What The Fentanyl!
Making sense of a deadly epidemic

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CA BRIDGE

No financial disclosures…

But we may say brand names on accident!

Let's talk about…

- Reducing Harm & Living Well
- Break it down: What's the deal with fentanyl?!
- Fentanyl & MAT

A few key acronyms:

SUD = Substance Use Disorder

OUD = Opioid Use Disorder

MAT = Medication for Addiction Treatment

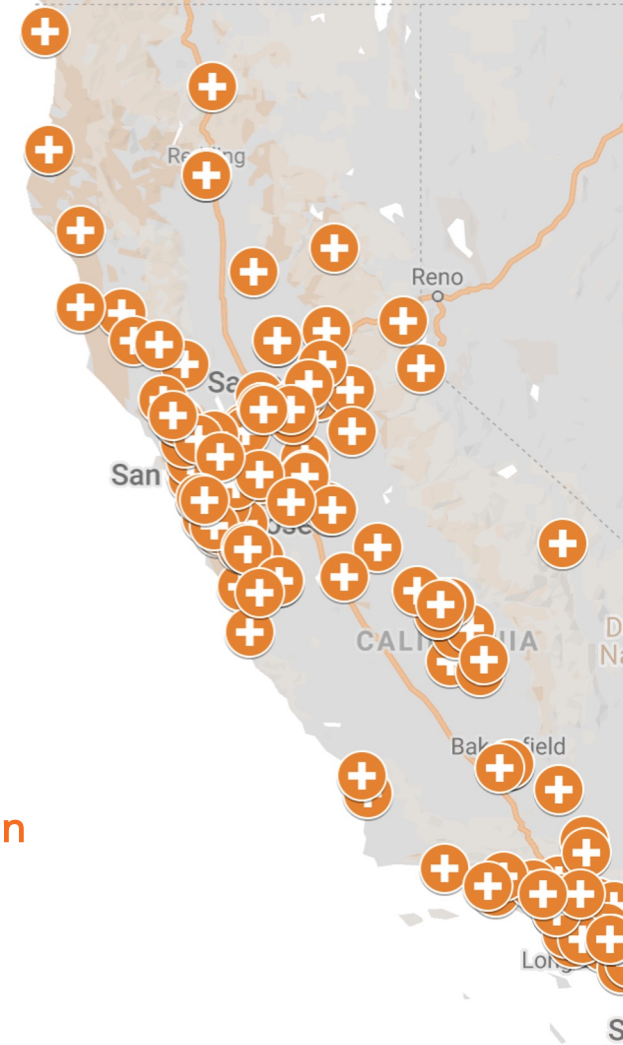
CA BRIDGE

Goal: 24-7 access to high quality treatment of substance use disorders in all California hospitals by 2025

Impact: From March 2019 - July 2020 over 50 hospitals treated patients with substance use disorders

Update: 2022 hospitals implement the CA Bridge model in 2022-23

Over 12, 000 encounters with MOUD to date



Some Terms

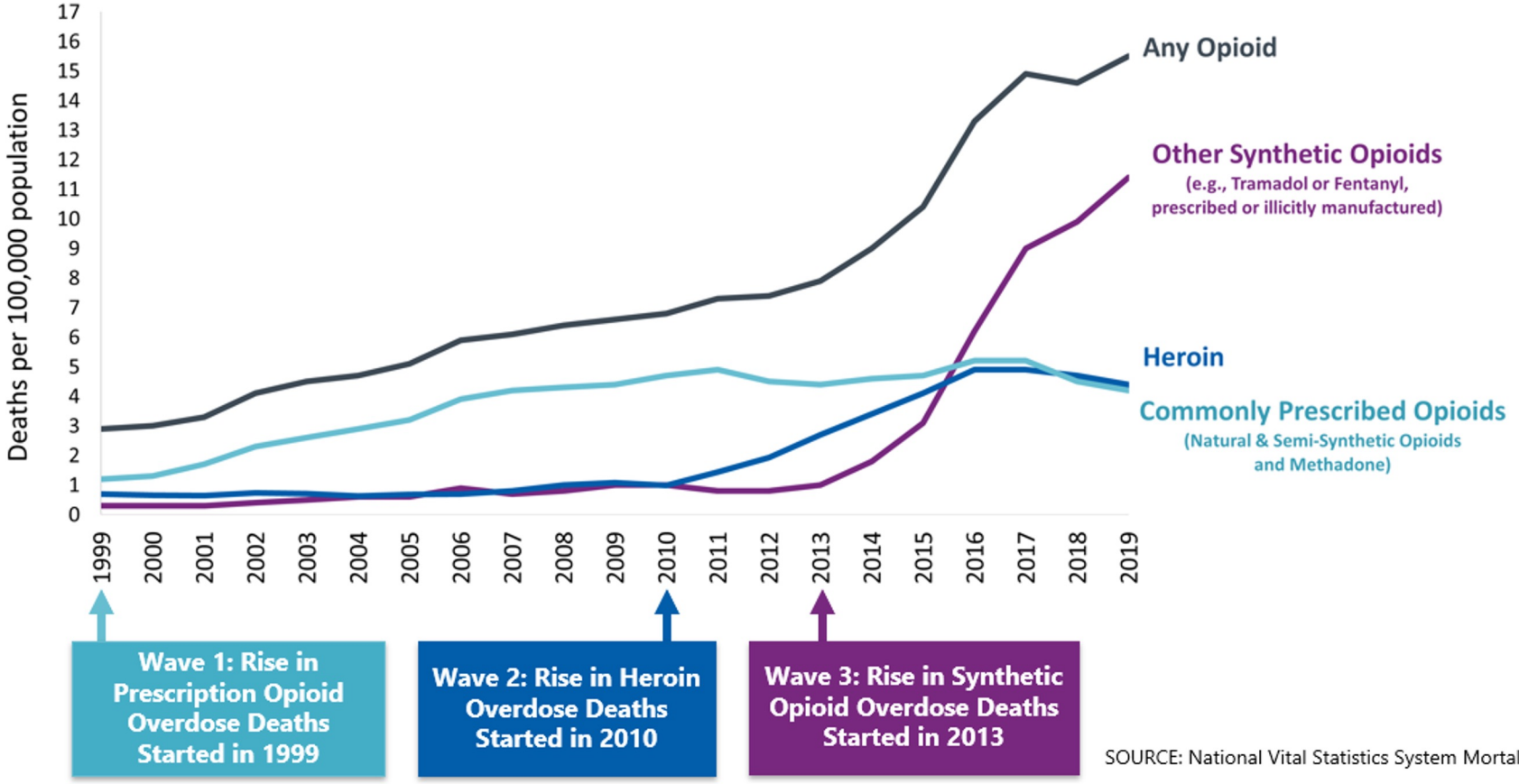
Regular Drug Use → Desensitization → Tolerance

- **Tolerance** - requires higher dose for same effect
- **Dependence** - will enter withdrawal without it, must use to feel normal
- **Addiction** - complex diagnosis related to negative psychosocial behaviors and consequences because of substance use disorder

Not all drug use is addiction.

*"**Pt with Substance Use Disorder**" – Not "addict," "druggie," etc.*

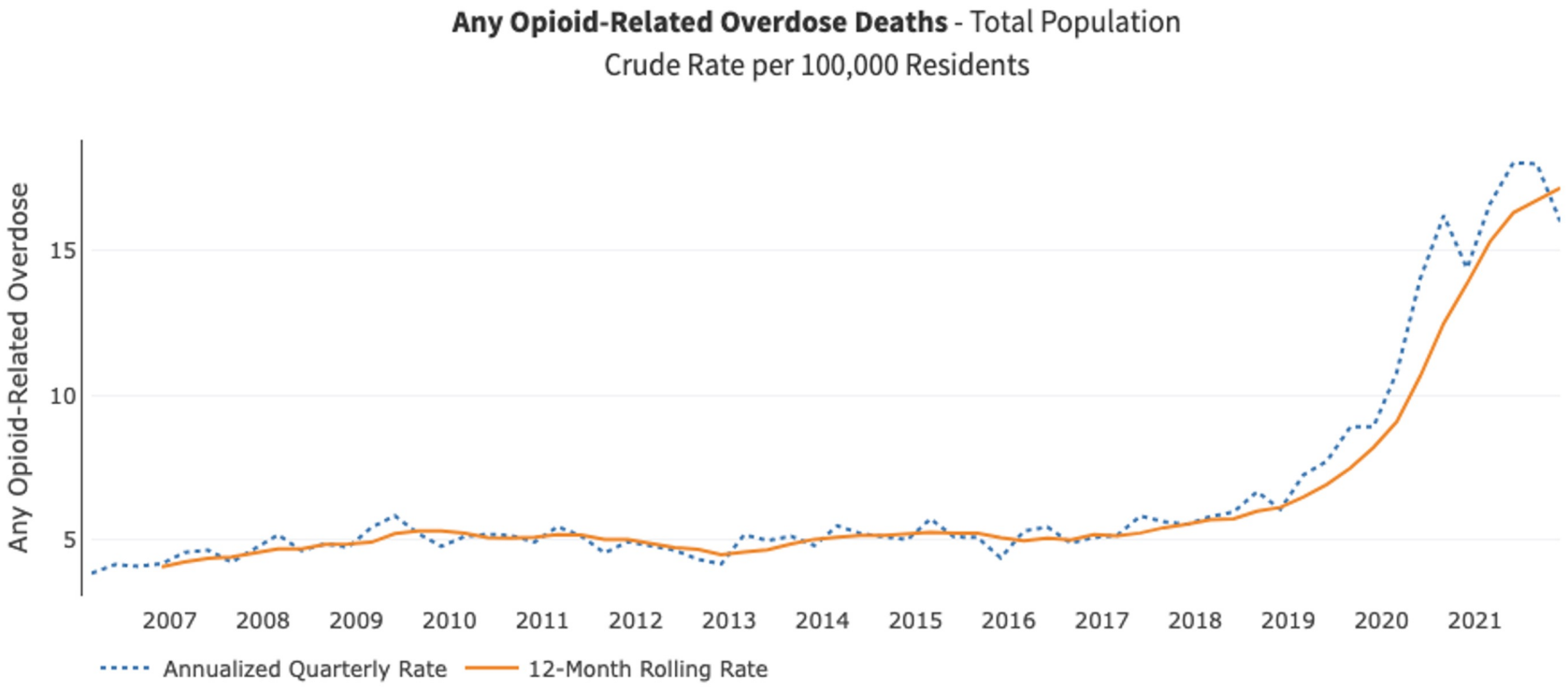
Three Waves of the Rise in Opioid Overdose Deaths



SOURCE: National Vital Statistics System Mortality File.

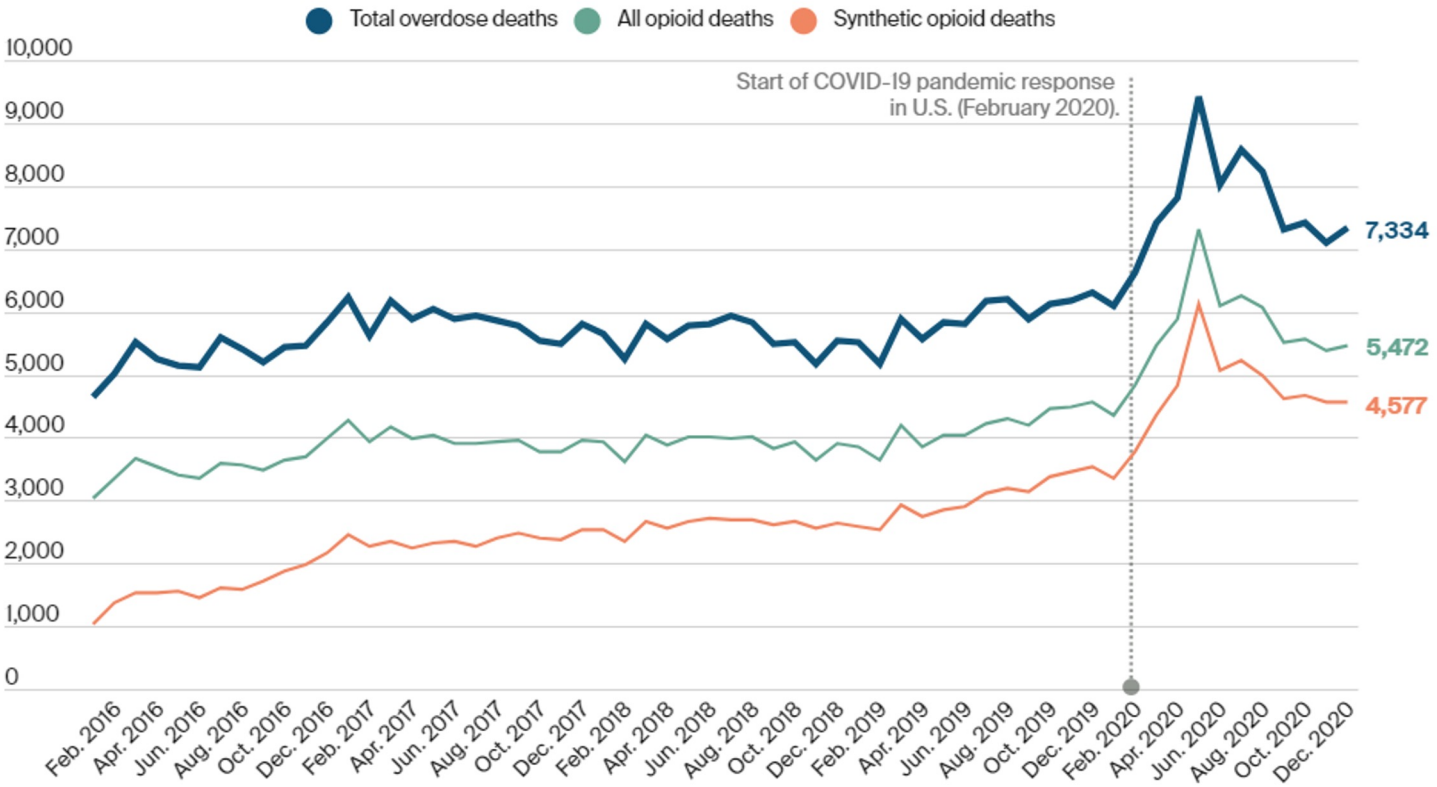
California

Graph | Table | Select Display Options | Time Trend



Overdose deaths spiked at the start of the pandemic and stayed high through the end of 2020.

Monthly drug overdose deaths



Since 1999, drug overdoses have killed approximately 1 million Americans

Last year, 621 people died of drug overdoses in San Francisco. To put this in perspective, 173 people died from COVID-19

Changing epidemic

- No longer a prescription epidemic
  - Opioid dispensing: 72.4/100 persons in 2006 46.7 in 2019
  - Deprescribing can drive illicit use
- Heroin to synthetic opioids
- Cocaine to meth

Four Steps to Reduce Opioid Overdoses

- Limit NEW CHRONIC opioid prescribing
- Identify and treat opioid use disorder (buprenorphine and methadone)
- Reduce risk of overdose in those who use (counseling, naloxone, fentanyl testing)

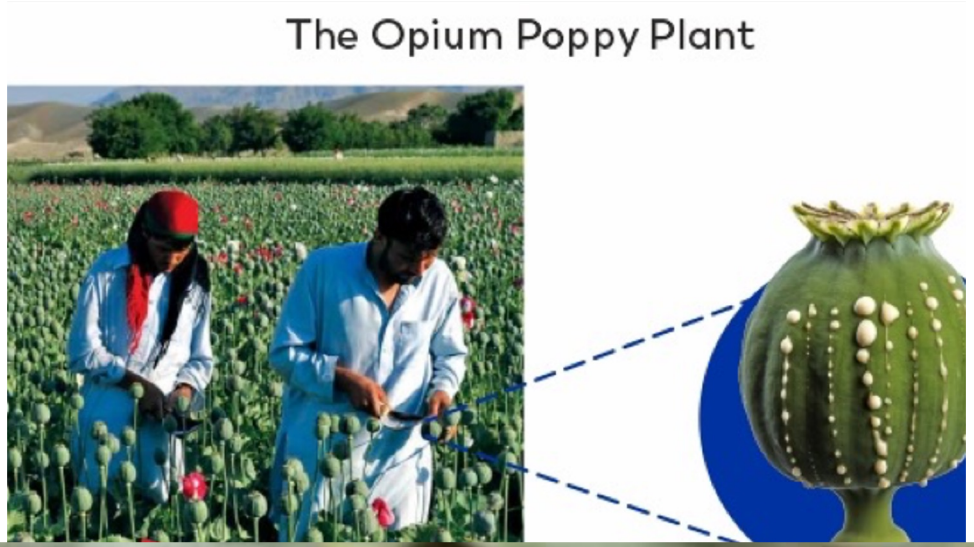
History of fentanyl

- 1960: Synthesized
- 1980s: First reports of misuse
- 2006: Fentanyl outbreak in heroin users
- 2013: Rise in fentanyl associated deaths begins
- 2014: Counterfeit pills enter market
- 2016: Carfentanil associated deaths
- 2018: Fentanyl become top cause of opioid overdose

Supply side drivers

- Supply driven (at least initially)
  - Sold as heroin
    - Polarized demand
  - Cheap
  - Easy to ship
  - Decreased regulation in international production regions

Heroin and cocaine are agricultural products



We are facing a community disaster

Heroin and cocaine are being replaced by synthetic fentanyl and crystal methamphetamine

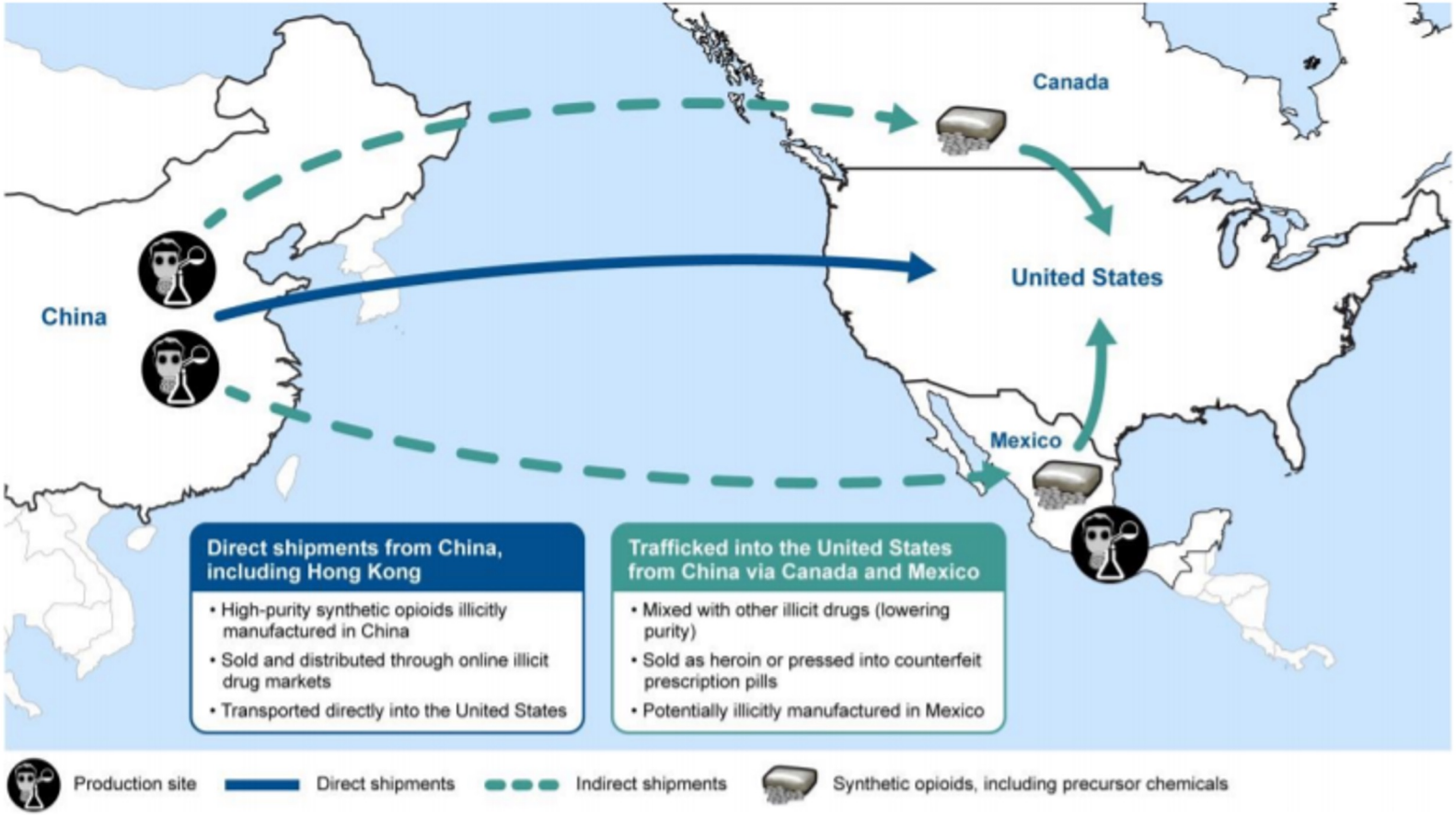
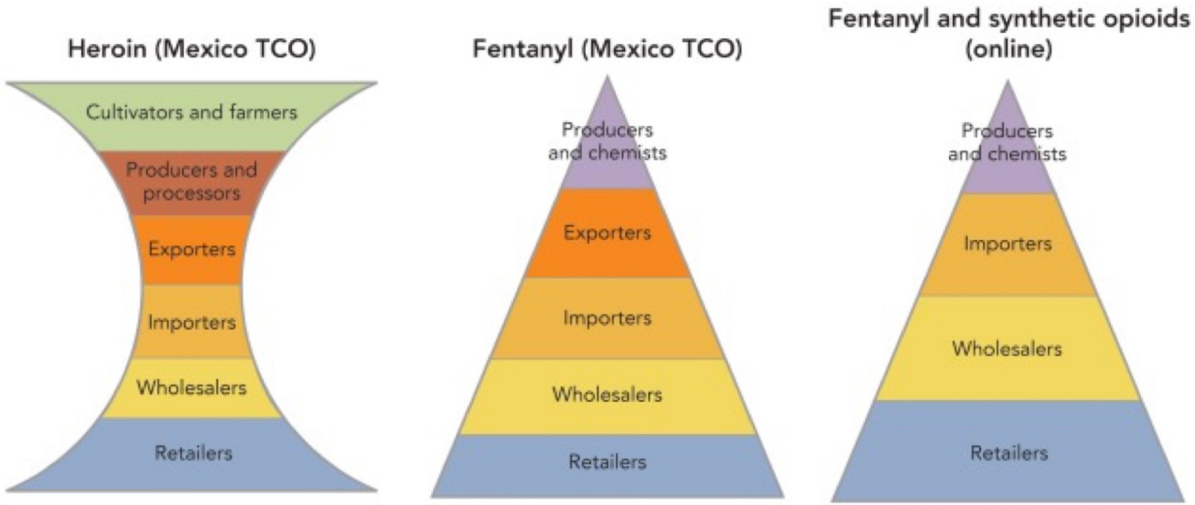


Figure 1 Illicit Synthetic Opioid Flows Originating from China[6]

Supply side economics

Drug Supply Chains for Heroin and Synthetic Opioids

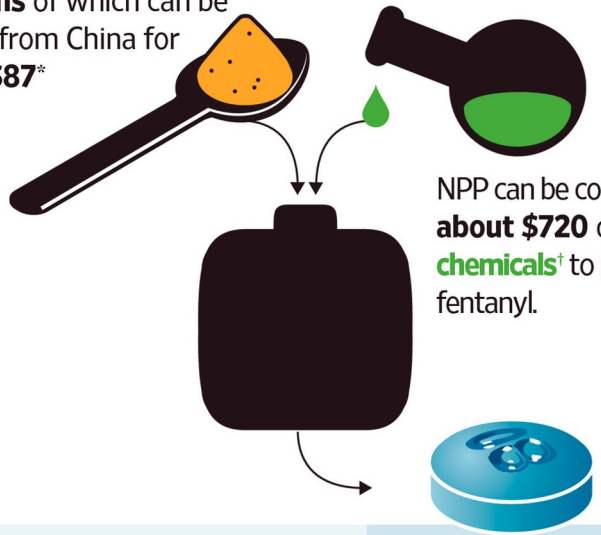


SOURCE: Adapted from Peter Reuter, Bryce Pardo, and Jirka Taylor, "Imagining a Fentanyl Future: Some Consequences of Synthetic Opioids Replacing Heroin," *International Journal on Drug Policy*, Vol. 94, August 24, 2021, Art. 103086.

Criminal Chemistry

Traffickers manufacturing fentanyl often purchase the key ingredient from China, which doesn't regulate its sale. Here's how the chemical building blocks become a highly profitable street drug.

The key ingredient is NPP, 25 grams of which can be bought from China for **about $87***



NPP can be combined with **about $720** of **other chemicals**† to produce fentanyl.

The resulting 25 grams of fentanyl cost about $810 to produce...

...and are equivalent to up to $800,000 of pills on the black market.

*Average current price from Chinese suppliers

†Prices from U.S. suppliers

Sources: NES Inc.; Drug Enforcement Administration; Calgary Police

THE WALL STREET JOURNAL.

When do we see fentanyl

Assume fentanyl!

- Heroin
- Opioid and benzo pills
  - 27% of pills seized by DEA in 2019
- Cocaine, methamphetamines
  - Naloxone responsive stimulant overdoses
- Fentanyl
  - Smoke, snort, IV

Demand Side Drivers (anecdote)

- IV or smoked= reduced vein preservation
    - West coast microcosm: black tar heroin - smoked fentanyl in setting of limited venous access
- At least you know what's in it (?)
- Cost effective
- Feels good
- High tolerance, still effectiveness
- Longer duration than heroin

Pharmacology

- 25 x potency of heroin—narrow “therapeutic” window
- Lipophilicity - High high volume of distribution (3 compartment model)
  - Rapid crossing of blood brain barrier
  - Rapidly distributed to adipose tissue/muscles, slowly returns
- Pharmacokinetics
  - 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)
- Hepatic metabolism (CYP3A4) to inactive metabolite
- Utox pos for mean 7.3 days in treatment program

Buprenorphine Barriers

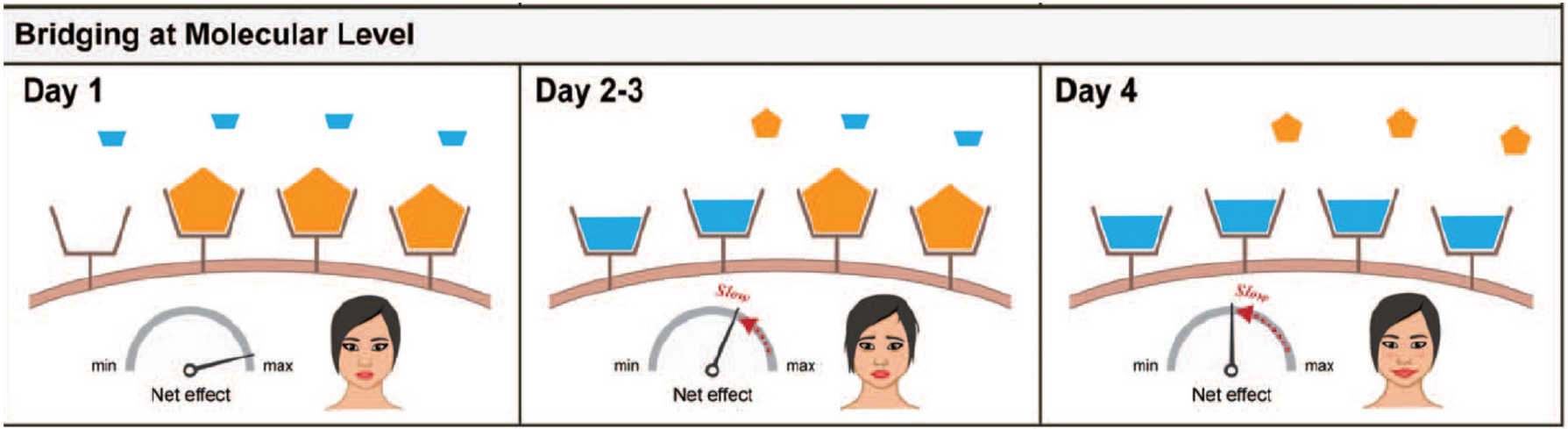
- Increased precipitated withdrawal
  - Not everyone though!
- Increased tolerance
- High overdose risk with return to use

Options for starting treatment

- Wait for bad withdrawal, do standard dose 4-8 mg
- Microdosing/cross tapering/bridging
  - Continue full agonist opioid, give small doses of buprenorphine, increase daily
- Single big dose 16-32 mg (?)
- Methadone
- Post naloxone initiation of 8-16
  - While in withdrawal

Microdosing

- Continue drug of choice vs inpatient prescribed full opioid agonists
- Small sublingual doses (0.5-1 mg) vs patch vs IV small doses
- Often used for methadone conversion
- Nice inpatient or with bubble packs
- 3-8 day duration



My personal approach: 2 options

- Wait longer
  - COWS 12, objective signs
  - >24 h, aim for >48 h
  - 8 mg SL first dose
  - Those who can't/wont access other opioids during start
- Microdose with patch or SL
  - Hospitalized/fragile patients
  - Those with prior precipitated withdrawal
  - Those who can handle complex dosing

Impact of Fentanyl Use on Buprenorphine Treatment Retention and Opioid Abstinence

Sarah E. Wakeman, MD, Yuchiao Chang, PhD, Susan Regan, PhD, Liyang Yu, MS, James Flood, PhD, Joshua Metlay, MD, PhD, and Nancy Rigotti, MD

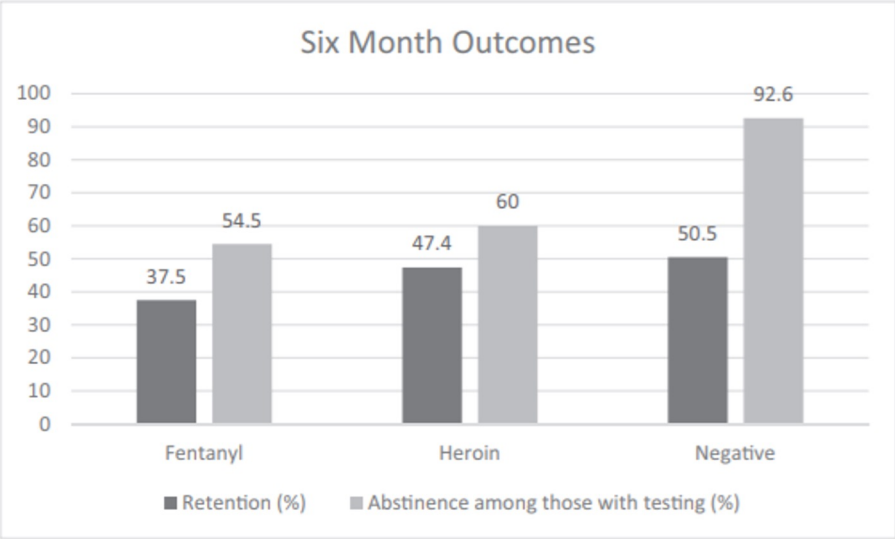


FIGURE 1. Retention and opioid abstinence among those retained at six-month follow-up.

Buprenorphine Best Practices

- Evidence
  - To achieve blockade, need <20% mu opioid receptor available (at least 16 mg)
  - For higher doses, higher potency, may need higher
  - 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)

Additional thoughts (with minimal evidence)

- Subcutaneous buprenorphine
  - High tolerance so dose may be appropriate
  - Increased adherence
  - Increased satisfaction

Table 6. Comparison of Buprenorphine Mean Pharmacokinetic Parameters Between SUBUTEX and SUBLOCADE

Pharmacokinetic parameters	SUBUTEX daily stabilization		SUBLOCADE		
Mean	12 mg (steady-state)	24 mg (steady-state)	300 mg# (1st injection)	100 mg* (steady-state)	300 mg* (steady-state)
$C_{avg,ss}$ (ng/mL)	1.71	2.91	2.19	3.21	6.54
$C_{max,ss}$ (ng/mL)	5.35	8.27	5.37	4.88	10.12
$C_{min,ss}$ (ng/mL)	0.81	1.54	1.25	2.48	5.01

#Exposure after 1 injection of 300 mg SUBLOCADE following 24 mg SUBUTEX stabilization

*Steady-state exposure after 4 injections of 100 mg or 300 mg SUBLOCADE, following 2 injections of 300 mg SUBLOCADE

Additional thoughts (with minimal evidence)

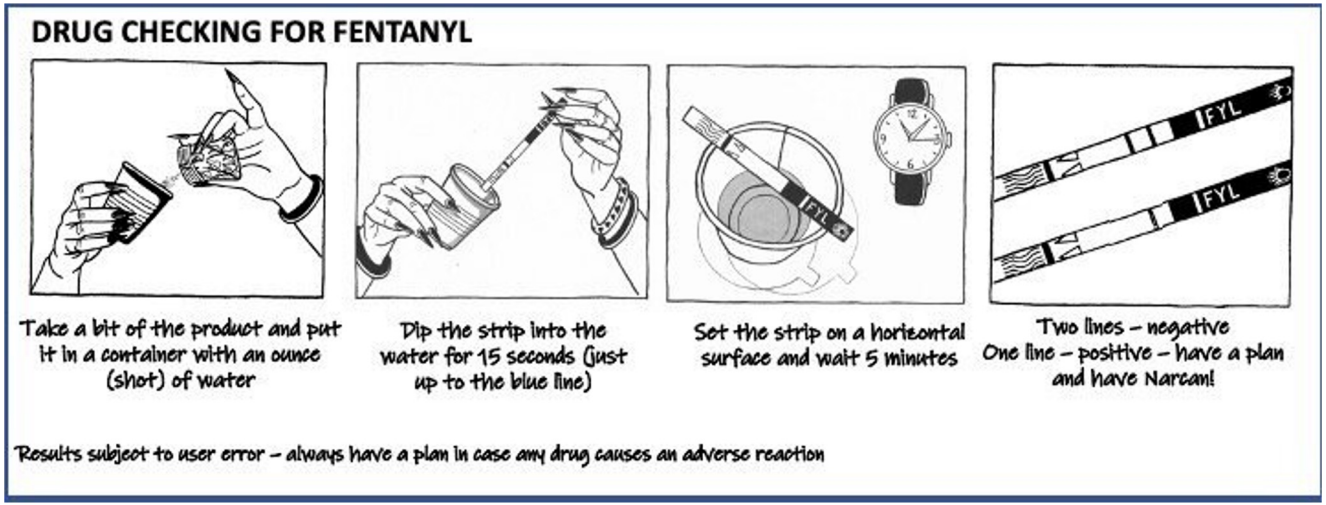
- Intramuscular naltrexone
  - Risks for loss of tolerance are heightened
  - May have some benefit in contaminated stimulants

Treatment Models

- Consider opioid agonists first line, consider higher doses
- Offer treatment for comorbid mental health, substance use
- Low barrier, high support
- Harm reduction embedded

Overdose prevention—fentanyl contamination

- Never use alone
- Test doses: start low, go slow
- Smoked/snorted
- Carry naloxone
- MOUD



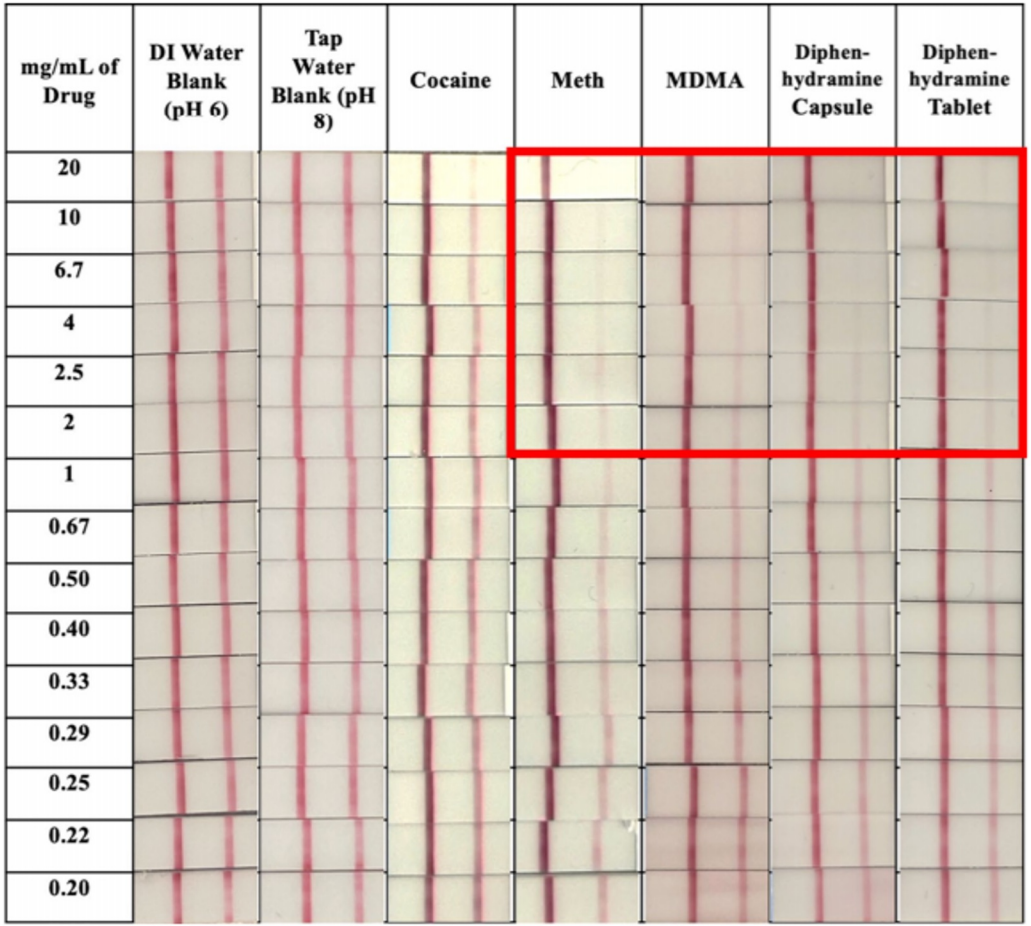


Fig. 2 Fentanyl test strip images of interference compounds: FTS were ran with water, cocaine, methamphetamine, MDMA, diphenhydramine capsules, and diphenhydramine tablets and were photographed after 5 min. The testing bar (right side of testing pad) for moderately concentrated samples (approximately > 2 mg/mL) of methamphetamine, MDMA, diphenhydramine capsules, diphenhydramine tablets did not appear indicating false positives

Overdose prevention—purchased fentanyl

- Never use alone
- Test doses: start low go slow
- Smoked/snorted
- Carry naloxone
- MOUD
- Injectable opioid agonist treatment

How to Use the Safer Fentanyl Smoking Kit

What's Included:
Sani Hand Wipes
Alcohol wipes
Foil
Straw/Tooter (many different options)

Recommended Use:

1. Sanitize hands with Sani hand wipes
2. Use the alcohol wipes to clean any shared materials and/or surfaces.
3. Prep the foil. If crumpled, lay the foil out on a flat surface and smooth it with a lighter. Make sure the foil is as flat and even as possible. Shape your foil so it has a catch for your drugs. A wrinkled surface can mess up the flow of drugs and increase risk of losing the drugs.
4. Tooters come in many shapes and sizes. Pick one that meets your personal preference.

But I heard—naloxone doesn't work

- Respond quickly
- Wait full 2-3 min between intranasal doses
- Rescue breathing
- Consider additional substances
- In hospital setting: increase dose to a max of 10-15 mg

With heroin, you feel it coming on, you feel the intensity. You feel like you're going to puke, you know, because it keeps coming and you know I'm going to go down [overdose]. Fentanyl, you're sitting there waiting for something and, the next thing you know, there is an ambulance attendant there. It hits you like a Mac truck. You don't feel it, nothing. It's just boom, down. You get up and you swear that you didn't even do your shot, and you're looking for it. (White man, age 23)

But I heard—first responders overdose

- Airborne
    - “At the highest airborne concentration encountered by workers, an unprotected individual would require nearly 200 minutes of exposure to reach a dose of 100 mcg of fentanyl. The vapor pressure of fentanyl is very low (4.6 x 10-6 Pa) suggesting that evaporation of standing product into a gaseous phase is not a practical concern”
- Transdermal
    - “If bilateral palmar surfaces were covered with fentanyl patches, it would take approximately 14 minutes to receive 100 mcg of fentanyl [using a body surface area of 17,000 cm2 , palm surface area of 0.5%, and fentanyl absorption of 2.5 mcg/cm2 /h”

3 policy steps (Dan Ciccarone)

- Supply reduction
- Demand reduction
  - Treatment
  - Community support
- Harm reduction

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