Fentanyl and other high potency synthetic opioids

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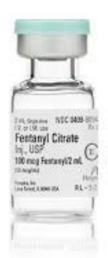
OUTLINE

- 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 and potential role for low-dose initiation

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.



Comer, 2018

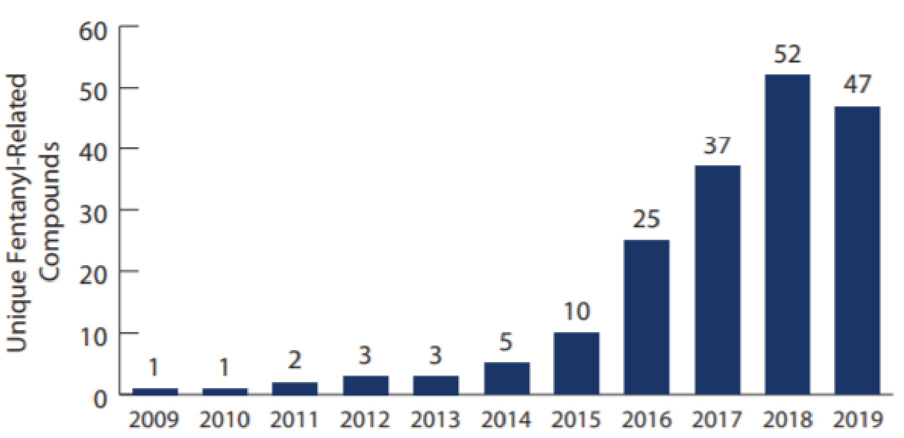
Pharmacology of Fentanyl

- 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 (2-4hours) and mu receptor affinity (Ki 1.35) are similar to morphine's; HOWEVER, it's high lipophilicity means confers 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)

Comer, 2018

Illicitly Manufactured Fentanyl Analogs

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



NFLIS Release December 2020: Tracking Fentanyl and Fentanyl-Related Compounds Reported in NFLIS-Drug, by State: 2018–2019

THE LEAST OF US

True Tales of America and Hope in the Time of Fentanyl and Meth

SAM QUINONES

- 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.

Quinones, Sam; The Least of Us.

3 waves of drug overdose deaths

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

Deaths per 100,000 population

17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0

1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019

Any Opioid

Other Synthetic Opioids
(e.g., fentanyl, tramadol)

Heroin

Commonly Prescribed Opioids
(Natural & Semi-Synthetic Opioids and Methadone)

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/.

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

CANADA
UNITED STATES
MEXICO
CHINA
INDIA

1. Fentanyls in powder form as well as unregistered pill presses, stamps, and dies are shipped via mail services
2. The powder fentanyls are processed and mixed with heroin, sold as heroin, or pressed into pills and sold in the Canadian drug market
   - 2a. Some fentanyl products are smuggled from Canada into the United States for sale, on a smaller scale
3. The powder fentanyls are processed and mixed with heroin, sold as heroin, or pressed into pills and sold in the United States drug market
4. The powder fentanyls are cut and diluted for further smuggling, or pressed into counterfeit prescription pills
5. Precursors for manufacturing fentanyls are shipped via mail services
6. Precursors are used to clandestinely manufacture fentanyls
7. Precursors are likely smuggled across the Southwest border into Mexico to manufacture fentanyls

DEA Intelligence Report: Fentanyl flow to the United States, DEA-DCT-DIR-008-20, Jan 2020

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 counter-fit pills (due to perceived safety).

Fatal drug overdoses

Based on data available for analysis on: 10/3/2021

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

Select Jurisdiction: United States

Predicted Value
Reported Value

Number of Deaths: 0, 20,000, 40,000, 60,000, 80,000, 100,000

12 Month-ending Period: Jan 2015, Jan 2016, Jan 2017, Jan 2018, Jan 2019, Jan 2020, Jan 2021

- April 1, 2020- March 31st 2021: 99,106 overdose deaths
- 75% of these involve opioids
- 63% of these involve synthetic opioids (not methadone)

National Vital Statistics System

Figure 1.5 Regional trends in fentanyl reported per 100,000 persons aged 15 or older, January–June 2006 to January–June 2020

Number of Fentanyl Reports (per 100,000)

45
40
35
30
25
20
15
10
5
0

West
Midwest
Northeast
South

Jan-Jun '06 | Jan-Jun '07 | Jan-Jun '08 | Jan-Jun '09 | Jan-Jun '10 | Jan-Jun '11 | Jan-Jun '12 | Jan-Jun '13 | Jan-Jun '14 | Jan-Jun '15 | Jan-Jun '16 | Jan-Jun '17 | Jan-Jun '18 | Jan-Jun '19 | Jan-Jun '20[1]

NFLIS 2020 mid-year Report

Increase in Fentanyl fatal overdoses

Figure 3: Percentage change in 12-months ending provisional[a] count of fatal overdoses involving synthetic opioids[b], 36 states, the District of Columbia, and New York City[c]: Deaths from 12-months ending in June 2019 to 12-months ending in May 2020[d]

- >=50% increase
- 25% to 49% increase
- 10% to 24% increase
- 0% to 9% increase
- 1% to 10% decrease
- Data not available

National Vital Statistics System

Overdose Death Rate by Drug Type, USA and WA (2000-2019)

WA Residents and USA Overall

Fatal drug OD involving heroin have remained relatively steady over the past 5 years, after rising between 2010 and 2014 in both WA and nationally.

Nationally OD deaths involving synthetic opioids (like fentanyl, fentanyl analogs, tramadol, etc) increased sharply starting in 2013-2014, while in WA's this rate of started increasing in 2016 and continues a sharp increase.

Washington State Department of Health

Source: WA DOH death certificates
CDC Wonder

Department of Justice • Drug Enforcement Administration

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.

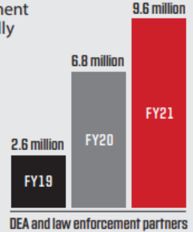
Authentic oxycodone M30 tablets

*Counterfeit oxycodone M30 tablets containing fentanyl

- 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®).

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

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.

- 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.

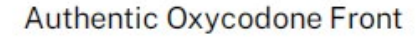
The only safe medications are ones that come from licensed and accredited medical professionals

- 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

Data as of September 2021

https://www.dea.gov/onepill


Authentic Oxycodone Front

Authentic Oxycodone Back

Counterfeit Oxycodone Front

Counterfeit Oxycodone Back

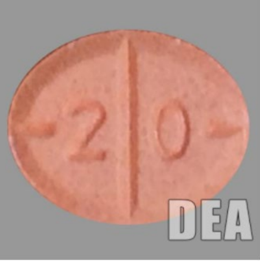
Authentic Xanax® Back

Authentic Xanax® Front

Counterfeit Xanax® Front

Counterfeit Xanax® Back

Authentic Adderall® Front

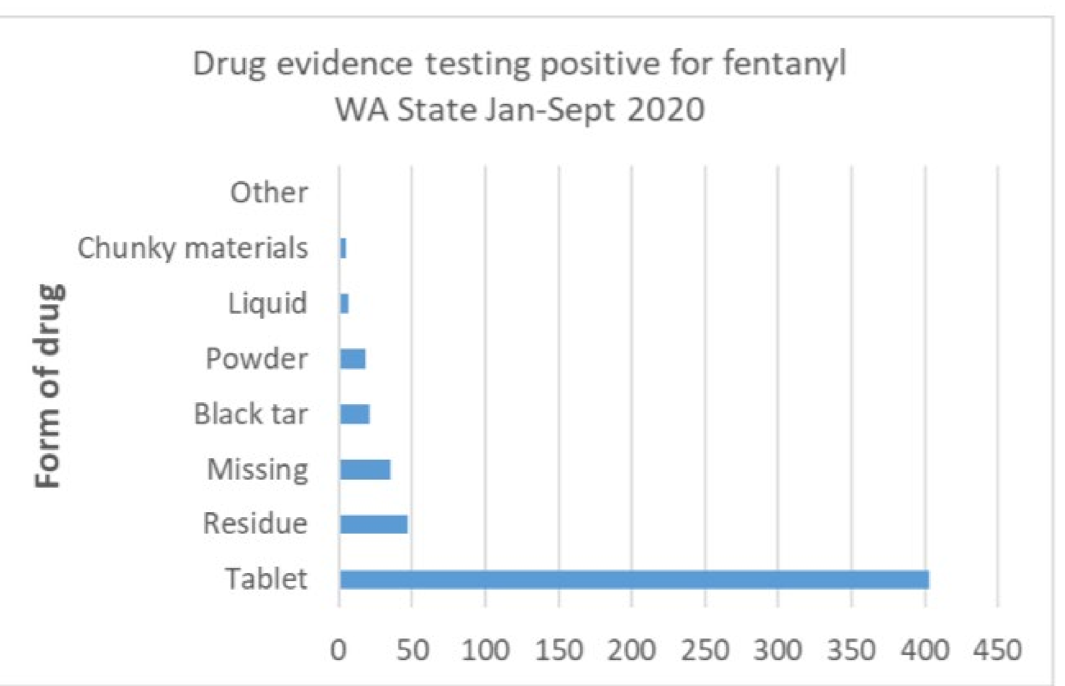


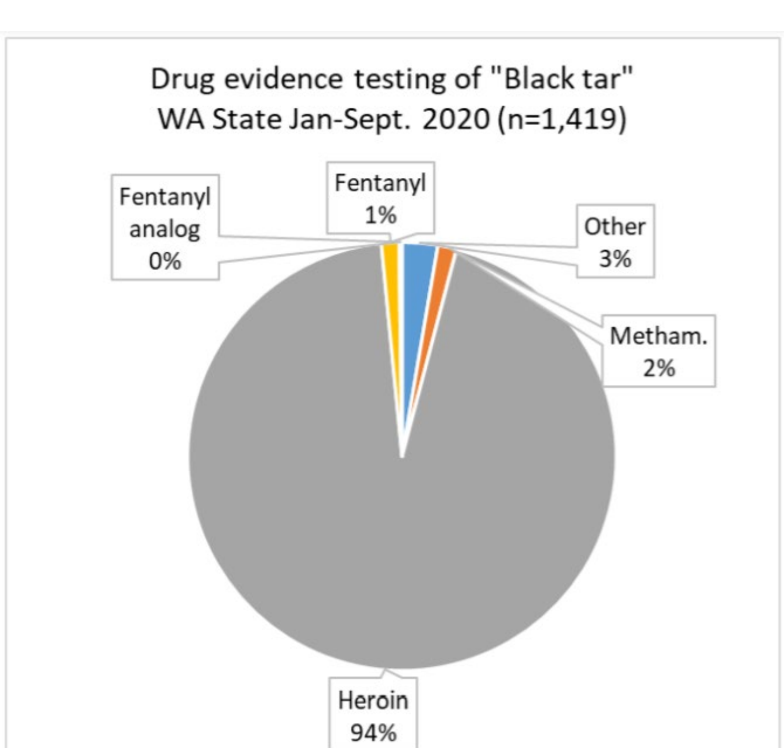
Authentic Adderall® Back

Counterfeit Adderall® Front

Counterfeit Adderall® Back

https://www.dea.gov/onepill





ADAI analysis of NFLIS data, from Banta-Green, Caleb; Illicit fentanyl in Washington State: Trends in law enforcement, treatment, and overdose, webinar.

Clinical Considerations

Overdose

- Window for intervention with heroin overdose as death typically does not occur until at leas 20-30 minutes after use. By comparison, when used intravenously, fentanyl can cause life threatening respiratory depression within two minutes.
- Fentanyl is so potent and amount in any counterfeit tablet or powder so 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.

Fairbain, et al 2017.

Naloxone and Fentanyl

- Increasing reports of multiple doses of naloxone being required.
  - Among interview of several dozen respondents who administered naloxone in the community, 83% reported the > 2 naloxone doses were used before the person responded (typical nasally administered dose in MA is 2mg/2mL).
- 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.

Somerville et al 2017

First Responder Safety

- The American College of Medical Toxicology (ACMT) and American Academy of Clinical Toxicology (AACT) released a position statement on first responders' fentanyl overdose risk, "Fentanyl and its analogs are potent opioid receptor agonists, but the risk of clinically significant exposure to emergency responders is extremely low. To date, we have not seen reports of emergency responders developing signs or symptoms consistent with opioid toxicity from incidental contact with opioids."

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 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 which 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.

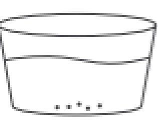
Kerensky, 2021.

Fentanyl Test Strips: Drug supply testing

Basics of fentanyl test strips

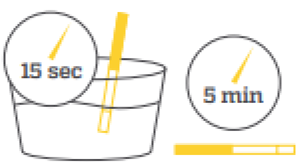
Step 1:

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



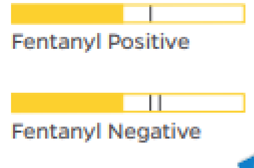
Step 2:

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



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.

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 (*n* = 62), participants reported[a]:	
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 (*n* = 62), the number (proportion) who received at least one positive FTS	31 (50.0)
Of the who received at least one positive FTS (*n* = 31), participants reported altering the way they used drugs[a]:	
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., Waye, 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
	% (n)			
Male	61% (94)	56% (28)	67% (49)	55% (17)
Caucasian (non-Hispanic/Latino)	82% (126)	76% (38)	85% (62)	84% (26)
Intake urine screen also containing:				
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 abstinance, % (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.

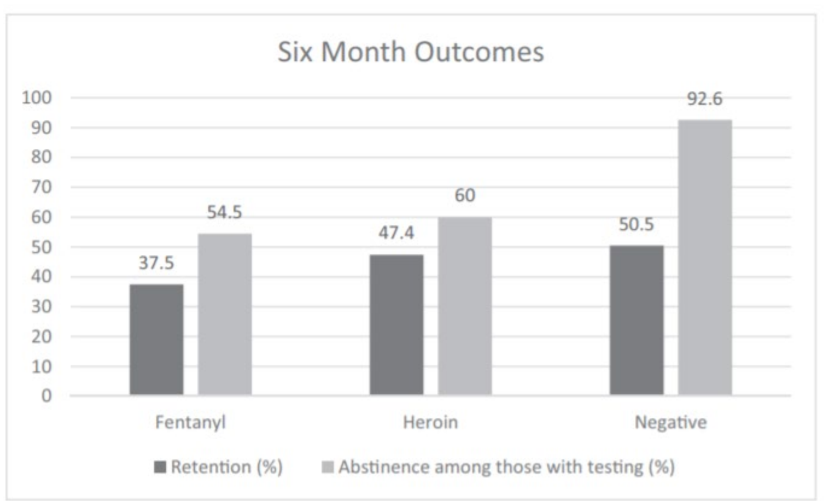


FIGURE 1. Retention and opioid abstinence among those retained at six-month follow-up.

- No difference in mean buprenorphine dose

Wakeman et al, 2017

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

" I was almost 72 hours into withdrawal --- and I took it [buprenorphine] and it made me . . . I couldn't believe it. Cuz I don't puke or get diarrhea, I don't have that happen ever . . . But immediately – Bam! Not even five minutes after I took it I was dripping with sweat. It felt like water had just gotten dumped all over me, I'm puking and it's coming out every end."

"[Buprenorphine] sends me into precipitated withdrawals every f**** time that I try to get off of fentanyl. Then I have these Sub doctors telling me that it's not real and it's like, go f**** ask the people that are buying it off the streets. It is real! I waited 80 hours. I was in a dotx and after 80 hours they gave me a Suboxone and it still put me into precipitated."

Silverstein et al. Int Journal of Drug Policy, 2019

Buprenorphine: Induction challenges

(a)

#1 #2

(b)

#3 #4

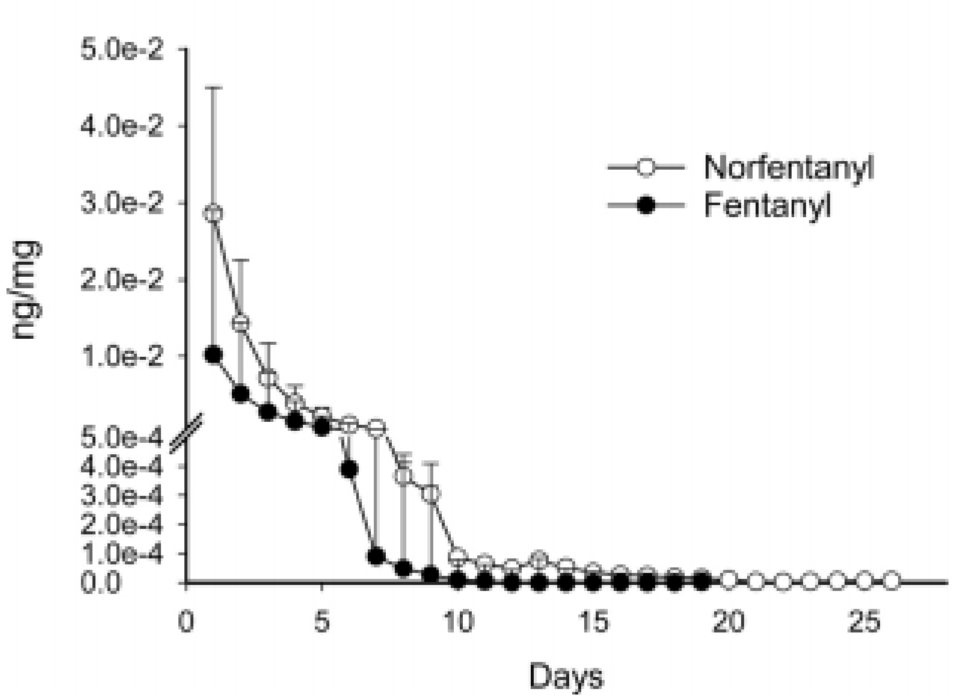
Clinical Opiate Withdrawal Scale (COWS) Ratings

Cumulative Buprenorphine/Naloxone Dose (mgs)

Time (minutes)

Antoine, D et al. The American Journal on Addictions, 2020

Buprenorphine: Induction challenges



Mean time for fentanyl clearance: 7.3 days
Meant time for norfentanyl clearance: 13.3 days

Huhn et al, Drug Alcohol Depend, 2020

Idea behind “microdosing”

Use ultra low doses to ease buprenorphine onto the receptor while continuing full agonists, to avoid the “wash-out” period of withdrawal

Ghosh et al. The Canadian Journal of Addiction, 2019

"Microdosing" Inductions

The micro-initiation method requires patients to significantly decrease their use of fentanyl while gradually increasing their dose of buprenorphine. After five days patients should have completely transitioned off fentanyl.

	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5
How Much Do I Take?	**¼ Film Strip** (0.5mg)	**½ Film Strip** (1mg)	**½ Film Strip** (1mg)	**1 Film Strip** (2mg)	**2 Film Strips** (4mg)
How Often Do I Take It?	**Every 12 hours** (2 doses per day)	**Every 12 hours** (2 doses per day)	**Every 8 hours** (3 doses per day)	**Every 8 hours** (3 doses per day)	**Every 8 hours** (3 doses per day)
What Is The Total Daily Dose?	**½ film strip** (1mg)	**1 film strip** (2mg)	**1½ film strips** (3mg)	**3 film strips** (6mg)	**6 film strips** (12mg)

DAY 6

We will adjust your dose on Day 6 depending on your withdrawal symptoms and cravings up to 24mg per day.

Clinical Drug Investigation (2021) 41:663–664
https://doi.org/10.1007/s40261-021-01048-z

LETTER TO THE EDITOR

Blister-Packing of 2 mg Buprenorphine Monoproduct as a Patient-Centered Method of Microdosing for Buprenorphine Induction

Anthony J. Accurso[1]

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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 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.

Discussion Questions

- How has your approach to overdose prevention changed with increases in fentanyl adulterating the drug supply?
- For patients seeking treatment whose primary drug is illicitly manufactured fentanyl, have you experienced difficulties with buprenorphine induction? Have patients generally required higher doses or had other difficulties with standard treatment?

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