

# The US Overdose Crisis: Rapid Shifts in Fentanyl and Novel Synthetic Substances

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## Key “Take-Aways”:

1. We are in the ‘fourth wave’ of the US overdose crisis, driven by polysubstance combinations with illicit fentanyls.
2. Become aware of new health risks to consumers due to rapid shifts in the illicit drug supply.
3. New clinical approaches are needed to address rising burden of disease.

## Presentation Transcript:

Hi everyone, my name is Joseph Friedman, and I work as a substance use researcher at UCLA. Today, I'm going to be presenting a talk titled the **U.S. Overdose Crisis, Rapid Shifts in Fentanyl and Novel Synthetic Substances**. The point of this talk is to provide clinicians with a high level view of how the U.S. overdose crisis is shifting and some of the potential implications for your patients.

Some of the highlights include:

- We are now in the quote fourth wave of the U.S. overdose crisis which is driven by polysubstance combinations with illicit fentanyls and other drugs mixed together.
- The illicit drug supply is rapidly shifting, which is creating new health risks for consumers, and
- New clinical approaches are needed to address the rising burden of disease that is resulting.

Throughout the talk, I'm going to use QR codes to reference papers and other forms of data. So, if you're interested in tracking down a piece of data that I'm showing, you can open up your phone camera, scan the code and access the information that way.

## *The Overdose Crisis in the United States:*

(01:23) It is important to understand as we get started that the overdose crisis in the United States is a uniquely American problem. Here on this graph, you can see the top 10 countries in terms of per capita overdose mortality from 1990 through 2019 before overdose death rates spiked during the pandemic. And even then, you can see that **the United States is by far the global leader in terms of this cause of death**. We have an overdose death rate that is something like 20 times the global average, and two to three times worse than the second most affected country, so clearly something unique is happening in the United States.

(02:11) This is some data from a very famous paper that was published in science a few years ago, again focusing on the per capita overdose death rate. On the right, you can see that overdose deaths in the U.S. have gone up year after year for the past four decades in a sort of smooth, exponential fashion. Now on the left, you can see the composite drugs that have contributed to this overall trend. You can see that at various moments in history drugs like prescription opioids, and heroin and cocaine, and other drugs have contributed differential to the overall trend, yet year after year in the aggregate overdose deaths continue to march steadily up unfortunately.

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## The Fourth Wave of the US Overdose Crisis:

(03:05) There are generally thought to be about four waves in the U.S. overdose crisis. Here, I'm showing the most common drug implicated in drug overdose deaths at various points in the U.S. history. You can see that from the 1990's through 2006 (this is sort of before we used this wave terminology,) **cocaine** was the most common drug implicated in overdose deaths. From 2007 to 2013, prescription opioids took over as the most common kind of drug implicated in overdose. Now in 2014 to 2015, that switched for a brief period to heroin, and it was quickly replaced by illicit fentanyls in 2016 through the present. However, in just the last couple of years, researchers and physicians have started to argue that we're actually now in the **fourth wave of the overdose crisis and this is characterized by the co-use of fentanyls with stimulants and other synthetic drugs**, which is really what I am going to be focusing on today.

(04:12) These are the characteristics that I would argue describe the fourth wave of the U.S. overdose crisis. First, it's **really driven by illicitly manufactured fentanyls and synthetic opioids**, that is the core of this crisis, by far. The most common substances involved in overdose now are fentanyls and other potent synthetic opioid analogs.

However, these synthetic opioids are also being mixed with other categories of drugs, which is what we call **polysubstance use** which is a key characteristic and there's also widespread **counterfeiting**. So people consuming all sorts of drug products right now in the U.S. buy something, and it turns out to actually be something else. There's very little security, or confidence in anything that is purchased in the illicit drug market right now.

We also see that there was an extreme **exacerbation of drug overdose during the COVID-19** pandemic. Deaths shot quickly up, and unfortunately they have not returned back to the pre-pandemic baseline and really have not gone down much at all, and unfortunately, the big increases we saw during COVID in the initial months of the lockdown have mostly persisted through till now.

And finally, there have been **sharply rising racial, and ethnic disparities** in overdose mortality. So African Americans and Native Americans are now greatly disproportionately affected by drug overdose deaths compared to other groups.

## Illicit Fentanyls:

(05:55) Fentanyls are a family of synthetic opioid agonists that are many times stronger than traditional heroin. They have really changed the risk environment for people who use drugs in several ways. A key characteristic is that they have **much shorter half-life** than heroin, and other opioids which involves **more injections per day** increasing the risk of infectious diseases and overdose, and kind of all of the risks that come along with injection, or consumption of an illicit drug.

Fentanyls were initially concentrated in the Eastern U.S, however we've now seen them kind of move west to the west coast of California and **take over the whole country**. So, there are very few pockets where fentanyl has not arrived now.

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And one of the things that's so dangerous about fentanyl is that it's very potent and it must be diluted with fillers and other kind of agents to kind of provide a product that is not so potent to be lethal, and unfortunately we see something called, the **chocolate chip cookie effect where small particles of fentanyl are kind of distributed in this larger mass of the pill**, or the kind of the powder sample, and it's **not distributed equally**, you could think about it like the chocolate chips in a chocolate chip cookie. And so depending on where you take a bite out of that cookie, you may receive more fentanyl, or less fentanyl and this is thought to kind of greatly increase the overdose risk in people who are buying a kind of a sample and taking small pieces out of it to use.

### Effect of Illicit Fentanyls on Overdose Crisis:

(07:45) To kind of illustrate some of the effects that fentanyl is having at the population level, here's a graph showing any opioid related overdose deaths as a per capita rate in California. And you can see that overdose deaths were pretty stable in California from 2008 through 2006, and just in the past kind of five years or so have started to rise rapidly in California. And of course, this is **perfectly aligned with the kind of rise of fentanyl in California**, and you can see that nearly all of the increases in overdose deaths in California can be explained by this huge increase in fentanyl related overdose deaths.

(08:28) To illustrate some of the risk involved in drug samples containing fentanyls, here's a nice graph from an analysis occurring in Canada where there's good drug checking data and they showed the fentanyl concentration of opioid drug checking samples in British Columbia. So you can see that the fentanyl concentration on average was on the lower end close to about five to 10%, however there were samples that did contain fentanyl concentrations up to as high as 75%. And so, you can imagine this kind of **massive range of the potency of this product** where it's sort of akin to going to a bar and ordering a mixed drink, and not knowing if it contains one shot of alcohol, or 20 shots of alcohol and the only way to find out is to start consuming it and see how you feel. You could imagine that if that were the case, we would have a lot of alcohol related poisonings which is exactly what we're seeing now with fentanyls.

### Potent Synthetic Analogues and Polysubstance Use:

(09:30) On the topic of polysubstance use and counterfeiting, this is an example of a single drug sample that was submitted to a drug checking service. This is in the United States, and you can see all of the components, all of the drugs that were found in this single bag of powder: diphenhydramine, several different fentanyl analogs, xylazine (which I'll talk about in a moment), cocaine, a designer benzodiazepine. All of these things are being mixed together in a single drug and sold as heroin, right, or sold as a powder opioid sample. So, you can imagine the kind of increased risks from all of these things being mixed together as opposed to just consuming kind one stable illicit product.

(10:24) Now, I am going to talk about the example of xylazine which is I think really illustrates a lot of the wider trends that we're seeing in the overdose crisis. Xylazine is a veterinary sedative which has never been approved for human consumption. It's an alpha-2 adrenergic agonist similar to clonidine, but with a little bit different receptor activity that is not fully known, because of course, it is not really ethical to administer this medication to humans and experimentation is limited. It's been noted that it's been used in

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the illicit drug supply of Puerto Rico for decades, but in the mainland U.S., overdose deaths just started to pop up in the mid 2010's, and it is now spreading nationally in an exponential fashion since 2019.

(11:27) Here is an article which kind of highlights the spread of xylazine across the country. We systematically searched for data from medical examiners highlighting where Xylazine is found in overdose deaths across the country. Unfortunately, xylazine, like many novel synthetics, is not being kind of robustly tracked by the CDC in a national fashion. So, we went and found a number of jurisdictions where Xylazine was being used and we found that the prevalence of Xylazine actually rose from 0.4% of overdose deaths in 2015 to 6.7% in 2020. And again, you can see kind of where Xylazine lands, and starts to increase tends to do so in an exponential fashion.

(12:28) We also found that xylazine is virtually always found added to fentanyls. So, **if xylazine is present, it's almost a 100% chance that it is found alongside Fentanyl**, and that really shows us how a lot of kind of novel synthetic drugs really exist to cut and modify fentanyl as opposed to just being used on their own.

Xylazine is showing us how fentanyl has really ushered in a new wave of deadly synthetic drugs across various drug classes. Part of this probably relates to the fact that the **barrier has been lowered to producing many novel compounds** because we've moved away from heroin being produced in agricultural setting to now fentanyl being produced in a laboratory. That has thought to have lowered the barrier to kind of synthesizing all kinds of novel synthetic drugs, mixing them in with fentanyls and selling them in the illicit drug market.

## Counterfeiting and Teenage Drug Use:

(13:30) Counterfeit prescription pills are really kind of changing the nature of the risk of illicit drug use in the United States. This is from an analysis published earlier this year in JAMA where we showed that for the first time, high school age teenagers are starting to overdose at much higher rates than before. So here in the graph you can see the teenage overdose death rate from several substances, cocaine, benzodiazepines, so on and so forth. And you can see that really overdose death rates have been quite low among adolescents for a long time, but just kind of in 2019, 2020, 2021 and now 2022 unfortunately, we're really seeing a very large magnitude increases in teen overdose deaths. This is occurring despite the fact that teen drug use rates are actually declining. So fewer teenagers are using drugs, illicit drugs, but the ones who do use are at more risk, so **teenage drug use is becoming more dangerous, but not more common**.

That has really been linked to the **spread of counterfeit prescription pills**. We've known for many years that teens are more likely to experiment with prescription drugs as opposed to other kinds of powder drugs. With the spread of counterfeit prescription pills which look like things like Percocet or Xanax, but actually contain fentanyl powder pressed into pill form, we're starting to see this increased risk.

## Clinical Implications of Polysubstance Use:

Regarding the clinical implications of polysubstance use, one key topic is **naloxone-resistant overdose**. It's well known that synthetic benzodiazepines, and many other drugs when combined with opioids can

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actually increase overdose risk substantially. The degree of outright respiratory suppression in many of these combinations with opioids is often poorly understood. In the case of xylazine, through fast-acting sedation, it induces a sort of 30-minute approximate period of CNS depression which can blunt the response to airway occlusion. So, regardless of if it is inducing respiratory depression what we can often see is that people when they're exposed to xylazine, they're not able to protect their airway and so they have airway occlusion.

In general, when thinking about polysubstance overdose, it is important to **give naloxone** if any respiratory depression is present. But increasingly, frontline providers facing polysubstance overdose have to do things like **managing airway in the field through kind of classic techniques** like placing patients in the recovery position, jaw thrusts, using pulse ox and possible intubation.

(18:52) It's also important to consider what polysubstance formulations mean for **withdrawal syndromes**. Of course, this can really complicate managing withdrawal. Physical dependence to xylazine and other polysubstance combinations with fentanyl have been reported among chronic users. And the effects of fentanyl may be relieved with methadone and buprenorphine withdrawal effects; however, the effects from xylazine, benzodiazepines, etc., would not be relieved. In many cases MOUD may be partially helpful, but there will still be a lot of anxiety unease and other withdrawal symptoms. It is controversial exactly how to manage this, but some good generic advice is to **treat these syndromes as sort of benzodiazepine or alcohol withdrawal and give benzodiazepines as the first line**.

(17:53) There are several other health risks, and to briefly summarize some of them, a potent and unstable drug supply can mean that people who are exposed to these drugs may experience things like **heavy sedation** that is kind of unexpected, above and beyond what would be kind of normal when using just opioids. And many people who use drugs have described an **increased risk of things like sexual assault or traffic accidents, or kind of other accidents** that occur when people are not able to be aware of their surroundings. And finally, there's also been a lot of reports of **soft tissue infection risk** increasing with polysubstance formulations.

### Tips on Counseling:

(19:35) In terms of some good general tips on counseling, many patients want to avoid xylazine and other synthetic polysubstance combinations. This is where I think **drug checking, and kind of counseling** and education can be so important.

When people understand **the risks** of what is in the drug supply, they often are more likely to switch to MOUD, or maybe even just a safer illicit drug option which although not ideal is still harm reduction. It is choosing the kind of safest option that is available that will work for folks in practice.

And of course, the general counseling for risks associated with fentanyl-based kind of drug use in general is **never used alone** because you can't administer Narcan to yourself. Always carry naloxone and give it to close friends and family. Make sure it's in your glove compartment of your car, in your purse, in your

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backpack. It has to be present and people around you have to know how to use it for it to be useful. And go slow, be suspicious of the drug supply every time you buy.

Thank you very much for your attention, this is my Twitter handle, and I post information about new research ongoing in this area here. And the articles I've referenced in this talk can be accessed here at the link in the top right-hand corner, thank you very much.