



Illicitly-Manufactured Fentanyl in the United States: Trends and Truths

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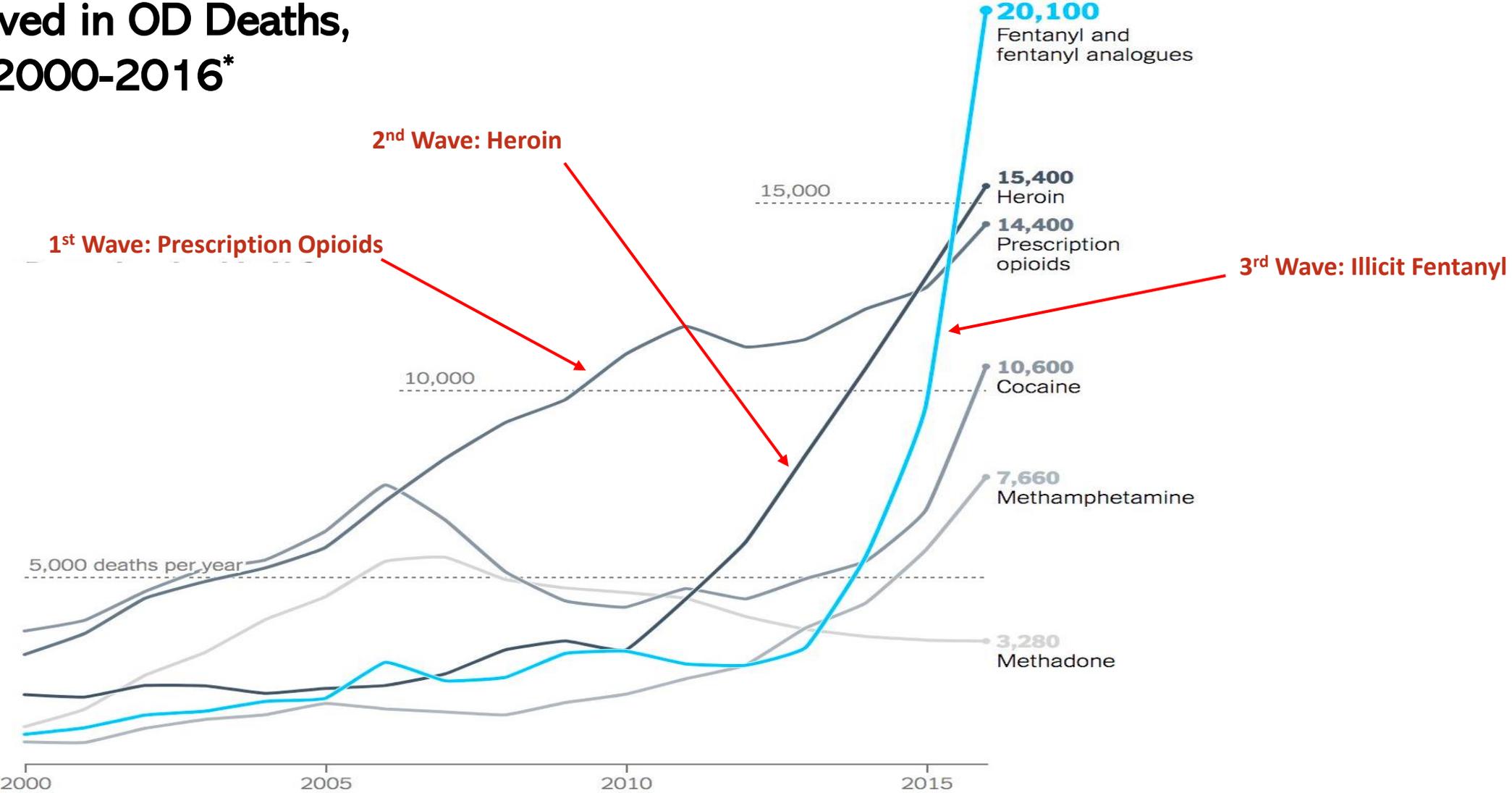
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Presentation Overview

- ❖ I will first present recent trends in drug overdose deaths and law enforcement drug exhibits to show how changes in the illicit drug supply can explain changing drug overdose mortality and show the continuing evolution of the opioid epidemic
- ❖ I will then describe fentanyl's pharmacologic profile with a particular focus on routes of administration to demonstrate how levels of fentanyl toxicity are contingent upon specific modes of consumption and pathways of exposure
- ❖ Finally, I will recount the experiences of people who use fentanyl to describe—from the consumer's point of view—its physiological effects and the types of unique overdose presentations that appear during toxic fentanyl events.
- ❖ Overall, this presentation will increase understanding of fentanyl pharmacology and fentanyl overdose risk and offer an evidence-based framework for reducing unwanted or unwitting fentanyl exposure

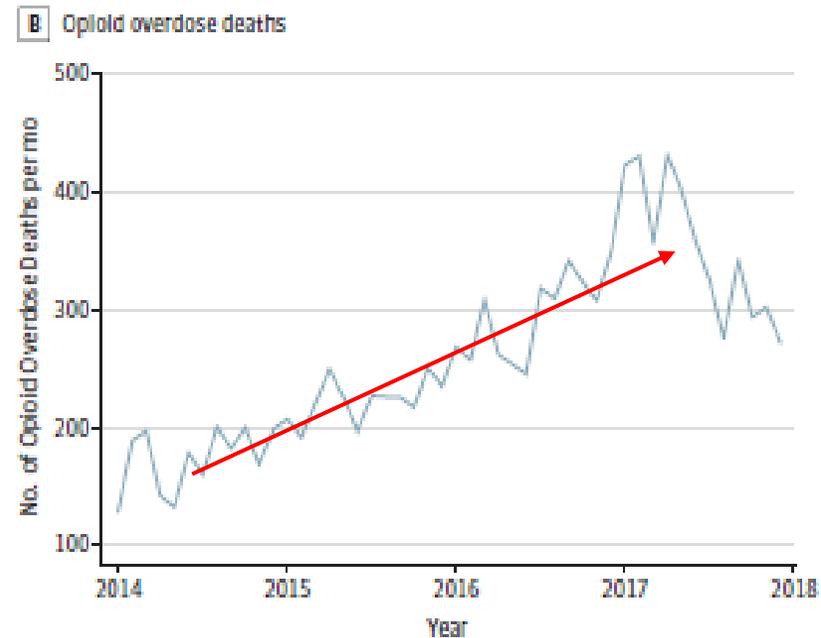
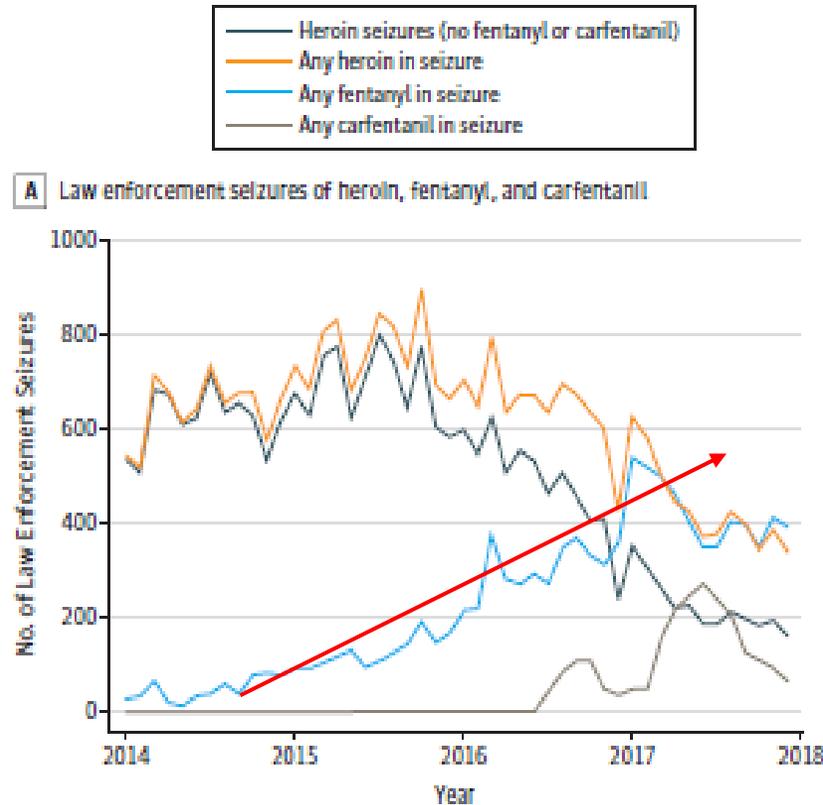
Drugs Involved in OD Deaths, U.S., 2000-2016*



*NYT Interactive, 09/02/2017, National Center for Health Statistics



Opioid OD Deaths & Law Enforcement Cases of Heroin, Fentanyl & Carfentanil, per Month, Ohio, 2014-2017



❖ Fentanyl exhibits were significantly associated with OD deaths
($\chi^2=3528$; $P<.001$)

❖ Every additional fentanyl exhibit was associated with 0.58 increase in deaths
(95% CI, 0.41-0.74; $P<.001$)

A, Law enforcement seizures of heroin, fentanyl, and carfentanil are shown by month. B, Opioid overdose deaths are shown by month.

A Growing Illicit Stimulant Crisis During a Fentanyl Epidemic



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Association between law enforcement seizures of illicit drugs and drug overdose deaths involving cocaine and methamphetamine, Ohio, 2014–2019

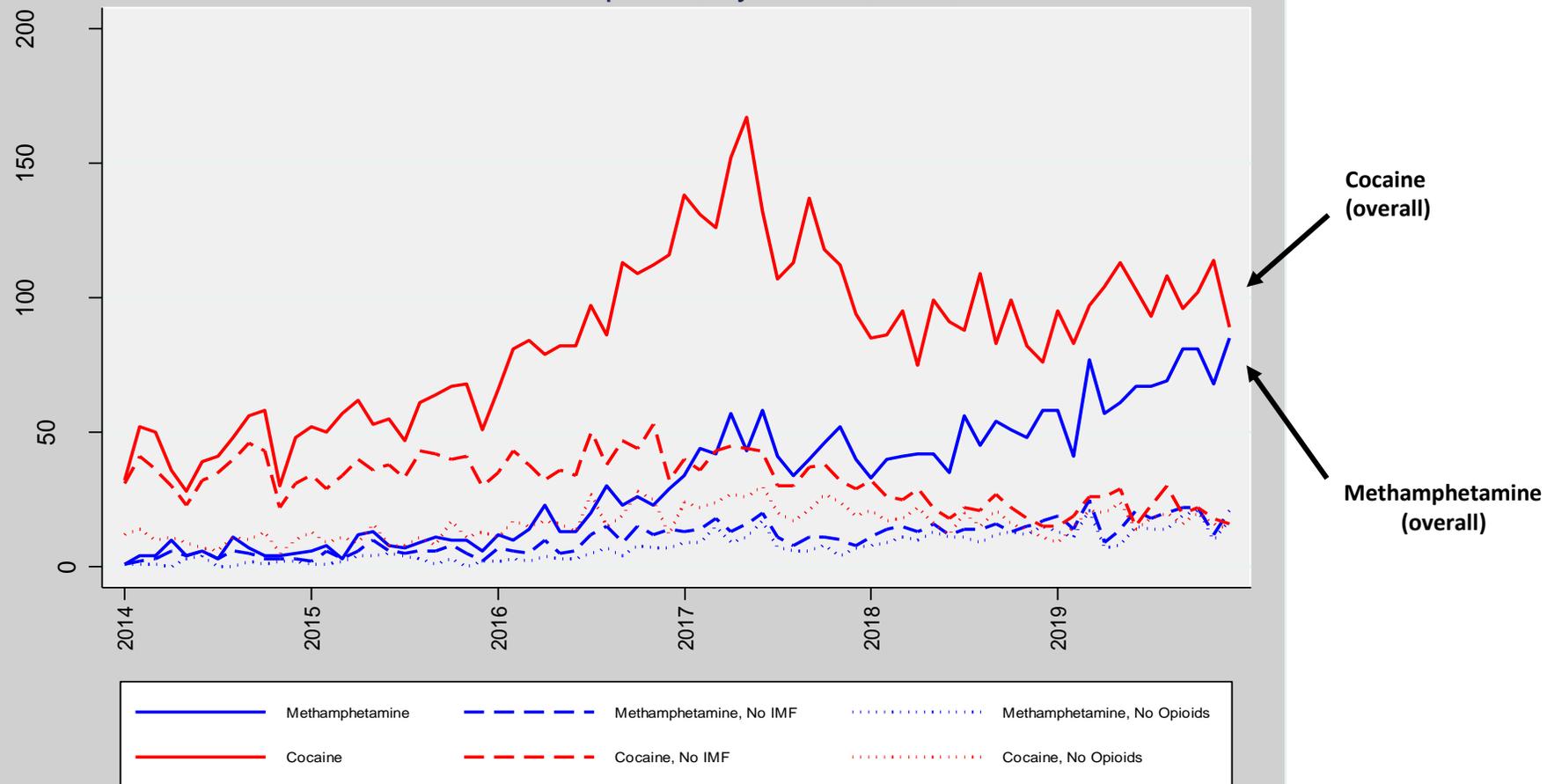
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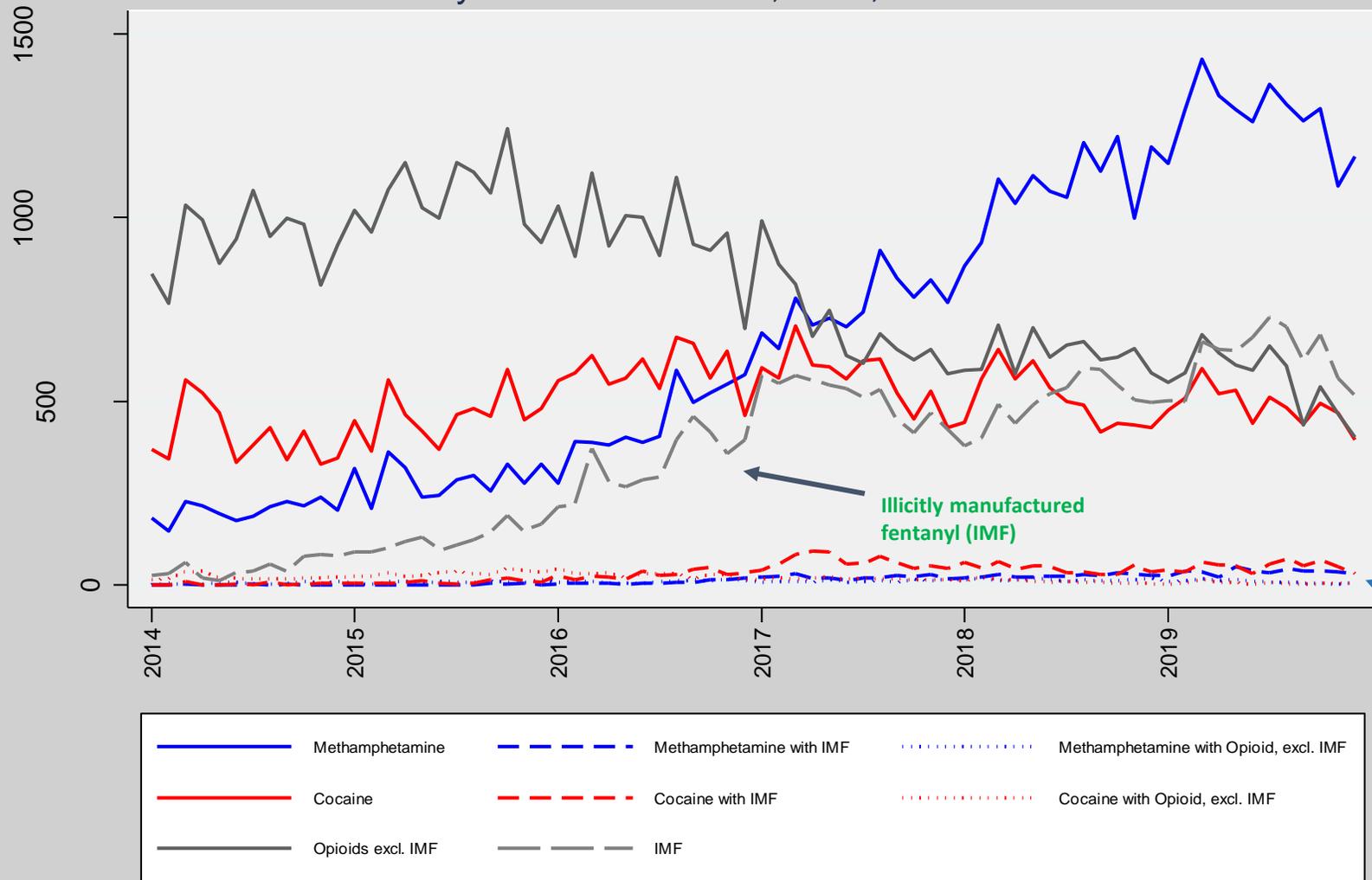


Figure 1. Overdose Deaths for Methamphetamine and Cocaine, Overall, excl. IMF, excl. Opioids, by Month, Ohio, 2014-2019



- Law enforcement seizure of illicitly-manufactured fentanyls (IMF) were the strongest indicator of both cocaine and methamphetamine-involved OD deaths from 2014-2019
- Each IMF seizure associated with additional stimulant deaths (0.119, $p < .01$)
- No significant associations found between overdose deaths and seizures of prescription opioids or heroin

Figure 2. Selected Drugs Detected in Law Enforcement Exhibits, by Month of Offense, Ohio, 2014-2019



IMF-adulterated Cocaine (11%) [0.493, $p < .01$]

IMF-adulterated Meth (3%) [0.551, $p = .087$]

Fentanyl Adulteration of Cocaine and Methamphetamine, Ohio, 2014-2017

- Heroin, cocaine and methamphetamine that tested positive for fentanyl were confiscated by law enforcement in packages with weights intended for street sales to individual consumers
 - Fentanyl adulteration of cocaine and methamphetamine was mainly found in seizure packages weighing ≤ 1 g, with second highest prevalence in the >1 g but <30 g category
 - Like heroin, packages of cocaine and methamphetamine were confiscated in weight classes intended for individual consumers (<1 g)

- *Key difference* between adulteration of heroin and the adulteration of cocaine/methamphetamine concerns the weight patterns of seized packages

Ohio, Law Enforcement Seizures by Weight, 2014-2017

Table. Percentage of Law Enforcement Seizures of Heroin, Cocaine, and Methamphetamine With Fentanyl or Carfentanil by Seizure Weight, Ohio, 2014-2017^a

Drug	Seizures, No. (% With Fentanyl or Carfentanil)			
	2014	2015	2016	2017
Heroin				
All seizures	7715 (3.4)	9151 (9.0)	7809 (25.0)	5242 (48.6)
All seizures with weight	5869 (3.3)	6778 (9.0)	6028 (25.4)	4500 (49.8)
By seizure weight, g ^b				
≤1	4654 (3.5)	5236 (9.9)	4767 (27.5)	3576 (52.0)
>1 but ≤30	1132 (2.4)	1412 (6.0)	1141 (18.0)	835 (44.7)
>30 ^c	83 (3.6)	130 (3.9)	120 (9.2)	89 (11.2)
Cocaine, with no heroin present				
All seizures	4898 (0.7)	5599 (1.7)	7102 (4.9)	6863 (11.3)
All seizures with weight	3727 (0.3)	3955 (0.4)	5197 (2.1)	5397 (5.9)
By seizure weight, g ^b				
≤1	2568 (0.5)	2545 (0.6)	3419 (2.7)	3611 (7.1)
>1 but ≤30	1071 (0.0)	1274 (0.0)	1607 (0.9)	1623 (3.8)
>30 ^d	88 (0.0)	136 (0.0)	171 (0.6)	163 (0.0)
Methamphetamine, with no heroin present				
All seizures	2517 (0.2)	3576 (0.5)	5519 (1.6)	9345 (2.9)
All seizures with weight	1610 (0.1)	2292 (0.0)	4127 (0.4)	7764 (1.2)
By seizure weight, g ^b				
≤1	1070 (0.1)	1534 (0.0)	2901 (0.5)	5364 (1.5)
>1 but ≤30	393 (0.0)	539 (0.0)	1031 (0.1)	2208 (0.8)
>30 ^e	147 (0.0)	219 (0.0)	195 (0.0)	192 (0.0)

Fentanyl Bioavailability Associated with Routes of Administration

➤ Oral

- Undergoes first-pass metabolism via cytochrome P450 3A with a bioavailability of **~30 %** after rapid swallowing.

➤ Sublingual

- First pass metabolism is circumvented by oral transmucosal with a bioavailability **40-60%**, with an onset of action of ~5-10 min

➤ Nasal Insufflation (Sniffing)

- A bioavailability of **~80%**, with a short onset of action (~3-5 min) and short duration of effect (~1-3 hours)

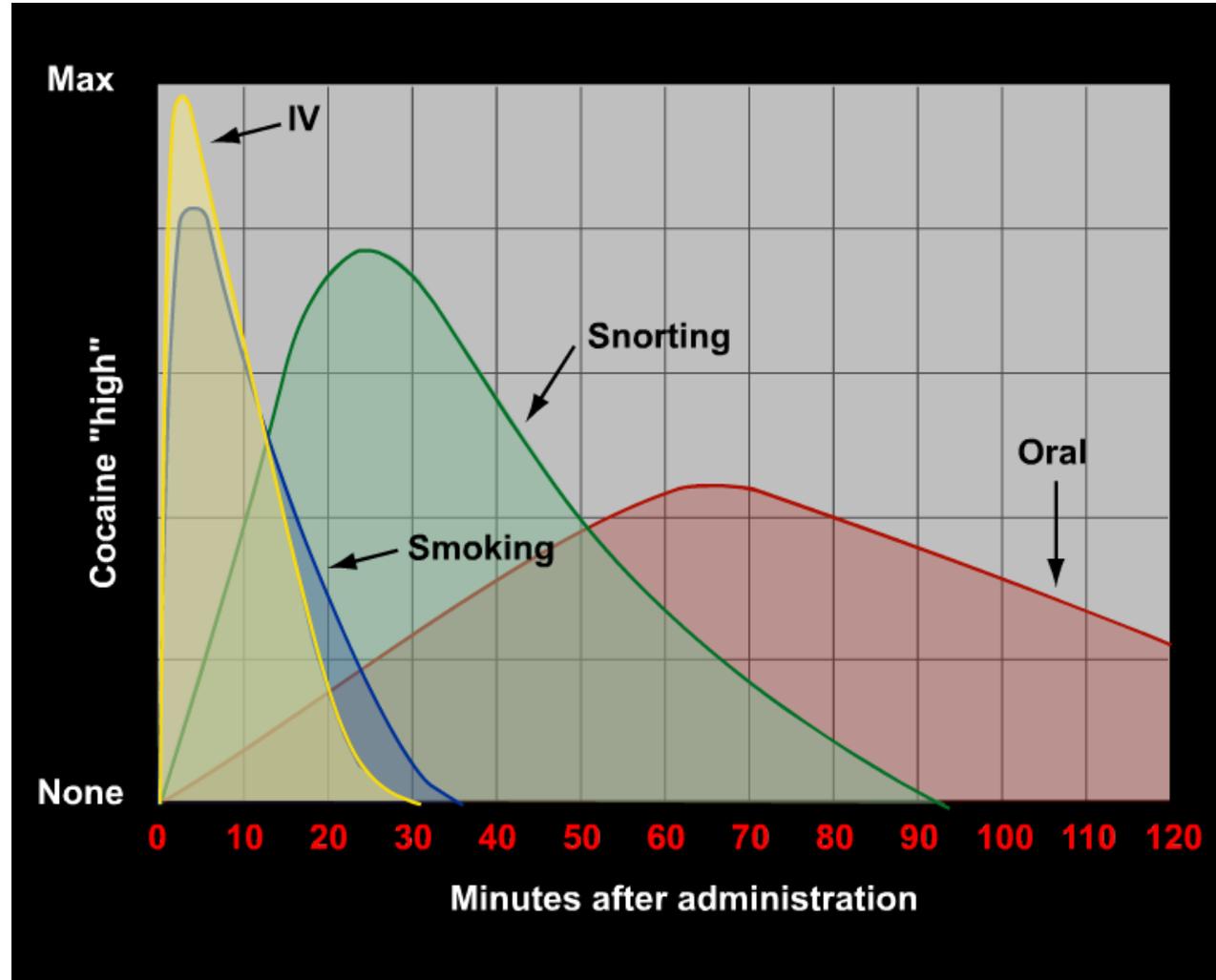
➤ Lung Insufflation (Smoking)

- A bioavailability of **90-95%**, with a shorter onset of action (~30 sec-2 min) compared with sniffing and similarly shorter duration of effect (~1-2 hour) compared with sniffing

➤ Intravenous Injection

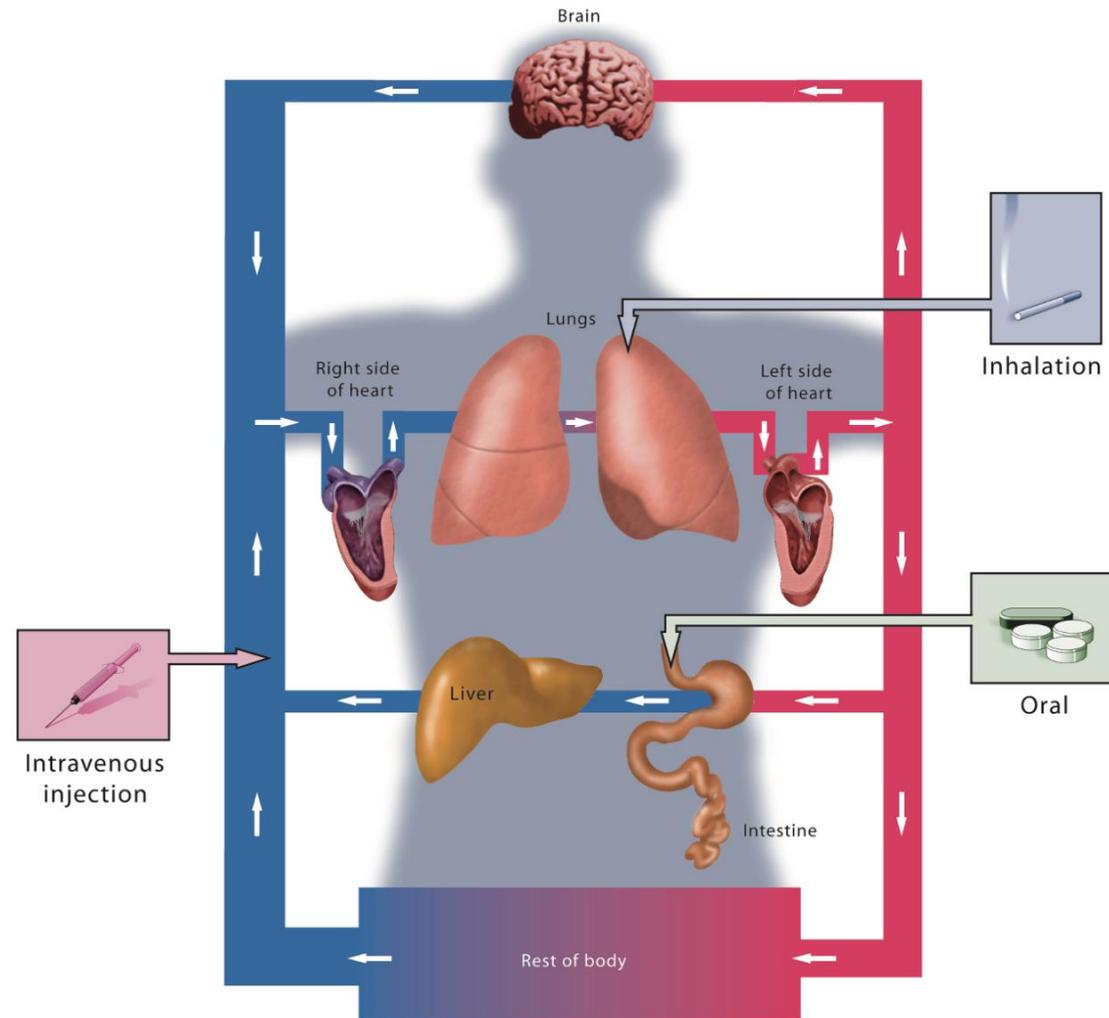
- A bioavailability of **99-100%**, with immediate onset of action (~5-10 seconds) and short duration of effect (~30 min to 1 hour)

Drug Onset and Duration of Effect by Route of Administration



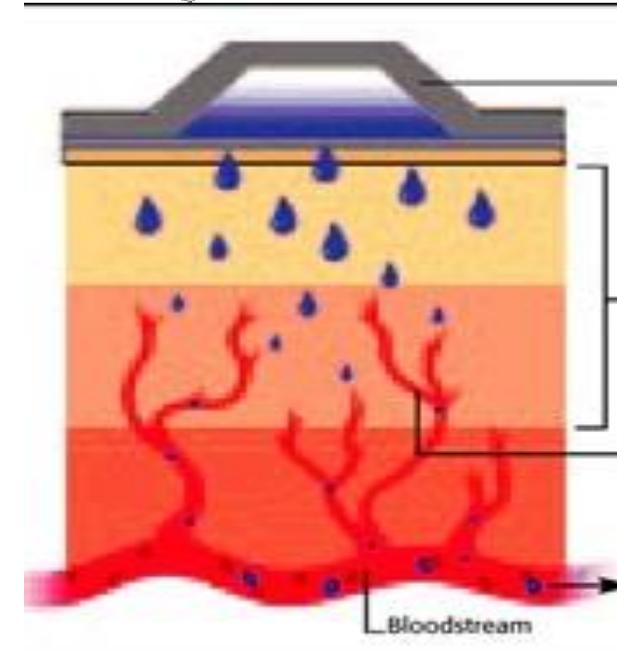
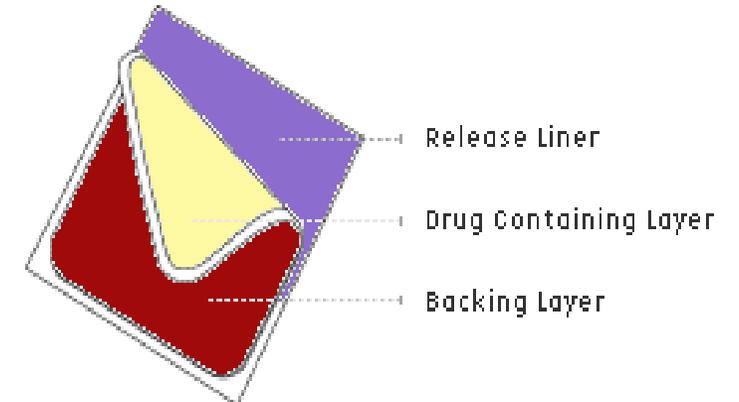
Modes of drug administration into the body

Red is the arterial side and blue is the venous side



Transdermal Exposure via Prescription Fentanyl Patches

- The sticky side of the fentanyl patch is a semipermeable membrane that lets medication pass through at a controlled rate.
- Fentanyl builds up in subcutaneous tissue under the patch. From this medication depot, blood vessels take up the drug and distribute it throughout the body
- Therapeutic blood levels are not reached for 13-24 hours after patch application, making it unsuitable for acute pain.
- Transdermal bioavailability is 60-84%
- Transdermal administration of fentanyl into bloodstream cannot occur without facilitation via a gel-reservoir or adhesive matrix



Perceived Occupational Risk of Fentanyl Exposure Among Law Enforcement

KEY ISSUE

- Law enforcement officers worry about the occupational hazards involved in responding to scenes involving drugs like fentanyl.
- Toxicologists and medical professionals have determined that the risk of overdose from dermal fentanyl exposure is extremely low for law enforcement.

MAIN FINDING

- Nearly all law enforcement leaders and officers interviewed *mistakenly* believed that **dermal exposure to fentanyl** was deadly and expressed fear about such exposure on scene.
- There is a substantial, pressing need for dissemination of facts about the lack of overdose risk when touching fentanyl through channels that law enforcement trust, including through their basic training academy, in-service training, and law enforcement organization's bulletins and newsletters.

Colombian-sourced Heroin (powder, granular, brownish)



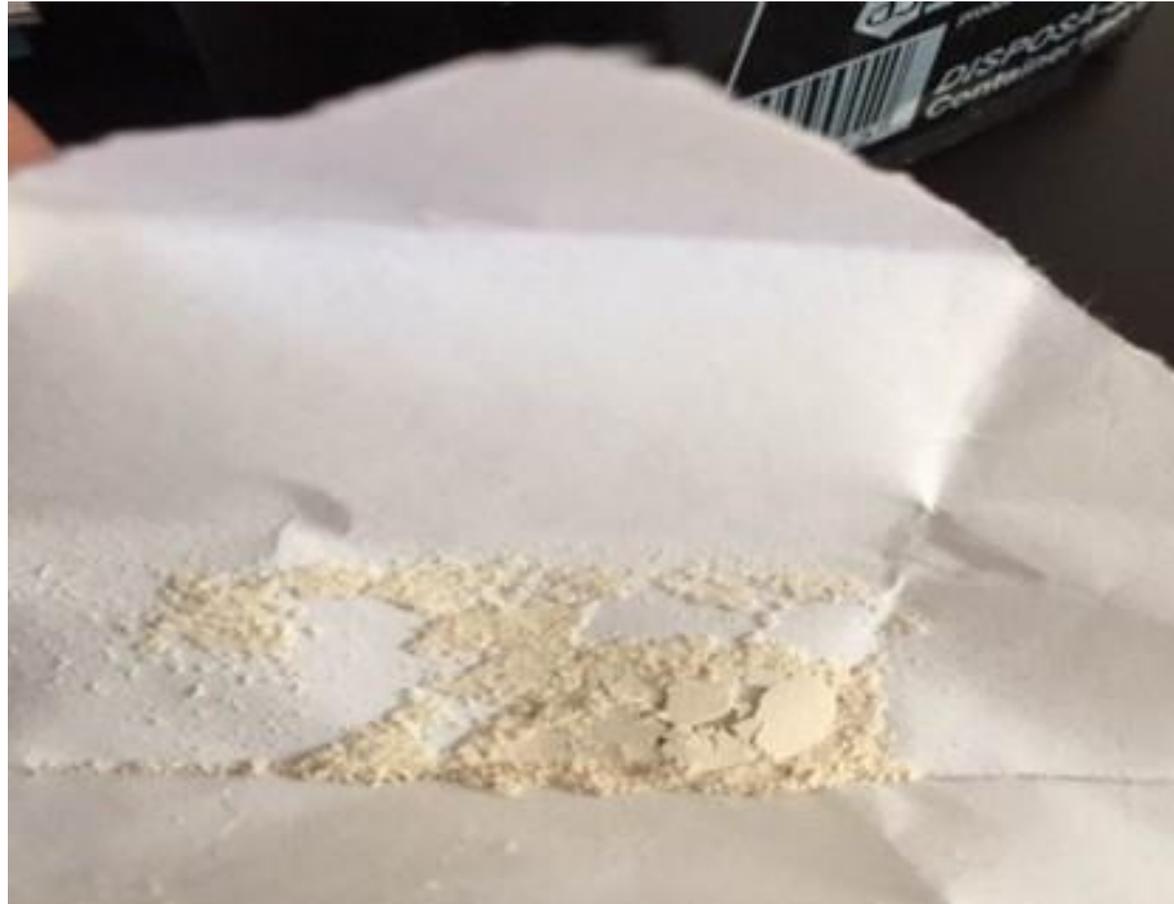
Mexican-sourced (Tar) Heroin



'Tar' Heroin, North Carolina



Heroin Adulterated with IMF, Massachusetts, 2017



Cocaine and Fentanyl, North Carolina, 2019



“Gray Death” in Atlanta



Counterfeit Pills in North Carolina



Fake Xanax (“Zanny”bars)



Fake Roxicodone (Dirty 30s”)

Undetermined Risk Factors for Opioid and Fentanyl-Involved Overdose — Massachusetts, 2014–2015:

Insights from Survivors, Bystanders and Decedents

Epi-Aid Investigation
Centers for Disease Control and Prevention



Overdose involving IMF progress rapidly—in seconds to minutes rather than minutes to hours like with heroin

- **75% of interview respondents reported fentanyl overdose occurring rapidly with little warning**

- **36% of fentanyl-related deaths had evidence of rapid overdose occurring in seconds to minutes:**
 - Needle still inserted
 - Syringe found in hand
 - Tourniquet still in place
 - Bystander reports

Clinical Manifestations of Fentanyl Overdose

➤ Respondents reported vivid description of fentanyl overdose:

- Prompt stiffening of body
- Immediate perioral cyanosis (blue lips)
- Abrupt 'air loss' (respiratory arrest)
- Seizure like activity
 - Foaming at mouth
 - Eyes rolling back in head
- One report specifically describing rigid chest
 - Related to prompt stiffening of body

Overdose Presentations: Quotes from Consumers

...with regular dope [heroin] they lean back and drop and then stop talking in a middle of a conversation and you look over and realize that they're overdosing; not like with fentanyl. I would say you notice it [a fentanyl overdose] as soon as they are done [injecting the fentanyl]. They don't even have time to pull the needle out and they're on the ground.

Overdose Presentations: Quotes from Consumers

With fentanyl, folks are going out so quick, like they were knocked out by a punch. Some people even look like they're going into seizures. I've seen people foaming at the mouth with eyes rolling back in their head. And when they finally wake up, they don't remember a thing—like a blackout.

Overdose Presentations: Quotes from Consumers

- “I was inducing my patient today. I pushed [bolus] 100mcg of sufentanil and could not manually ventilate. I have always been told of the horrors of chest wall rigidity with the 'fentanyl family'. Seen some mild effects but nothing in which I could not ventilate (Nurse, 8/24/06).”*

It [IMF] takes your breath away—instantly. Right when they [person OD'ing] reach for their mouth, you know they're going out. That's the number one warning sign right there. When they reach for their mouth, prep the Narcan.



Fentanyl Overdose Response and Community Engagement (FORCE) Study



Physical Sensations (compared to heroin)

- ❖ Shorter duration of effect
- ❖ Heavier sedation
- ❖ Rapid onset

“Yeah, it’s warm . . . If you do too much, it’s like a massive rush, and then it’s almost like a panic state.”
(male, 34)

“I did this little sprinkle of fentanyl and it just put me out. And I’ve never nodded out on dope.”
(male, 33)

Growing co-use of fentanyl with cocaine or methamphetamine

“Heroin’s my drug of choice. These days the meth I do is mainly to counteract the sedation of fentanyl.”
(male, 36)

“Fentanyl is so strong that if I were just doing it by itself, I couldn’t get my head out of my lap. I don’t want to be just zonked out so I use meth.”
(male, 47)

Conclusions

- **IMF** is the illicit opioid responsible for most (80%) drug overdose deaths in the US, with prescription opioids and heroin-involved deaths and supply in steady decline since 2014.
- **Fentanyl adulteration of cocaine and methamphetamine** is occurring and contributing to overdose deaths but with *significantly less* prevalence compared with heroin.
- **Fentanyl toxicity** is contingent upon route of administration and pathways of exposure.
- **Fentanyl toxicity via unwitting exposure** requires direct contact with mucus membranes. Fentanyl powder is ineffectively spread by aerosol and cannot enter the bloodstream through direct contact with the skin.
- **Fentanyl-involved overdoses** have unique presentations and acute onset characterized by abrupt unresponsiveness that significantly reduce response time compared with heroin.
- **Law enforcement and first responders** should be taught evidence-based techniques to reduce fentanyl exposure and recognize the lack of risk they face when in close proximity to fentanyl. Increased knowledge and less fear is key to ensuring better outcomes during policing encounters.

Thank You!

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