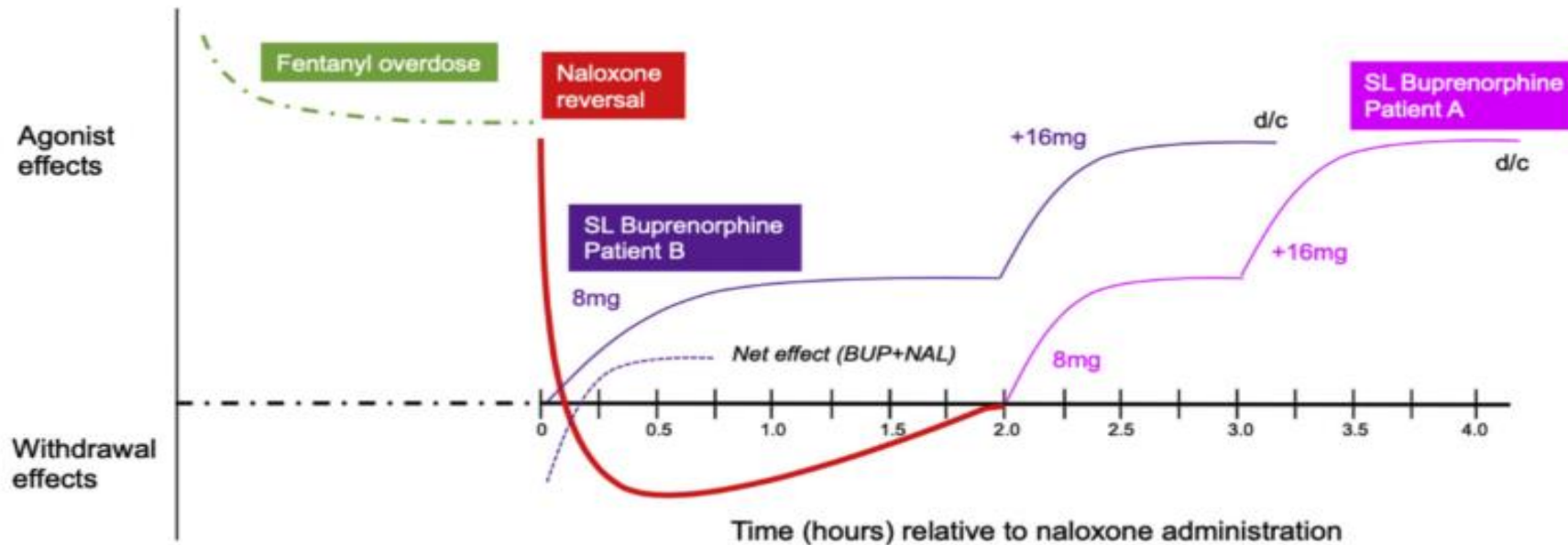


Fig. 3. Hypothesized opioid agonist/withdrawal outcome of ED-based naloxone reversal and buprenorphine administration for patients A and B following fentanyl overdose.

Sources:  
Herring, 2019

**I believe you all have more experience than the peer reviewed case literature discussed here.**

***Are you having more trouble with precipitated withdrawal as the incidence of fentanyl use has increased in California?***

- A. Yes**
- B. No**
- C. I don't know**



# FOLLOW UP

If yes, please describe your experience with this in chat.



## TREATMENT RETENTION RATES

- 6-month treatment retention rates for persons on buprenorphine
  - Fentanyl positive groups, “other” opioid positive group and those who tested negative at baseline did not differ
- 6-month opioid abstinence rates
  - Fentanyl positive groups and other opioid positive group did not differ
  - Fentanyl positive group had lower abstinence rate than those who tested negative
- Doses did not differ between groups
  
- Current trials underway
- Buprenorphine SL vs XR in ED 04225598, includes people presenting with fentanyl use
- Fentanyl to Buprenorphine in person presenting to OTP NCT04794790; enroll 30 patients
  - Standard intervention 4mg buprenorphine if COWS>8
  - Macro Dose
  - Micro Dose

Sources:  
Wakeman, 2019  
ClinicalTrials.gov

# How to manage a patient who is not in withdrawal when evaluated

## HISTORICAL TREATMENT OF OPIOID WITHDRAWAL: “COMFORT MEDICATIONS” WHILE AWAITING BUPRENORPHINE INITIATION FOR FENTANYL

1. Clonidine: start 0.1 mg bid for bone pain & arousal; may increase dose, but watch for hypotension
2. Imodium (loperamide) 4mg 1-2 tabs q1 hr for diarrhea, NTE 16 mg/day
3. Motrin (ibuprofen) 600 mg q 6hr for bone pain or NSAID of your choice
4. Tylenol (acetaminophen) 975 mg up to qid for pain not relieved by NSAIDs
  - Can use both Tylenol and NSAIDS at the same time
5. Benadryl (diphenhydramine) 25 to 50 mg q6hr for nasal congestion, insomnia or anxiety
6. Compazine (prochlorperazine) 10mg qid for nausea/vomiting; give by any route available
7. Bentyl (dicyclomine) 10 mg qid for abdominal cramping, not relieved by controlling diarrhea
8. Valium (diazepam):10-15 mg for muscle spasms and insomnia

## REEVALUATION

- Do you have procedures in place to re evaluate patients who are not yet in withdrawal?
- Do you have procedures for reevaluating someone who has been using fentanyl?
- Do you have procedures in place to reevaluate someone you started on buprenorphine?
  - Who reevaluates patients? Or what combination of people reevaluates patients?
    - Custody
    - Nursing
    - BH provider
    - SUD provider
    - Medical provider
  - How frequently are patients reevaluated?
  - Coming soon: Bureau of Justice AHP NCCHC Jail Withdrawal Guidelines

## SUMMARY

- Fentanyl has rapid onset of action and death due to
  - Lipophilic (goes into brain quickly)
  - Wooden Chest Syndrome which is more than respiratory depression
- Treatment of fentanyl overdose
  - Currently unclear if we need higher doses of naloxone
  - May need additional interventions in different pharmaceutical classes
  - Start buprenorphine after naloxone reversal of fentanyl overdose
- Treatment of OUD related to fentanyl use
  - More difficult to initiate buprenorphine for fentanyl vs heroin
  - Current recommendations: wait until person is in moderate withdrawal (not just objective evidence of withdrawal) before starting buprenorphine; this may take over 24 hours
  - Start with low dose of buprenorphine
  - If no precipitated withdrawal, then proceed as usual\*
  - Some patients may require micro-dosing approaches\*
- To manage a patient who is not yet in withdrawal and has recently used fentanyl
  - Comfort medication
  - Reevaluation

\*Clinical trials underway

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## **POLLING QUESTIONS**

**1. Overall, today's webinar was:**

- A. Very useful**
- B. Somewhat useful**
- C. Not very useful**
- D. Not useful at all**

**2. The material presented today was:**

- A. At the right level**
- B. Too basic**
- C. Too detailed**

## CONTACT US

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**FOR ANY QUESTIONS OR COMMENTS**

[MATinCountyCJ@healthmanagment.com](mailto:MATinCountyCJ@healthmanagment.com)

or

[CountyTouchpoints@healthmanagement.com](mailto:CountyTouchpoints@healthmanagement.com)

News Release 4.7.21

“Federal funds (CDC and SAMHSA) may now used to purchase fentanyl test strips”

<https://www.cdc.gov/media/releases/2021/p0407-Fentanyl-Test-Strips.html>

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HEALTH MANAGEMENT ASSOCIATES

