

# Fentanyl and Other High Potency Synthetic Opioids

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# Disclosures

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No conflicts of interest or relationships to disclose

# Outline

- Properties of fentanyl
- History of the spread of illicitly manufactured synthetic opioids
- National epidemiology and regional variations
- Fentanyl and overdose prevention and treatment
- Fentanyl testing: Urine drug testing and drug supply testing
- Treatment for Fentanyl opioid use disorder
  - Methadone
  - Buprenorphine
    - Induction challenges

# Pharmacology, History, and Epidemiology

# History of Pharmaceutical Fentanyl

- Pharmaceutical fentanyl was synthesized by Belgian Chemist Paul Janssen in 1959.
- Highly potent drug with increased receptor specificity would exhibit a greater safety profile.
- Synthetic opioid (i.e. made in a lab, no opium precursor).  
Now available as transdermal patch, buccal/SL tablets, sublingual spray, injectables.



# Pharmacology of Fentanyl

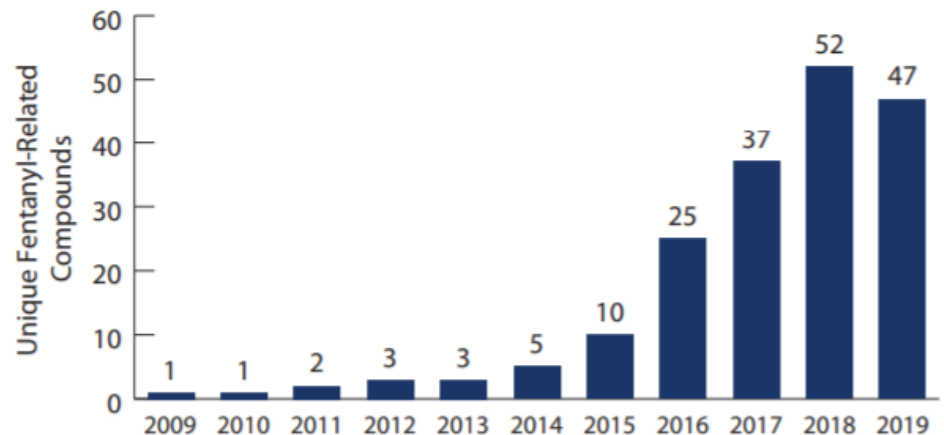
- Potent Mu opioid receptor agonist
  - Approximately 100x more potent than morphine, 50x more potent than diacetylmorphine (heroin)
- Metabolized by cytochrome p450 3A4, 8-10% renally excreted (detectable in urine)
- Half-life (2-4 hours) and mu receptor affinity ( $K_i$  1.35) are similar to morphine's; HOWEVER, its high lipophilicity means a
  - Faster onset of action (due to ability to cross blood-brain barrier)
  - Shorter duration of action when used acutely (due to redistribution to other tissues and rapid sequestration into body fat)

# Illicitly Manufactured Fentanyl Analogs

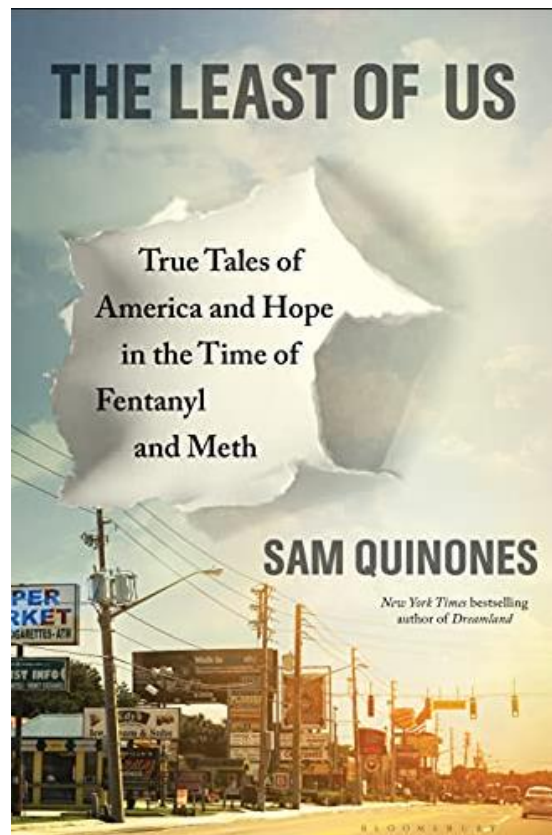
- Seizure data has detected numerous fentanyl analogs (furanylfentanyl, acetylfentanyl, butyrylfentanyl) in certain jurisdictions.
- Carfentanil is roughly 100x the potency of fentanyl.



**Figure 2.** Number of unique fentanyl-related compounds in NFLIS-Drug: 2009–2019



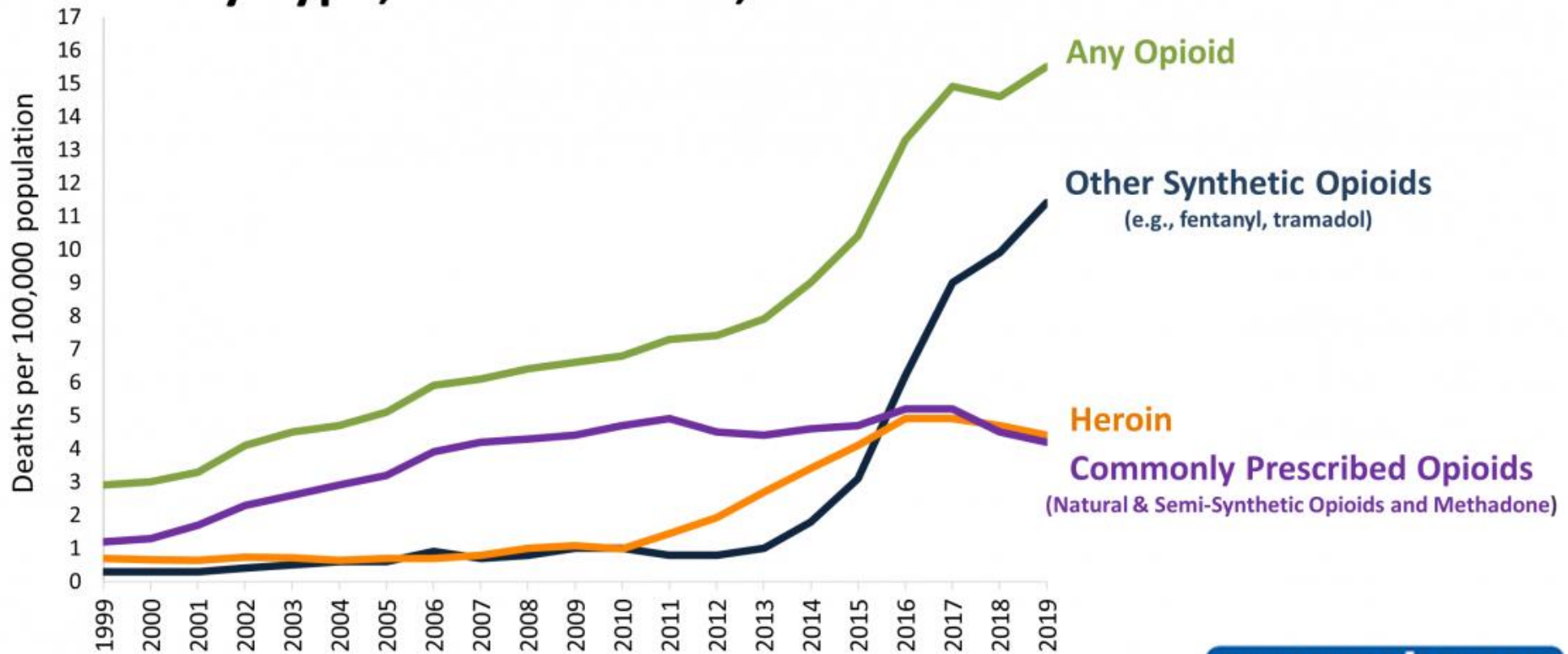
- Drug producers learned the value of synthetic drug processing from methamphetamine in the late 1990s.
- 2006: Fentanyl synthesized in a lab in Toluca, Mexico. Causes first major wave of overdose deaths in Midwest. Lab is shut down by DEA and precursors scheduled, bring outbreak to an end.
- Demand for heroin continues to grow in United States. Fentanyl overdoses begin occurring in 2013, mainly on the East coast, mainly admixed with powdered heroin.
- 2015 synthetics surpass heroin among drug overdose deaths.





# 3 Waves of Drug Overdose Deaths

## Overdose Death Rates Involving Opioids, by Type, United States, 1999-2019

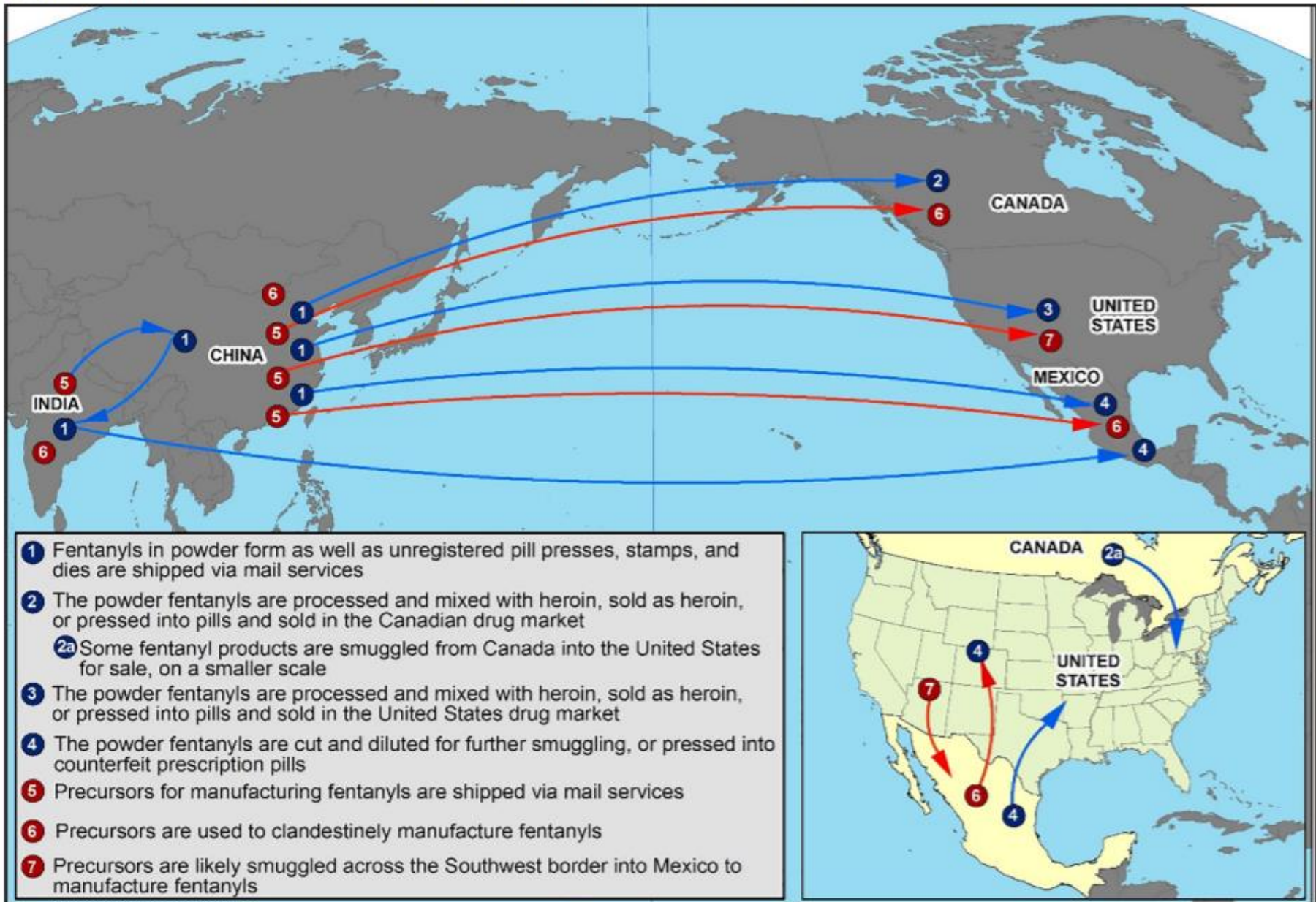


SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2020. <https://wonder.cdc.gov/>.

[www.cdc.gov](http://www.cdc.gov)  
Your Source for Credible Health Information



(U) FIGURE 1. FENTANYL FLOW TO THE UNITED STATES 2019



# Why Synthetics?

Preferable for the producers/suppliers

- Easier to produce (cheaper, less detectable, more reliable – no need to wait for growing season – from abundant chemical precursors)
- Easier to smuggle due to high potency (“the iron law of prohibition”)
- Broader market for counterfeit pills (due to perceived safety)

# Fatal Drug Overdoses

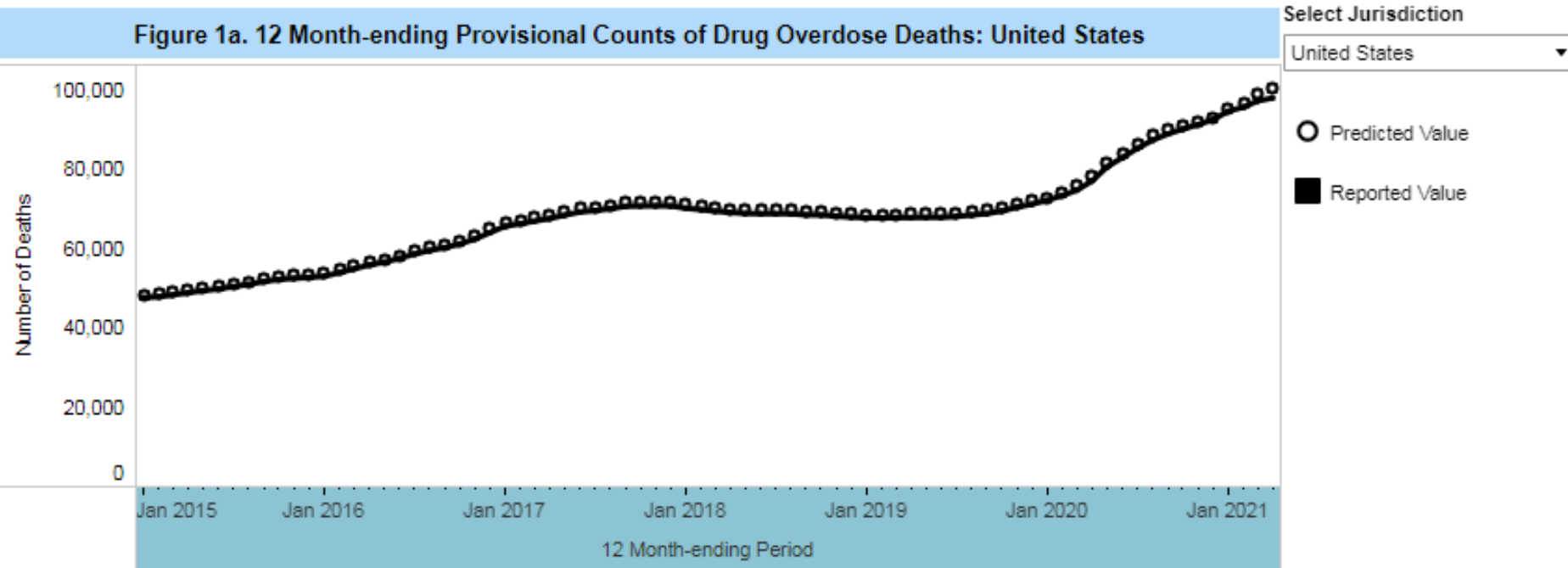
## *Overdose Deaths Reached Record High as the Pandemic Spread*

More than 100,000 Americans died from drug overdoses in the yearlong period ending in April, government researchers said.

Based on data available for analysis on:

11/7/2021

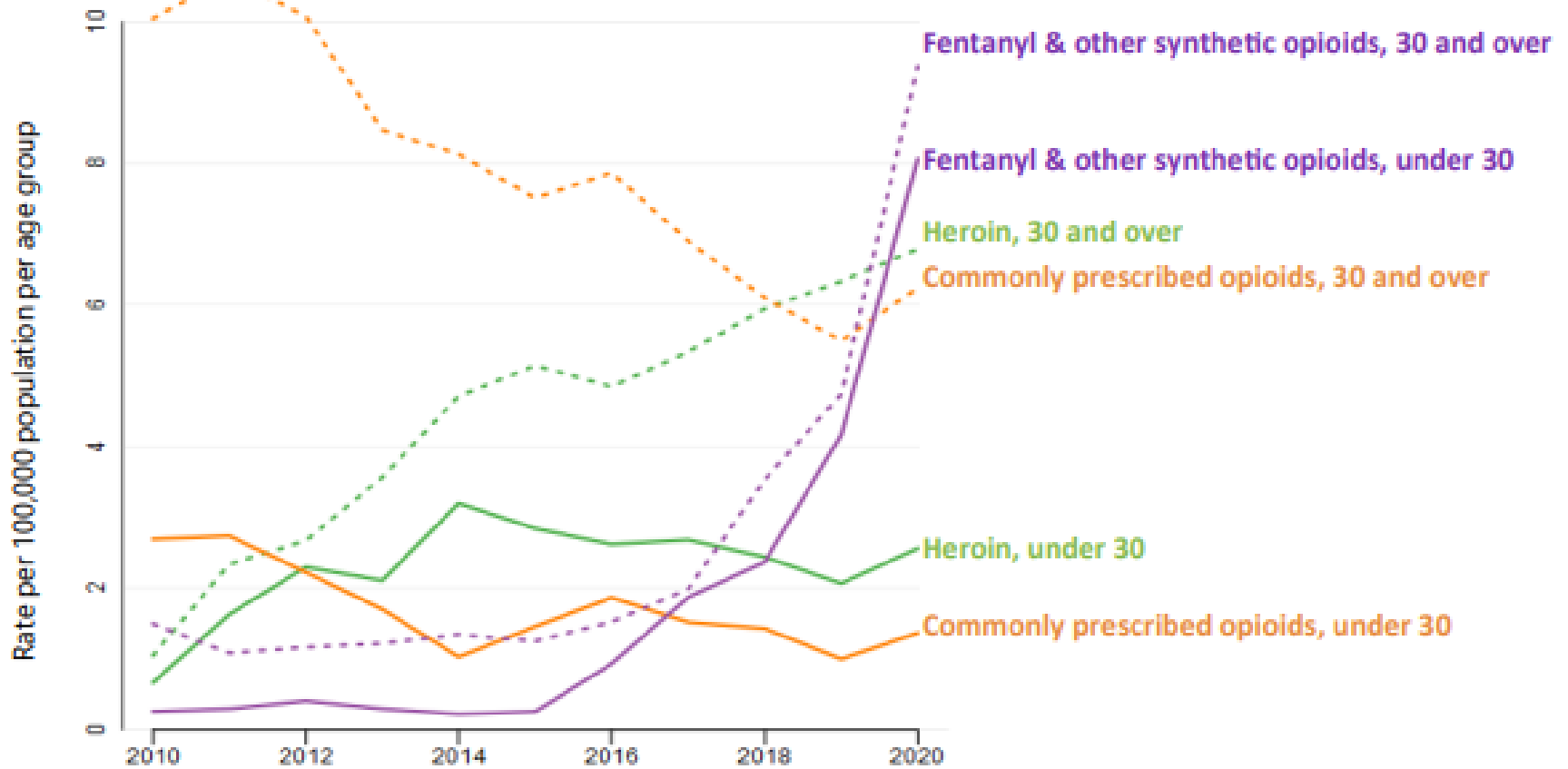
Figure 1a. 12 Month-ending Provisional Counts of Drug Overdose Deaths: United States



- April 2020 – April 2021: 100,306 overdose deaths
- 75% of these involve opioids (75,673)
- 64% of these involve synthetic opioids (64,178)



## Rates of opioid-involved overdose deaths in Washington State



Data source: Washington State Department of Health, Center for Health Statistics Data visualization: ADAI



# COUNTERFEIT PILLS FACT SHEET

FAKE PRESCRIPTION PILLS • WIDELY AVAILABLE • INCREASINGLY LETHAL

## CRIMINAL DRUG NETWORKS ARE FLOODING THE U.S. WITH DEADLY FAKE PILLS

- Criminal drug networks are mass-producing fake pills and falsely marketing them as legitimate prescription pills to deceive the American public.
- Counterfeit pills are easy to purchase, widely available, often contain fentanyl or methamphetamine, and can be deadly.
- Fake prescription pills are easily accessible and often sold on social media and e-commerce platforms—making them available to anyone with a smartphone, including teens and young adults.
- Many counterfeit pills are made to look like prescription opioids such as oxycodone (Oxycontin®, Percocet®), hydrocodone (Vicodin®), and alprazolam (Xanax®); or stimulants like amphetamines (Adderall®).



Authentic oxycodone M30 tablets



\*Counterfeit oxycodone M30 tablets containing fentanyl

## COUNTERFEIT PILLS OFTEN CONTAIN FENTANYL AND ARE MORE LETHAL THAN EVER BEFORE

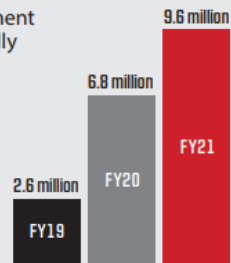
- The number of DEA-seized counterfeit pills with fentanyl has jumped nearly 430 percent since 2019.
- Officials report a dramatic rise in the number of counterfeit pills containing at least 2 mg of fentanyl, which is considered a deadly dose.
- Drug traffickers are using fake pills to exploit the opioid crisis and prescription drug misuse. CDC reports more than 93,000 people died last year of an overdose in the U.S., the highest ever recorded.
- Fentanyl, the synthetic opioid most commonly found in counterfeit pills, is the primary driver in this alarming increase in overdose deaths.



**DEA lab testing reveals that 2 out of every 5 pills with fentanyl contain a potentially lethal dose.**

## COUNTERFEIT PILLS ARE WIDELY AVAILABLE ACROSS EVERY STATE IN THE COUNTRY

- DEA and its law enforcement partners are seizing deadly fake pills at record rates.
- More than 9.5 million counterfeit pills were seized so far this year, which is more than the last two years combined.
- Counterfeit pills have been identified in all 50 states and the District of Columbia.



DEA and law enforcement partners are seizing deadly fake pills at record rates

- Drug trafficking is also inextricably linked with violence.
- This year alone, DEA seized more than 2,700 firearms in connection with drug trafficking investigations—a 30 percent increase since 2019.

## THE ONLY SAFE MEDICATIONS ARE ONES THAT COME FROM LICENSED AND ACCREDITED MEDICAL PROFESSIONALS

- DEA warns that pills purchased outside of a licensed pharmacy are illegal, dangerous, and potentially lethal.



For more information about counterfeit pills, go to [www.DEA.gov/onepill](http://www.DEA.gov/onepill)

Data as of September 2021





Authentic Oxycodone Front



Authentic Oxycodone Back



Counterfeit Oxycodone Front



Counterfeit Oxycodone Back



Authentic Xanax Back



Authentic Xanax Front



Counterfeit Xanax Front



Counterfeit Xanax Back



Authentic Adderall Front



Authentic Adderall Back



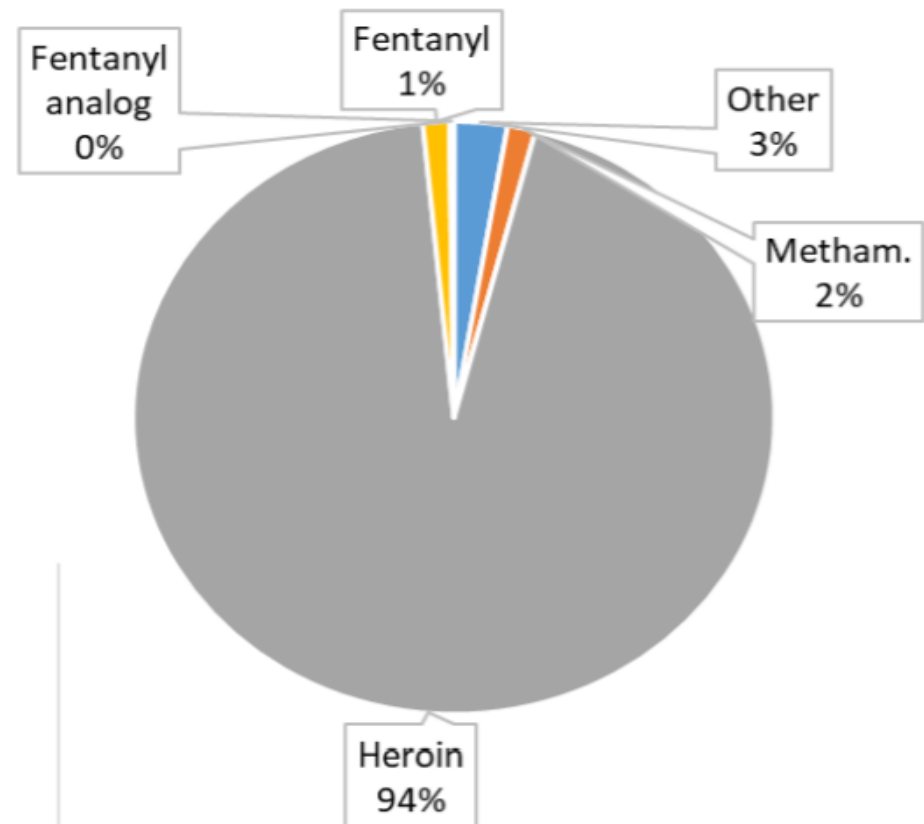
Counterfeit Adderall Front



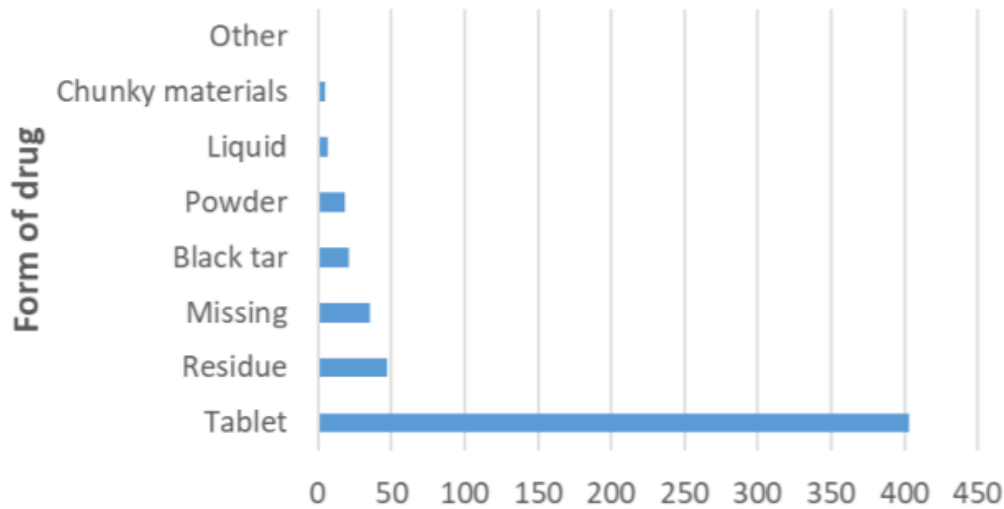
Counterfeit Adderall Back



Drug evidence testing of "Black tar"  
WA State Jan-Sept. 2020 (n=1,419)



Drug evidence testing positive for fentanyl  
WA State Jan-Sept 2020



# Clinical Considerations

# Overdose

- Window for intervention with heroin overdose as death typically does not occur until at least 20-30 minutes after use. By comparison, when used intravenously, fentanyl can cause life threatening respiratory depression within two minutes.
- Fentanyl is extremely potent and amount in any counterfeit tablet or powder extremely variable.
- Users may not be aware that they are using fentanyl or fentanyl-adulterated opioids.
- If a stimulant or other non-opioid is adulterated, the user may not have protective opioid tolerance.
- Chest wall rigidity (described in the anesthesia literature of the 1960s with IV fentanyl use) may further complicate overdose response.

# Naloxone and Fentanyl

- Increasing reports of multiple doses of naloxone being required.
  - Among interview of several dozen respondents in MA who administered naloxone in the community, 83% reported that > 2 naloxone doses were used before the person responded.<sup>1</sup>
  - Increase in number of cases requiring multiple naloxone administrations among first responders during period-over-period comparison in NC.<sup>2</sup>
- Naloxone **does** reverse a fentanyl overdose, although in some cases it may take more doses because of fentanyl's potency. Washington DOH recommends responding to suspected fentanyl overdose similarly to other opioids: i.e. wait 2-3 minutes in between doses. Give single doses each time, no need to give two at a time.
- Consider prescribing multiple doses for patients who use fentanyl.
- FDA Approved 8mg IN naloxone formulation in April 2021.

# Overdose Prevention Counseling

- In WA and surrounding area, non-prescription pills available illicitly are almost certain to be counterfeit and contain fentanyl
- Emphasis on NOT USING ALONE
- Do not use simultaneously if using IV
- “Tasting” – using a small test dose to judge potency
- Minimize mixing with other sedatives (benzos, alcohol)
- Be aware of potential for unintentional exposure in the opioid naïve (consider prescribing naloxone for stimulant users at risk)

# Fentanyl Urine Drug Screening

- Does not show up on many standard urine drug screens and need specific immunoassay screen, with confirmatory testing via gas or liquid chromatography.
- Study out of BMC among 11,873 urine samples that underwent fentanyl immunoassay testing showed positive predictive value (PPV) of 85.7% (in a population where nearly 9% of all UDS were fentanyl positive). Populations with lower prevalence will have lower PPV.
- Haloperidol, risperidone, trazodone, labetalol, fluoxetine, and amitriptyline may cross-react.
- Fentanyl analogues may or may not cross-react with IA.

# Fentanyl Test Strips: Drug Supply Testing

## Basics of fentanyl test strips

### Step 1:

Dissolve a few grains of the drug in a clean container (such as a cooker or cup)



### Step 2:

Dip the strip to the blue line for 15 seconds, lay the strip flat to dry for 5 minutes



### Step 3:

Read the strip - one line means the test detected fentanyl, two lines means the test did not detect fentanyl



Fentanyl Positive



Fentanyl Negative

Remember, this doesn't mean that the drugs are safe. Even if the result is negative, the test is not 100% accurate. If you test a pill, rock, or powder, you might test a portion that does not contain fentanyl. Or the drugs could contain another toxic contaminant.



Actual Representation

# Fentanyl Test Strips

Characteristic	N (%)
Participants who used at least one test strip	62 (76.5)
Of the participants who used at least one FTS ( <i>n</i> = 62), participants reported <sup>a</sup> :	
Regular heroin use	23 (37.1)
Regular cocaine use	24 (38.7)
Non-medical prescription pill use	13 (21.0)
Lifetime injection drug use	29 (46.7)
Of the participants who used at least one FTS ( <i>n</i> = 62), the number (proportion) who received at least one positive FTS	31 (50.0)
Of the who received at least one positive FTS ( <i>n</i> = 31), participants reported altering the way they used drugs <sup>a</sup> :	
Used less	14 (45.2)
Used with someone else around	12 (38.7)
Went slower	13 (41.9)
Did a tester	11 (35.5)
Threw them out	3 (9.7)
Sold them	3 (9.7)
Gave them away	2 (6.5)

Goldman, J.E., Wayne, K.M., Periera, K.A. *et al.* Perspectives on rapid fentanyl test strips as a harm reduction practice among young adults who use drugs: a qualitative study. *Harm Reduct J* **16**, 3 (2019). <https://doi.org/10.1186/s12954-018-0276-0>





# Treatment: Methadone

- Retrospective study of a single OTP in RI, 2016- 2017.

Table 1

Demographics, intake data and outcomes for all individuals admitted to MMT during a 10 month period, followed for 6 months.

	All intakes N = 154	Fentanyl only N = 50	Both fentanyl and other opioids N = 73	Other opioids only (opiates) N = 31
Age (mean, SD)	37, 11	37, 11	36, 10	39, 12
Male	61% (94)	56% (28)	67% (49)	55% (17)
Caucasian (non-Hispanic/Latino)	82% (126)	76% (38)	85% (62)	84% (26)
<i>Intake urine screen also containing:</i>				
Benzodiazepine	15% (23)	14% (7)	16% (12)	13% (4)
Cocaine	38% (59)	36% (18)	40% (29)	39% (12)
Oxycodone	16% (24)	14% (7)	14% (10)	23% (7)
Retention at six months	68% (105)	72% (36)	67% (49)	65% (20)
	Among patients who were retained in MMTP at six months, % (n)			
	N = 105	N = 36	N = 49	N = 20
At least one subsequent fentanyl-positive urine screen	71% (75)	80% (28)	75% (36)	55% (11)
Abstinence = Three consecutive urine screens without unexpected opioid	89% (93)	92% (33)	88% (43)	85% (17)
	Median (Q1;Q3)			
Dose at abstinence (mg)	100 (70;130)	90 (75;120)	100 (73;140)	100 (70;120)
Days until abstinence	64 (39;97)	57 (34;105)	71 (40;94)	59 (45;83)
	Among patients retained in MMTP who achieved abstinence, % (n)			
	(N = 93)	(N = 33)	(N = 43)	(N = 17)
Relapse	57% (53)	61% (20)	58% (25)	47% (8)

# Treatment: Buprenorphine

- Retrospective cohort study of 251 adult patients newly enrolled in OBOT program in Boston, 2016 – 2017.

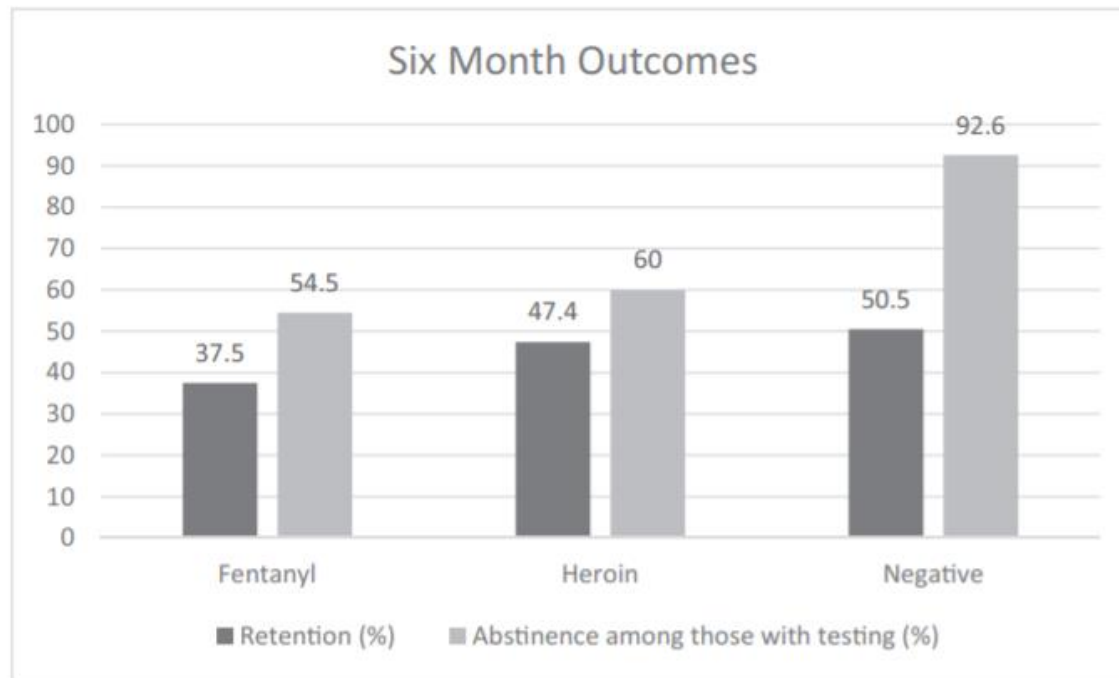


FIGURE 1. Retention and opioid abstinence among those retained at six-month follow-up.

- No difference in mean buprenorphine dose

# Buprenorphine: Induction Challenges

- Though prior pharmacokinetic studies of fentanyl report half lives ranging from 1.5-7 hours, these studies generally relied on brief periods of drug administration.
- Fentanyl is highly lipophilic, allowing it to be sequestered in adipocytes in chronic users, similar to THC.

# Buprenorphine: Induction Challenges

- May need to wait longer (>36 hours) after last fentanyl use
- May want to await higher COWS score (>12)
- May want to start with lower doses (1-2mg)
- May benefit from “microdosing” or ultra-low dose induction strategy (check out ECHO talk on 01/13/2021)

# Take-Home Points

- Adulteration of the drug supply with fentanyl and other high potency analogs is major driver for increasing fatal overdose rate. The Western States are seeing increasing fentanyl drug cases and fentanyl overdoses.
- Tablets/pills obtained illicitly -- particularly “M30s” -- should be assumed to contain fentanyl.
- People who use drugs should not use alone, should use test doses, and should carry naloxone (and be prepared to administer repeat doses.) Fentanyl test strips are under-studied but may serve as conversation starter.
- Treatment with methadone and buprenorphine is effective, but higher doses may be necessary. Buprenorphine induction may be more difficult for some patients.

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