Policies to Protect Our Communities From Illicit Drug Threats

March 26, 2026
US House Of Representatives
Committee on Energy and Commerce

Subcommittee on Health

Written Testimony of Dr. Nabarun Dasgupta

Dr. Nabarun Dasgupta is a street drug scientist at the University of North Carolina at Chapel Hill, working in overdose prevention for over 24 years. He is a recipient of the 2025 MacArthur "Genius" Award. At the UNC Opioid Data Lab (OpioidData.org) his team has analyzed over 20,000 street drug samples from frontline public health organizations, health departments, paramedics, and clinics. He pairs the resulting nuanced understanding of the illicit drug supply with large database analytics on overdose deaths to make sense of shifting drug use patterns. From molecules to populations, his work is deeply rooted in community engagement.

He has advised the World Health Organization on the scientific basis for international drug scheduling. He has trained military and police forces in Mexico on illicit drug supply variability, and assisted federal government agencies identify counterfeit, adulterated, and illicit drugs coming from China.

Since 2002 he has done pioneering work in overdose prevention and addiction treatment, including co-founding two non-profits that distribute the overdose antidote naloxone: Project Lazarus and Remedy Alliance For The People (over 7 million doses nationwide).

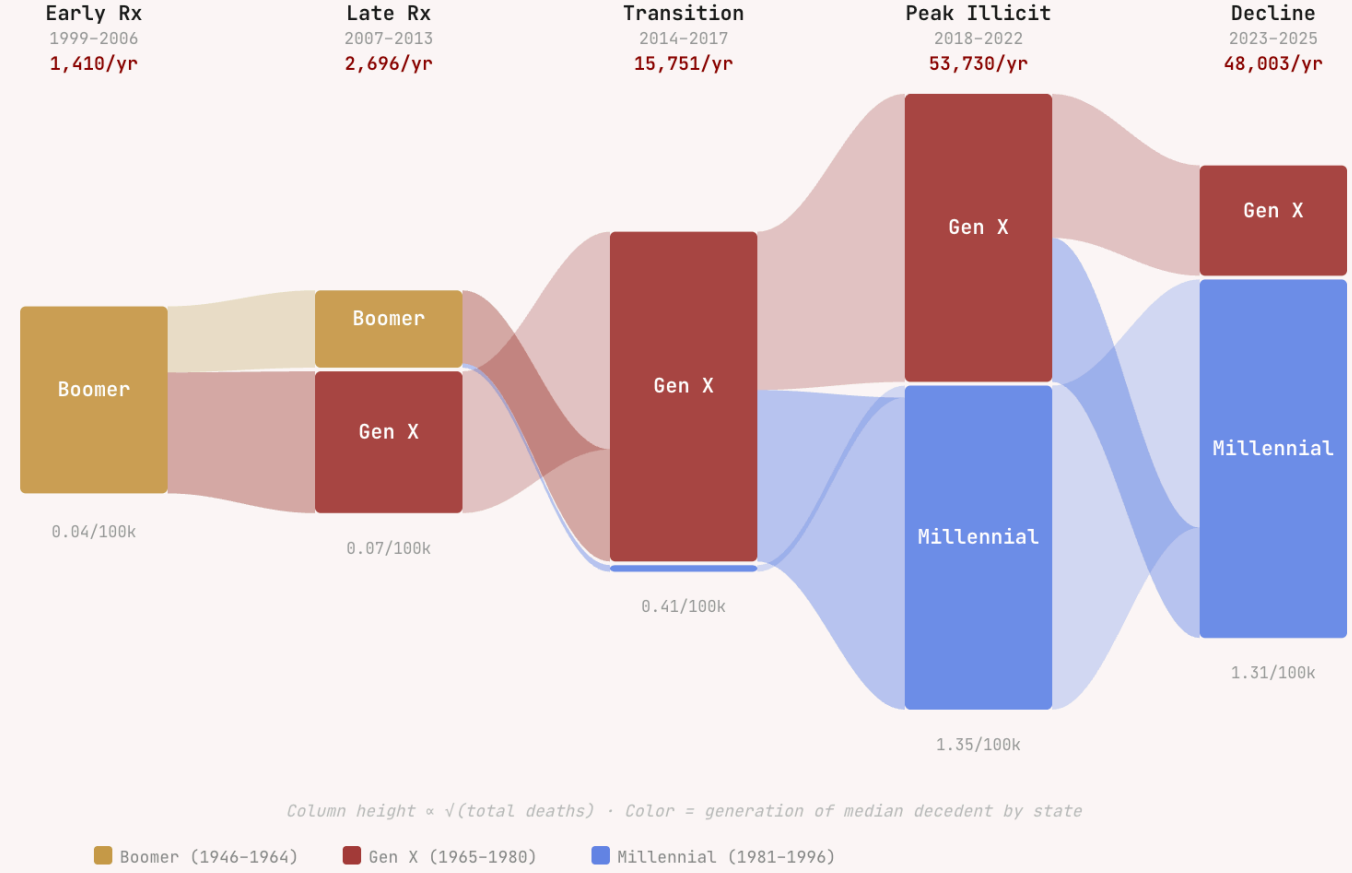
Dr. Dasgupta is an editor at the *American Journal of Public Health,* and has published over 140 papers on drugs and overdose. Since 2018, his research has been funded by the US Food and Drug Administration, in close partnership with the University of Kentucky. He also trained in infectious disease epidemiology, including development of veterinary test kits for bovines.

He was featured on the 2023 TIME100 Next list of rising global leaders, and the 2026 TIME100 Health list of the most influential leaders in health. He is the recipient of the 2026 Dogwood Award from the North Carolina Attorney General for keeping people safe, healthy, and happy in their communities.

Right now, for the first time in 4 generations, we have a unique opportunity to end the opioid overdose epidemic.

Overdose deaths have declined for 28 consecutive months, and are now -40% lower than peak.

70% of Overdose Deaths are in Gen X and Millennials. Gen Z has much lower overdose rates than their parents & grandparents had at the same age. We need to make it as easy as possible for middle-aged adults to reduce illicit opioid use. Rolling back treatment access is squandering our gains. The transition in generations can be seen below for Rx fentanyl through to illicit fentanyl:



The Boomer Exit
The early columns are small (few deaths) and gold (Boomers). As the columns grow, gold vanishes — Boomers weren't saved from a growing epidemic; they were *replaced* in it.

Gen X Absorbs the Explosion
The tallest columns (2018–2025, 250k+ deaths) are dominated by dark red. Gen X bore the full weight of the fentanyl era at its most lethal scale.

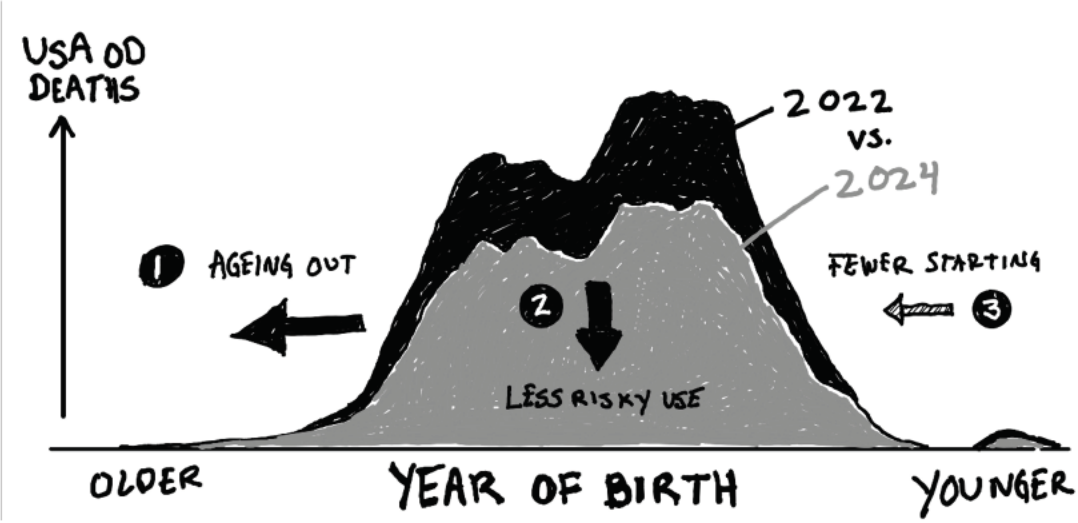
Blue Creeps In — Then Stalls
Millennials appear in the post-peak column, but the column is also *shrinking*. The question: is the crisis contracting before it can fully recruit the next generation?

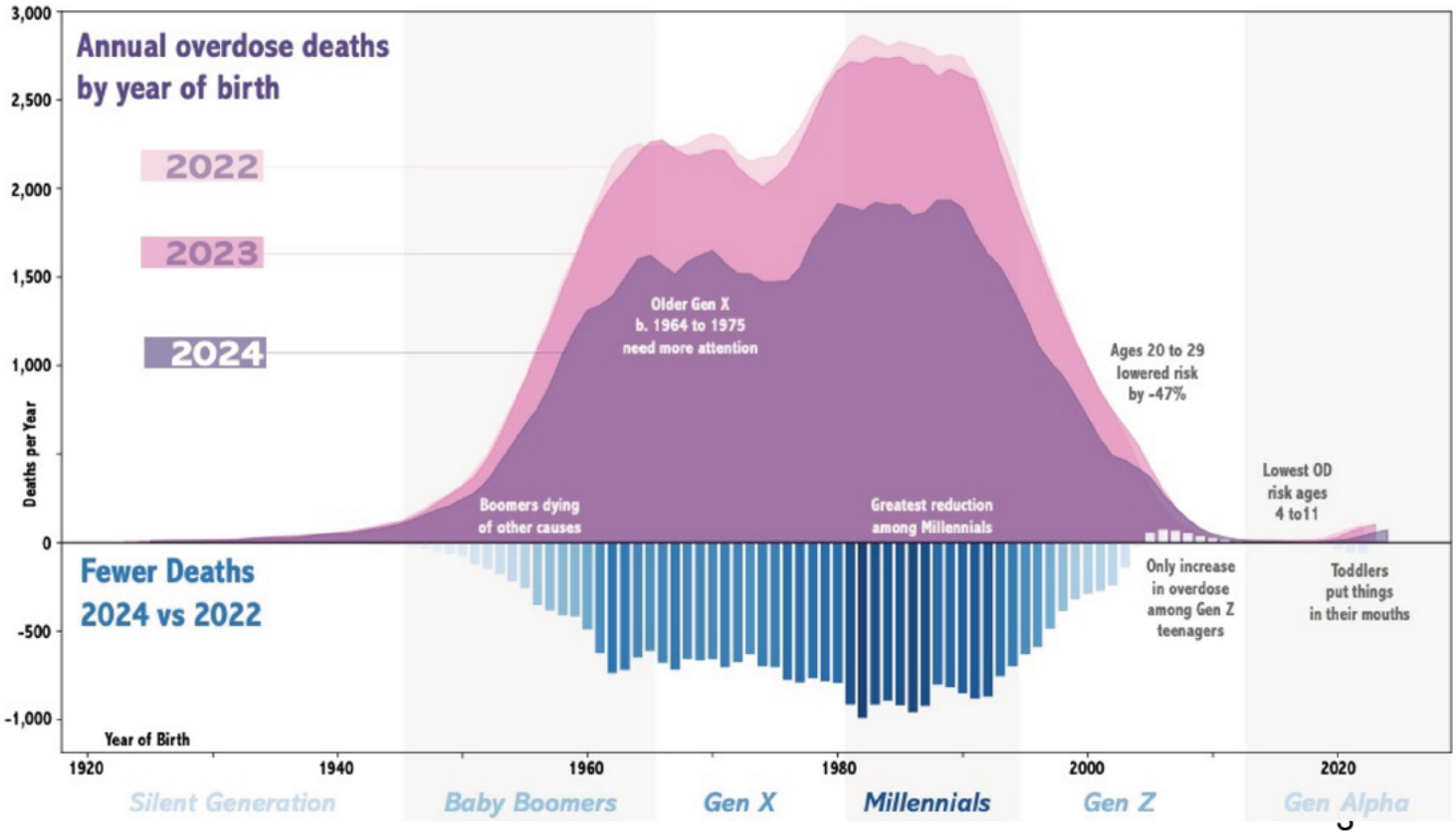
Inferred birth year by median age of fentanyl overdose death, by state. Data from CDC processed by OD Pulse at Northwestern University.

Why is this happening?

1. Baby Boomers and older Gen X are ageing out of street drug use.
2. Millennials and younger Gen X are reducing their death risk (e.g., naloxone, treatment).
3. Gen Z is not initiating illicit fentanyl use at the same rate.

However, the Gen Z cohort that was in middle school and early high school during COVID restrictions are the only ages who's overdose numbers (albeit relatively small) are rising. Those born between 2005 and 2011 are a special cohort that will need targeted prevention and treatment.

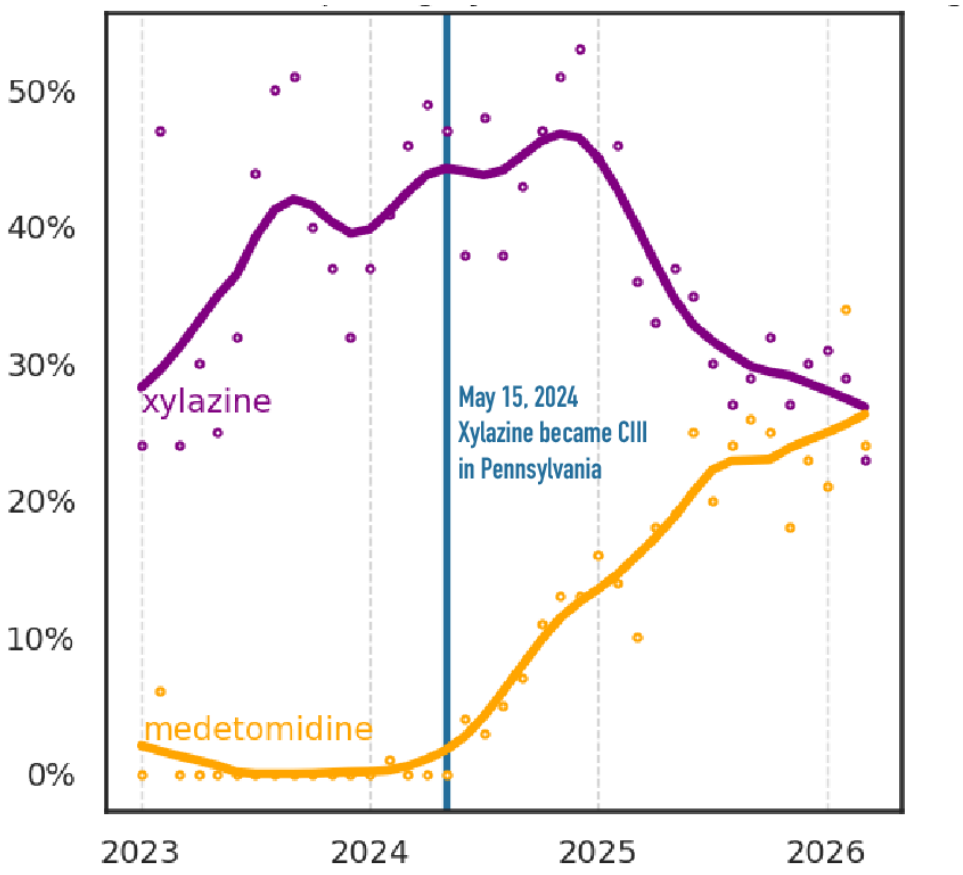




Xylazine Is Being Replaced with Medetomidine Nationally.

What you do with xylazine today you will have to do with medetomidine tomorrow.

Figure: Prevalence of medetomidine and xylazine in fentanyl samples analyzed at UNC
Medetomidine: N=1,020 from 20 states
Xylazine: N=3,115 from 28 states



However, xylazine is being replaced with medetomidine in fentanyl rapidly. These molecules are very similar in structure. While xylazine is only used in veterinary medicine, **medetomidine (Precedex®) is used widely in hospitals for sedation (e.g., babies on respirators) because it is not a controlled substance.** It is also an adjunct treatment for bipolar disorder and schizophrenia. If xylazine is a precedent, then scheduling medetomidine too restrictively will be massively disruptive to human medicine.

Good news: Unlike xylazine, medetomidine does not cause skin wounds.

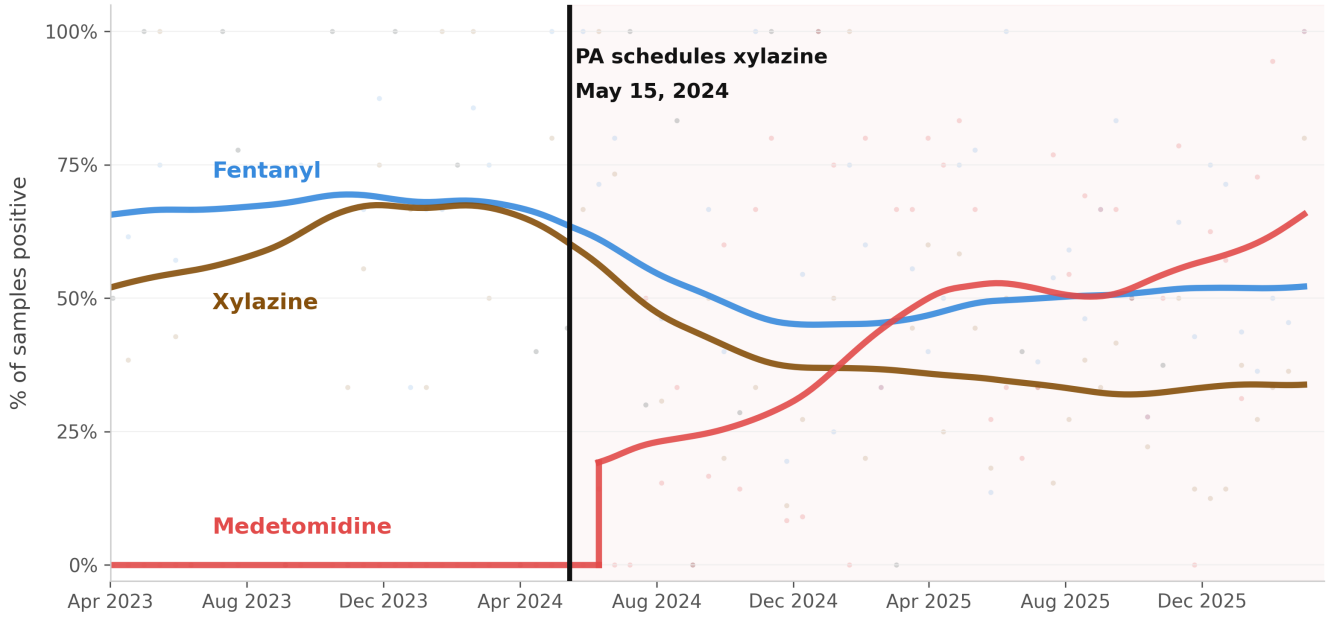
Bad news: Abruptly stopping medetomidine-fentanyl is causing expensive weeklong hospital detox stays. Methadone, buprenorphine, and naltrexone are insufficient. Abstinence-based treatment now carries serious heart attack risk not seen with fentanyl alone.

Medetomidine Emerged Within Weeks of Xylazine Being Put In Schedule III in Pennsylvania.

Permanent scheduling of xylazine to CIII in Pennsylvania on May 15, 2024 is a strong test case of what could happen nationally. Immediately following CIII scheduling, medetomidine started replacing both xylazine and fentanyl in the illicit drug supply. In Philadelphia, medetomidine started emerging a little before scheduling, in line with temporary scheduling in June 2023. In Pittsburgh, medetomidine is now more prevalent than fentanyl.

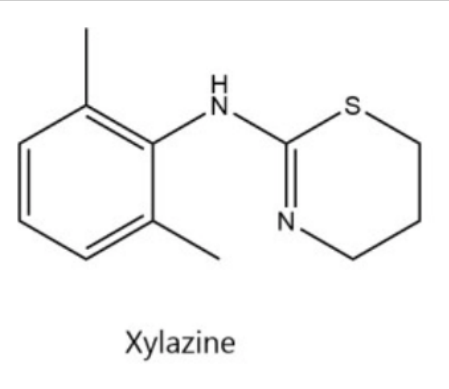
Emergence of medetomidine in the Pittsburgh drug supply after state scheduling of xylazine

Biweekly prevalence from community drug checking samples, April 2023 – March 2026 (n = 599)

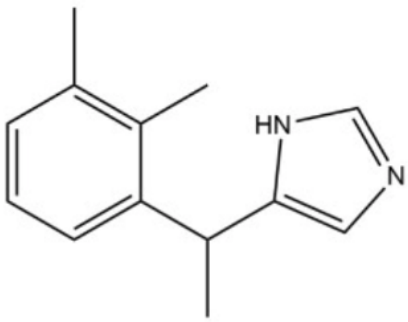


Source: UNC Street Drug Analysis Lab | Lines show locally weighted regression

Medetomidine is a very similar molecule to xylazine.



Xylazine



Medetomidine

Medetomidine Requires Expensive Weeklong Stays in ICU

Medetomidine in the illicit drug supply is a nightmare. Managing this syndrome requires intensive medical support that outpatient and abstinence-based residential treatment settings simply aren't equipped to provide.

Medetomidine withdrawal is unlike anything most emergency physicians have seen before. When people use fentanyl that's been laced with medetomidine, abrupt stopping can trigger a crisis that hits fast and hard, sometimes within just four to six hours of the last dose. It typically starts with intense nausea and vomiting that won't respond to the usual anti-nausea medications, then rapidly escalates to a racing heart, dangerously high blood pressure, drenching sweats, tremors, and delirium. What makes it so alarming is that the standard tools doctors rely on — benzodiazepines, opioids, even common anti-nausea drugs — do remarkably little to slow it down. Doctors who have treated it describe a visceral sense of encountering something fundamentally different from anything in their experience. In early reports from Philadelphia and Pittsburgh, roughly **8 or 9 out of every 10 patients diagnosed with this syndrome ended up in the ICU**, many needing round-the-clock IV sedation for days.

Medetomidine withdrawal:
- Onset within hours of last illicit substance use
- Nausea and vomiting
- Tremor, myoclonic jerks, anxiety, diaphoresis
- Tachycardia and hypertension
- Encephalopathy
- Minimal or no response to GABA and opioid agonists

Antiemetic therapy:
- Ondansetron rarely effective
- Prochlorperazine 10mg IV/IM/PO, repeat as needed
- Droperidol 2.5-5mg IV/IM, repeat as needed
- Olanzapine 5-10mg IV/IM, repeat as needed

Oral and Transdermal Alpha-2 Agonists
- Clonidine 0.3mg PO; repeat up to 2 additional doses in hour 1 as loading dose (total of 0.9mg)
- Transdermal clonidine 0.3mg weekly
- Guanfacine 2mg PO q8 hours
- Clonidine 0.2-0.3mg PO q2 hours for COWS of >5 or >15, respectively
- Tizanidine 2mg PO q8 hours can be considered
- Benzodiazepiness/barbiturates for additional sedation if needed

Parenteral Alpha-2 Agonist Therapy:
- Dexmedetomidine
  - 1 mcg/kg IV bolus
  - 0.5-1.5 mcg/kg/hr IV infusion titrated to Riker 3-4 or RASS -1-0 (or sedation if scores not recorded)
  - For severe cases: ↑ up to 2.4 mcg/kg/hr
- IV Dexmedetomidine can typically be weaned with overlapping oral regimen over 24-72 hours
- Benzodiazepines/barbiturates or ketamine for agitation uncontrolled with dexmedetomidine if needed

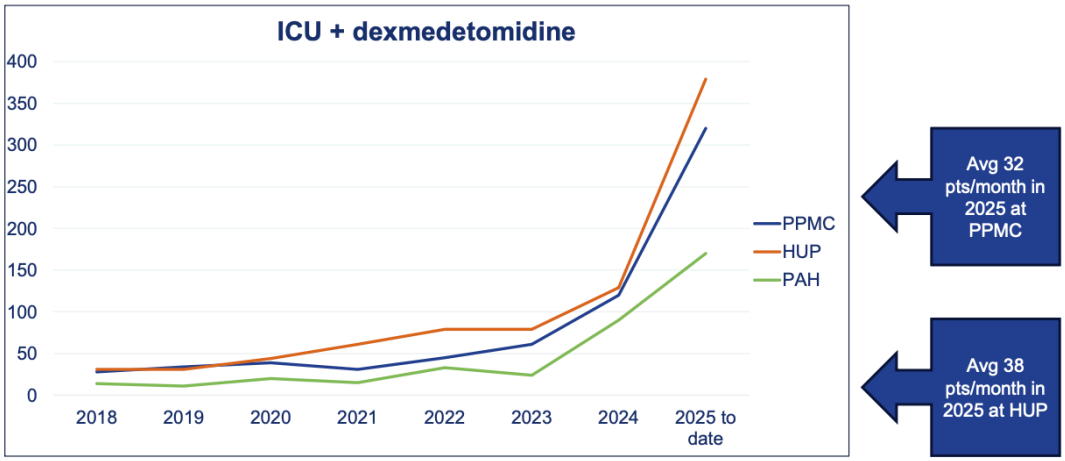
Maintenance and Taper:
- PO regimen can typically be weaned after 3-5 days:
  - As PRN clonidine needs resolve, wean guanfacine to 2mg PO BID x 1 day, then 1mg PO TID x 1 day, then 1mg PO BID x 1 day, and 1mg PO once x 1 day and remove clonidine patch
- Other symptom-triggered medications as needed

The medications that normally anchor addiction treatment — buprenorphine, methadone, naltrexone — can't address medetomidine withdrawal. In fact, starting buprenorphine or naltrexone too early based on symptoms that look like opioid withdrawal but are actually medetomidine withdrawal can backfire and precipitate opioid withdrawal on top of everything else. And because there's no routine test for medetomidine, clinicians have to recognize it based on the pattern alone — **a patient swings from deep sedation to full-blown crisis in a matter of hours, with none of the usual treatments making a dent.** This also makes abstinence-based approaches to treatment genuinely dangerous: the extreme spikes in heart rate and blood pressure — with reports of heart rates above 170 and systolic pressures over 240 — can cause serious cardiac damage, including elevated troponin levels and acute drops in heart function, essentially **putting patients at risk for heart attacks** during unsupervised withdrawal.

Lynch MJ, Pizon AF, Yealy DM. Emergence of Medetomidine in the Illicit Drug Supply: Implications for Emergency Care and Withdrawal Management. *Annals of Emergency Medicine*. 2026 Jan 23.

Hospitals in Pittsburgh and Philadelphia Are Overwhelmed With Patients Seeking Treatment For Medetomidine-Fentanyl

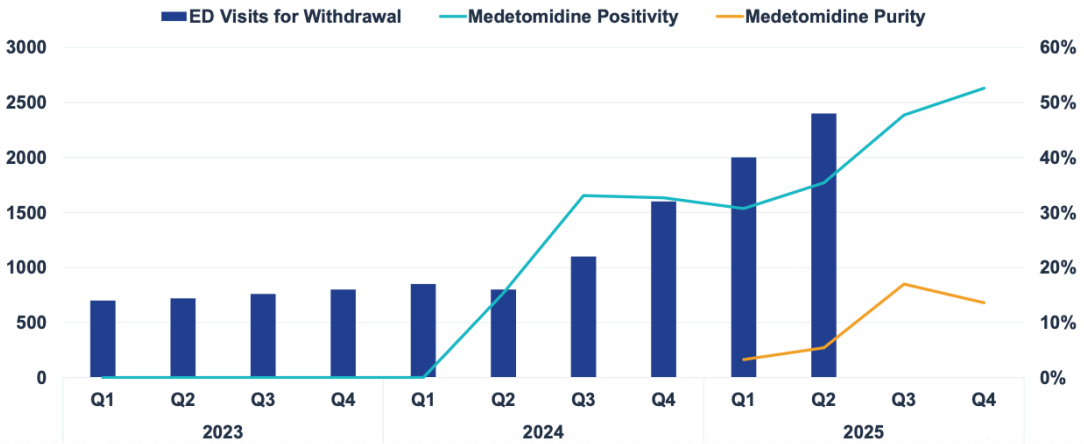
ICU Admissions for patients with OUD



Courtesy of Maggie Lowenstein, MD: Penn OUD Dashboard and Data

2026 Annual Scientific Meeting + Symposia #ACMT2026

Medetomidine Trends vs. ED Visits for Withdrawal



2026 Annual Scientific Meeting + Symposia *Note: Data from Philadelphia region.* #ACMT2026

Ostrowski SJ, Krotulski AJ, Adams A, Lynch MJ, Perrone J. Operationalizing toxicosurveillance medetomidine data for clinical care. Presented at: American College of Medical Toxicology (ACMT) 2026 Annual Scientific Meeting + Symposia; Boston, MA. March 19, 2026.

Xylazine paradoxically reduces fentanyl use and overdoses are less severe.

Our FDA-funded field study in Michigan and Pennsylvania showed that **when xylazine is mixed into fentanyl, people consume less, use less often, and are more likely to seek treatment.**

Hospital data from Philadelphia show xylazine-fentanyl causes less severe overdoses than fentanyl alone.

(Sibley et al., *International Journal of Drug Policy*, November 2025; Love et al., *Clinical Toxicology*, March 2023)

Our qualitative study of people with recent overdose reversal experience (n=52) finds that the emergence of xylazine in the unregulated opioid supply—while widely viewed as undesirable and harmful—has paradoxically prompted shifts toward safer use behaviors.

Participants consistently reported reducing fentanyl use (in amount and frequency), initiating periods of abstinence or treatment, alternating between xylazine-positive and negative supplies, and changing routes of administration (e.g., from injecting to smoking or snorting) to avoid harms. These changes were driven by a combination of diminished desired opioid effects, fear of severe health consequences (especially necrotic wounds), impaired day-to-day functioning due to prolonged sedation, and concerns about overdose and reversibility. Together, these findings suggest that xylazine may be altering risk environments in ways that reduce overall opioid consumption and encourage behaviors that mitigate risks from wounds, overdose, and over-sedation. These quotes from our study reveal **a major dissatisfaction with the illicit opioid supply**:

“I use a lot less, that's for sure. If you do too much of it, you're just going straight to sleep. You waste the whole day.”

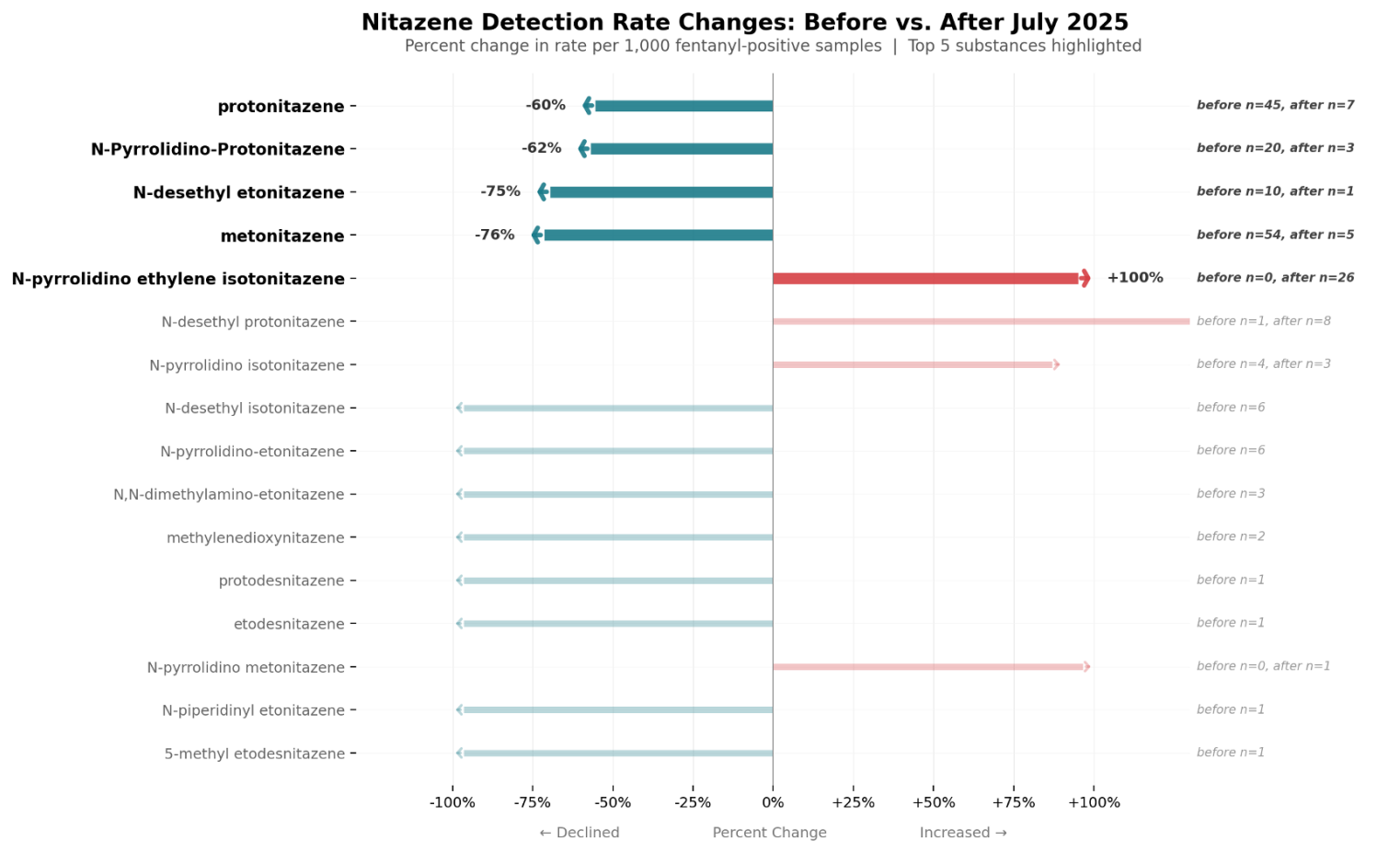
“I'm to the point where I'm like, in 30 years, I have not been able to quit doing dope. But I have days where I don't do it. And that's never happened. Never happened out of rehab, for 30 years. I've been a hardcore addict for about 30 years. And xylazine scares the fuck out of me.”

“There's a lot of things that you will accept, if it was going to be as good as it was when you first started. You'll go through a lot of bullshit to get there, but if it's not even going to be that, then you're kind of done."

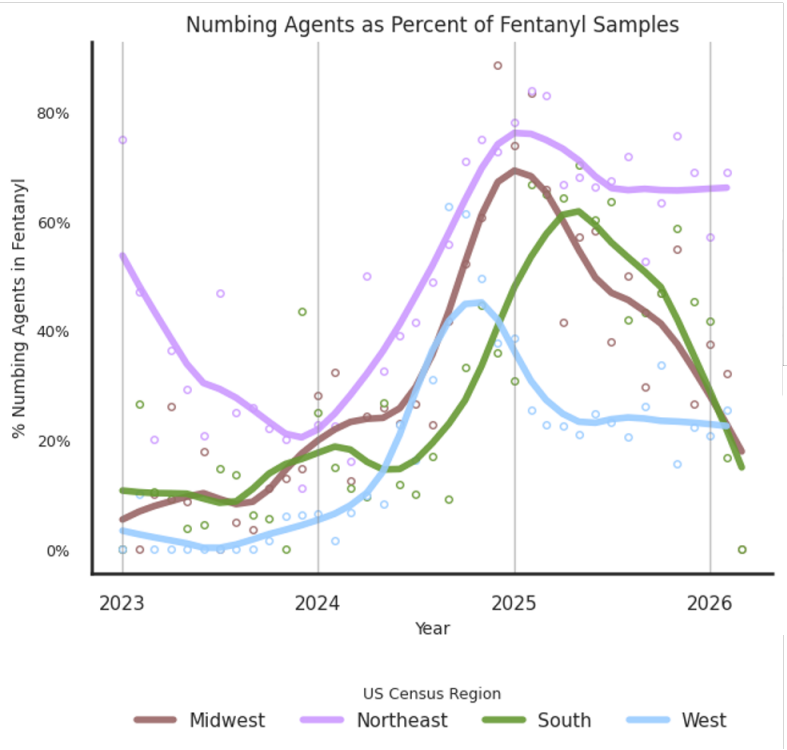
Nitazenes Have Changed Since July 2025

Since the Chinese generic ban on nitazene production on July 1, 2025, nitazene species have changed substantially. There are fewer one-off variants, and older protonitazene and metonitazine have declined -60% to -76%. The new subclass are the desnitazenes, which are harder to detect using test strips and in autopsy. The dominant nitazene is **N-pyrrolidino ethylene isotonitazene**. We saw the same market consolidation happen with fentanyl analogues in the late 2010s.

According to the Center for Forensic Science Research and Education, “N-Pyrrolidino ethylene isotonitazene has not be explicitly studied; however, available data suggest that some substitutions and lengthening of the linker group may **lower affinity and potency** compared to their non-substituted counterparts.”



#1 Adulterants in Fentanyl are Numbing Agents



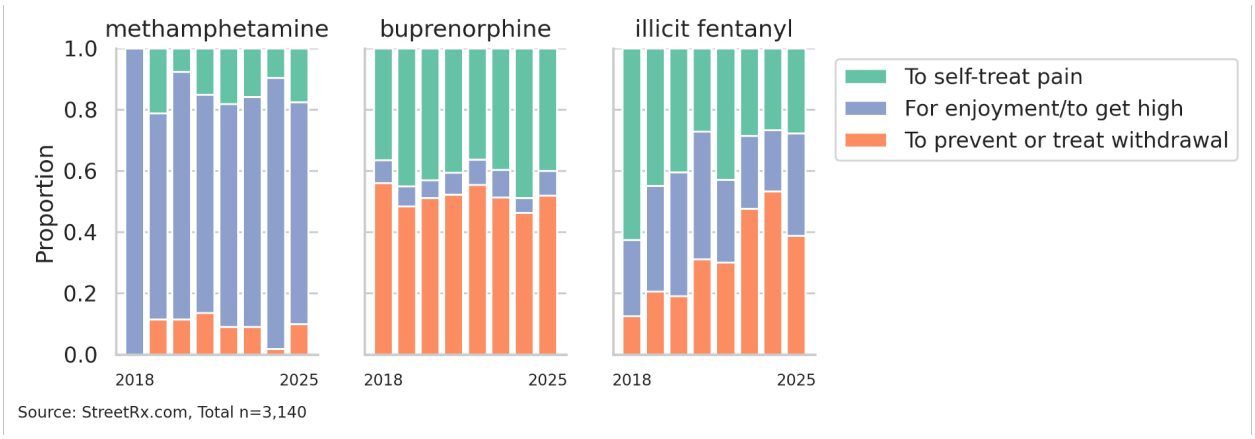
The most common adulterant of illicit fentanyl are local anesthetics or numbing agents: lidocaine, procaine, and tetracaine. These are similar to what is used by dentists. They have been most common in the Northeast for years. They started appearing around the country in mid-2024, but are declining in the South and Midwest.

Substance	Samples	%
lidocaine	1,613	73.7%
procaine	417	19.1%
tetracaine	158	7.2%
Total Mentions	2,188	100.0%
Unique samples	1,935	

Buprenorphine “diversion” is mostly for pain or withdrawal.

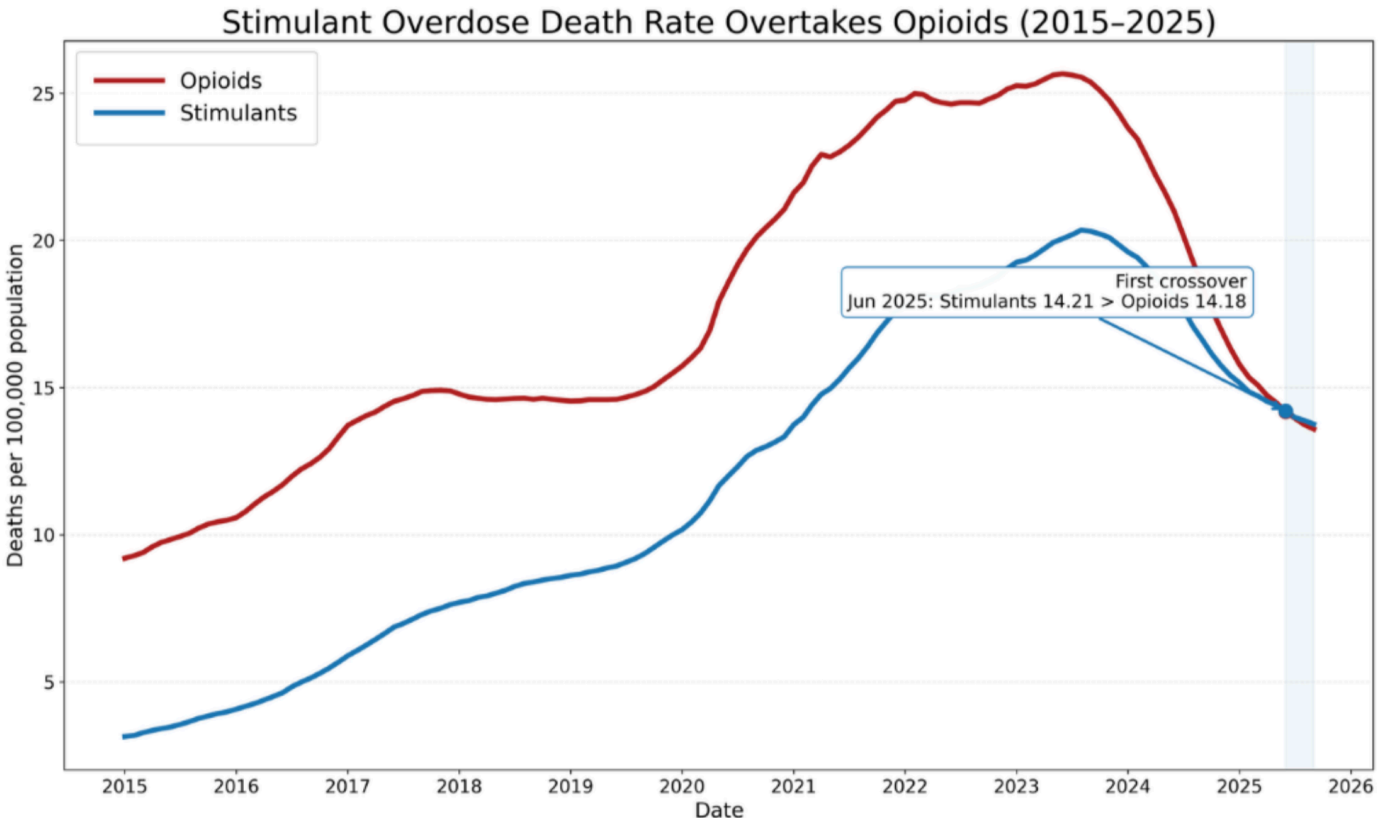
Data from the street price crowdsourcing website StreetRx.com shows that **only 7.1% of people reported using buprenorphine (middle graph, blue) for enjoyment**.

The reason for using illicit fentanyl has shifted over time (right graph), away from “getting high” and towards treating withdrawal. Consistent with the generational analysis above, 53.3% people reporting illicit fentanyl use said the primary reason was to to prevent or treat withdrawal.



Stimulants now exceed opioids in fatal overdoses.

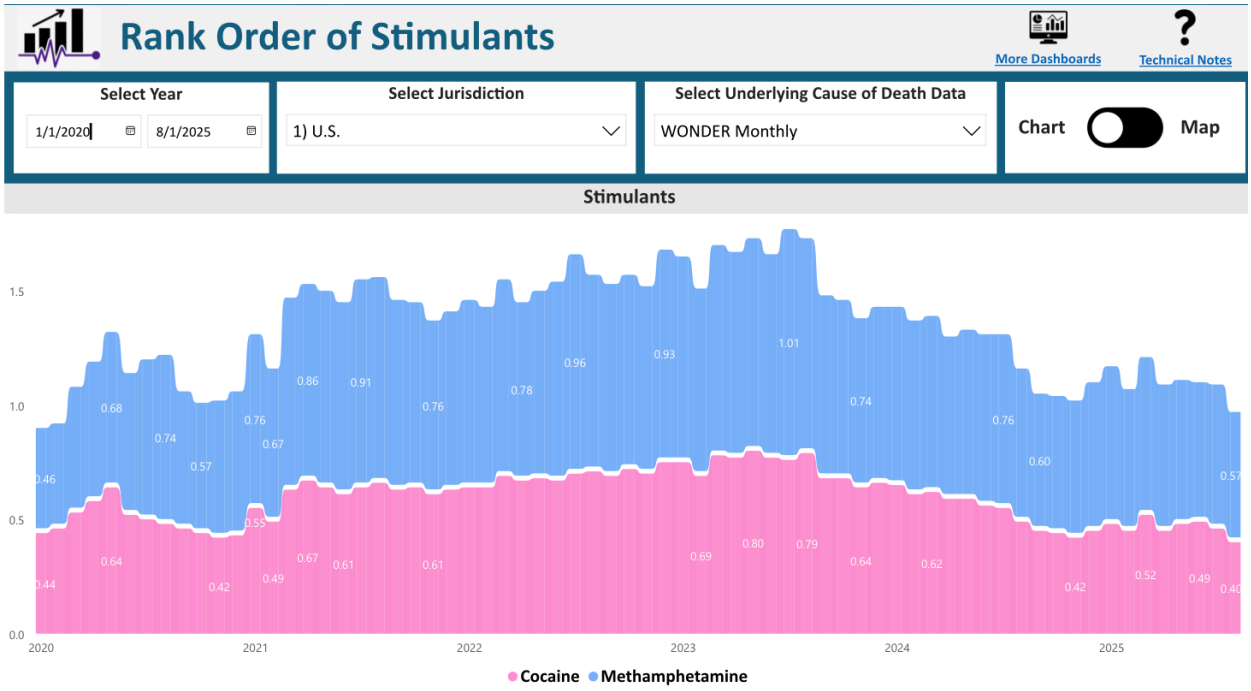
From OD Pulse at Northwestern University: “In June 2025, stimulants suppressed opioids as the underlying cause of death on US death certificates. For the first time in modern surveillance, stimulants are more likely than opioids to be listed as the primary drive of a fatal overdose.”



Stimulant Overdose Deaths Are Also Declining.

Both cocaine and methamphetamine involvement in overdose deaths are declining.

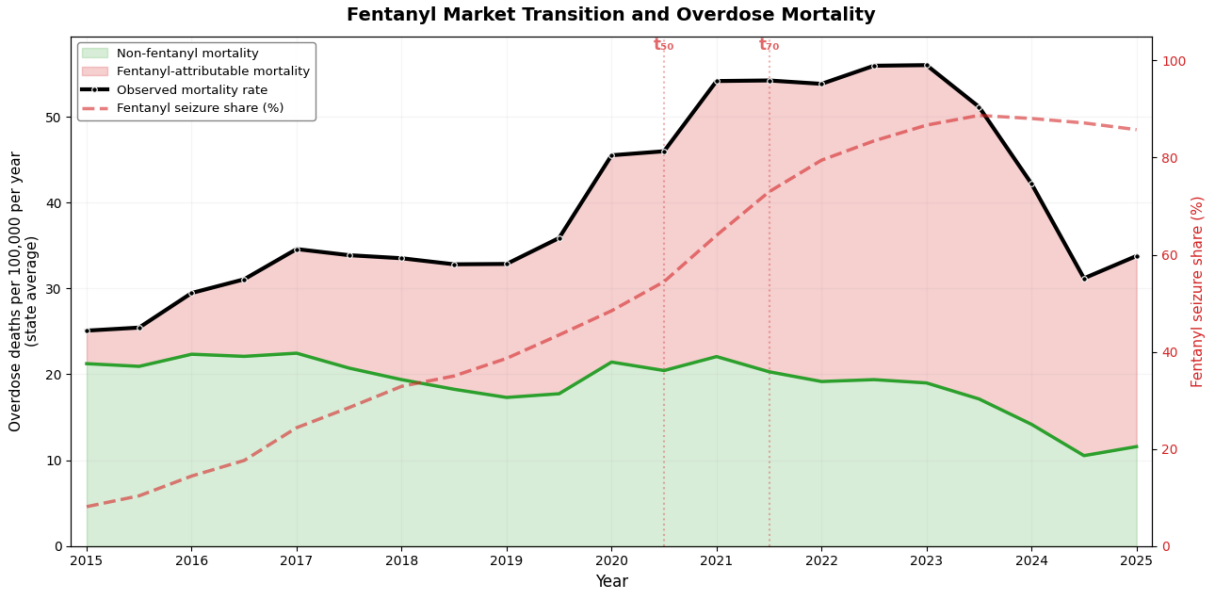
Source: OD Pulse @ Northwestern University



The recent decline in U.S. overdose deaths is not automatic — it reflects years of public health investment that was invisible while fentanyl was flooding the drug supply, and will reverse if that investment is cut.

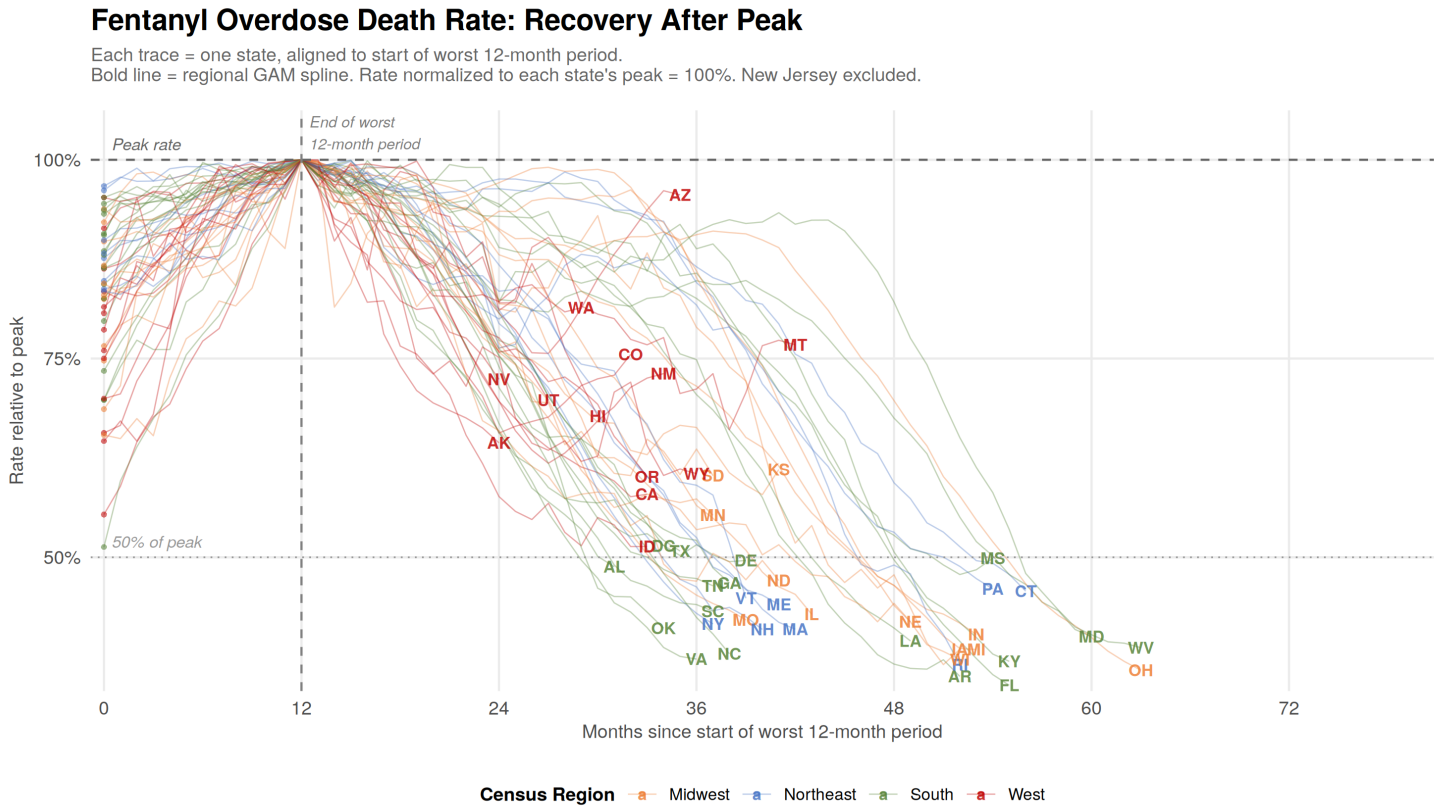
This figure shows overdose mortality over the past decade broken into two components. The red area represents the portion of overdose deaths associated with fentanyl taking over the illicit drug supply. The green area represents everything else — the baseline level of overdose mortality driven by factors like access to treatment, naloxone availability, and the social conditions surrounding drug use. The black line on top is total observed mortality — the sum of both areas. The dashed red line, read on the right axis, shows how far fentanyl had penetrated the drug market at each point in time — its S-shaped rise from near zero in 2015 to over 85% by 2023. Two things are visible in this figure. First, the red area grew rapidly as fentanyl took over the market, then stopped growing once the takeover was complete — marked by the vertical lines at t_{50} and t_{70}, when fentanyl reached 50% and 70% of the market nationally. **Fentanyl didn't stop being dangerous at that point — it stopped being new**. The market stabilized, people and systems adapted, and fentanyl's contribution to excess death plateaued. Second, the green area has been shrinking the entire time. That represents the work of public health, treatment programs, naloxone, and community-based overdose response. These investments were saving lives throughout the crisis — but you couldn't see it in the total numbers because fentanyl was adding deaths faster than the public health system could prevent them. **Once fentanyl saturated the market and stopped adding new deaths, the ongoing impact of these programs became visible as falling total mortality**. The decline we're seeing now is not an accident and it's not automatic. It is the result of sustained public health investment that predates the decline by years. If that investment is cut, the green area stops shrinking, and mortality flattens at its current level rather than continuing to fall.

Data *Sources: DEA NFLIS and CDC WONDER. Courtesy of Dr. Adams Sibley at UNC.*



Recovery From Peak Overdose Reflects When Fentanyl Saturated The Market.

There are 3 clusters of overdose peaks by state. Declines started earliest where fentanyl had been around longest and achieved 50-70% saturation, in about ⅓ of states around 2021. Another cluster of states peaked in later 2022 and early 2023. A third cluster of West Region states peaked later, in later 2023 and 2024.

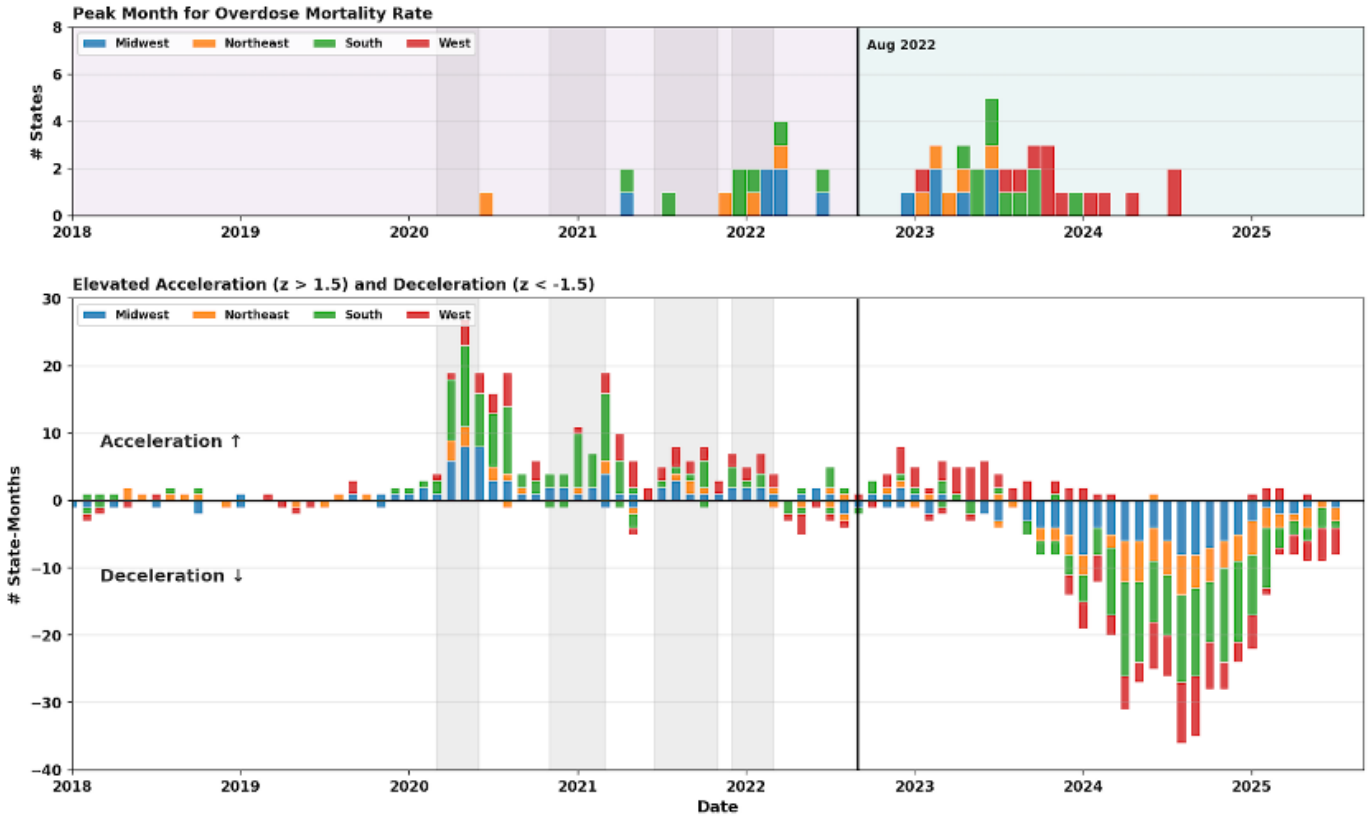


Source: OD Pulse at Northwestern University, based on CDC NVSS

There Were Waves of Fentanyl Overdose Acceleration During COVID Affecting US Regions Differently.

Another factor explaining the increase and decline in fentanyl overdose deaths is COVID.

COVID waves (Wild-type, Alpha, Delta, Omicron) are shaded in grey.
Data source: OD Pulse at Northwestern University



Key Takeaways

We have a unique opportunity to end opioid overdose deaths. The policy changes instituted in recent years are having a major positive impact. Rolling them back would risk the United States re-entering another phase of opioid overdose.

1. **Provide every possible treatment and naloxone access to Gen X and Millennials. Increasing access to medications for opioid use disorder in this population is critical.**

2. **Help Gen Z stay away from illicit opioids.**

3. **In Pennsylvania, CIII Scheduling of xylazine was immediately followed by the emergence of the related molecule medetomidine, and led to massive increase in hospital ED and ICU burden.**

4. **Variability of fentanyl accelerated overdose rates until fentanyl statured the illicit opioid supply. Once it reached 50-70% saturation, public health interventions and behaviors became more effective.**

5. **Buprenorphine "diversion" is overwhelming used to treat pain and withdrawal, not for pleasure.**

6. **As fentanyl-deaths fall, stimulants are becoming more of a concern. Long-term methamphetamine use becomes more lethal as the population ages. Helping middle-aged adults decrease stimulant use now is key to reducing overdose deaths.**

7. **Drug checking programs like ours can provide rapid and reliable data. Funding and support for these programs should be expanded immediately.**

8. **We need immediate research support to understand nitazenes and adulterants in the drug supply.**

List of Attached References

Xylazine

Sibley AL, Miller CW, Joniak-Grant E, Bell A, Visnich M, Alsum S, Dasgupta N. A brick to a bundle: A qualitative study of behavioral responses to xylazine adulteration. *International Journal of Drug Policy*. 2025 Nov 1;145:105017.

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Medetomidine

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Research Paper

A brick to a bundle: A qualitative study of behavioral responses to xylazine adulteration

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ABSTRACT

Background: Xylazine, a veterinary tranquilizer, has emerged as a widespread adulterant in the U.S. illicit drug supply, detected in over 90 % of street fentanyl samples in some regions and identified in a growing number of overdose deaths. While xylazine's health risks are well-documented, little is known about how its presence influences substance use behaviors. We aimed to explore behavioral changes among people encountering xylazine in illicit drug markets.

Methods: We conducted semi-structured in-depth interviews with people with recent overdose reversal experiences in two Midwestern cities ($n = 52$) as part of a larger study on naloxone administration. Participants were asked about their knowledge and perceptions of local drug supply trends. Data were analyzed using the Rigorous and Accelerated Data Reduction technique. Protection Motivation Theory provided a theoretical framework.

Results: Participants overwhelmingly preferred opioids without xylazine. Almost all reported adjusting use toward safer practices in response to xylazine exposure: using less in amount or frequency, changing route of administration, or abstaining or seeking treatment. Behavior change was motivated by fear of negative outcomes, including physical health risks (particularly chronic wounds and limb loss), not experiencing intended opioid effects, loss of functionality due to unwanted sedation, and concerns about overdose reversibility.

Conclusion: Findings suggest that people who use drugs are adapting consumption patterns and adopting harm reduction practices as coping responses to xylazine's adverse effects. Unlike previous major opioid market transitions that primarily differed in pharmacokinetics, xylazine introduces new risks while replacing desired psychoactive effects with undesirable ones. The widespread dissatisfaction with xylazine represents a unique opportunity to expand harm reduction interventions and explore safe supply policies while risk salience is high and user motivation for safer practices aligns with public health goals.

Introduction

Xylazine, a veterinary tranquilizer not approved for human use, is a rapidly expanding constituent of the United States' unregulated drug supply. It typically appears mixed with fentanyl or other opioids, in a combination known as 'tranq' or 'tranq dope.' Xylazine has agonist properties at alpha-2 adrenergic, kappa opioid, dopamine, and sigma receptors (Bedard et al., 2024), imbuing sedation and analgesia partially mirroring the effects of opioids (D'Orazio et al., 2023). As of 2023, xylazine-adulterated fentanyl has been identified in 48 states (Kariisa, 2023). Xylazine is increasingly identified in fatal drug overdoses, with mortality rising from 0.03 to 1.80 per 100,000 persons between 2018 and 2023 (Zhu & Cano, 2025). Understanding how people who use drugs have responded to xylazine's emergence has become critical for informing harm reduction strategies and treatment approaches.

Xylazine emerged as a heroin adulterant in Puerto Rico in the early 2000s, reaching the mainland at the end of the decade (Rodríguez et al., 2008; Wong et al., 2008). Its proliferation across the country has generally exhibited an east-to-west trend, appearing earlier and with greater prevalence in mid-Atlantic states (Cano et al., 2024).

In Philadelphia, an early hotspot, xylazine was identified in 78 % of urinalysis samples that also contained fentanyl as early as 2021 (Korn

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et al., 2021). In the same year in Maryland, 80 % of fentanyl samples collected from syringe service programs also contained xylazine (Russell, 2023). Prevalence may be lower in the Midwest, where one-third of fentanyl samples were recently estimated to contain xylazine (Thomas et al., 2024). Its presence has more recently been detected in California, though typically in low concentrations (Friedman et al., 2025).

At least two factors likely explain xylazine's market emergence. First, xylazine can be purchased online from Chinese pharmaceutical distributors for $6–20 per kilogram, making it an affordable and accessible cutting agent (Drug Enforcement Agency, 2022). Second, xylazine may extend the perceived physiological effects of fentanyl (i.e., give it 'legs'), which typically has a shorter duration of action than heroin (Marshall and Nelson, 2025; Montero et al., 2022).

This market shift differs fundamentally from previous transitions between opioids (e.g., heroin to fentanyl), as xylazine can exacerbate opioid-related complications and introduce entirely new health risks. People who use drugs (Carroll, 2024) and medical professionals (Edinoff et al., 2024) report that xylazine can intensify bradycardia, hypotension, and loss of consciousness, increase the risk of overdose from fentanyl by exacerbating respiratory depression, and cause severe skin and soft tissue damage that is long-lasting and often necrotic (Demery et al., 2025; Semancik, 2024; Yeung & Worrilow, 2024). Current harm reduction responses include wound care, education, and drug checking services. Further, although debate continues regarding naloxone's effectiveness against xylazine-involved overdoses (Bedard et al., 2024; Choi et al., 2024; Morris & Hoang, 2024; Shrestha et al., 2025), community responders are now advised to administer naloxone regardless and monitor respiration rather than consciousness as a sign of resuscitation, given xylazine's profound sedative effects (Bufanda et al., 2025; Datta et al., 2025).

Importantly, among people exposed to xylazine, the vast majority find it an undesired constituent of the drug supply (Hochheimer et al., 2024; Michaels et al., 2024; Salwan et al., 2025; Shrestha et al., 2025). This widespread rejection suggests that xylazine's presence may be influencing how people approach drug use. As overdose mortality has begun declining in some areas, understanding factors that contribute to behavioral changes—including responses to unwanted adulterants—becomes crucial for sustaining these improvements (Dyer, 2024).

Understanding how people who use drugs respond to xylazine exposure is essential for developing effective interventions. If people are already adopting protective behaviors in response to xylazine, interventions can support and amplify these changes rather than working against them. Conversely, identifying potentially harmful adaptations—such as mixing stimulants to counteract unwanted sedation or seeking drugs from unfamiliar sources to avoid xylazine—can reveal where targeted harm reduction education and services are most urgently needed.

Given xylazine's unique position as a widely rejected supply constituent, the purpose of this qualitative study was to understand how xylazine exposure influences opioid use, and may motivate behavior change, from the perspectives of individuals in two U.S. cities.

Methods

Data were collected as part of a larger mixed methods study on community-based naloxone utilization, including quantitative analysis of reversal data and analysis of drug samples collected by partner harm reduction programs in two mid-sized US cities in Pennsylvania (PA) and Michigan (MI). The University of North Carolina-Chapel Hill (UNC) also provides mail-in drug checking analysis using gas chromatography-mass spectrometry (GCMS) as a service to community programs; both sites voluntarily participate in drug checking independently from the current research study (PA site since April 16, 2023; MI site since May 4, 2023) (Wagner et al., 2023). Drug checking data from both sites are presented in the Results to contextualize qualitative findings (drug checking methodology, Appendix A).

Participants (N 52) in the present study were recruited by convenience from the partner harm reduction programs or by peer referral in Pennsylvania (n 27) and Michigan (n 25). Inclusion criteria were: 1) aged 18 years or older, 2) administered naloxone in past 12 months, 3) currently using drugs with overdose risk or have direct social contacts (e.g., intimate partners, family members, or friends) who use drugs with overdose risk (participants determined the meaning of 'current' and 'drugs with overdose risk'). These criteria were intended to be inclusive of participants who may have recently reversed an overdose, the primary research question. In interviews, however, all participants reported either currently using drugs or having used drugs recently enough to be exposed to xylazine.

The partner programs assisted in identifying potential participants. Program staff regularly ask clients seeking naloxone if they have recently reversed an overdose; these clients were then asked if they wanted to learn about a research study. Prospective participants were screened on-site and offered to participate immediately or schedule for a later date. MI participants were all screened and interviewed at the program's physical location in a private office. PA participants were variously recruited from the program's physical location or one of three mobile sites. Interviews were conducted in a program office or in private areas near the mobile locations (e.g., library meeting rooms, cars).

Semi-structured in-depth interviews were conducted between October-November 2024 by two research team members, including one with lived experience of substance use. Topics included: overdose reversal experiences, attitudes toward overdose reversal agents, and perceptions of the current unregulated drug supply. The interview guide was developed in consultation with epidemiologists and behavioral scientists from the U.S. Food and Drug Administration, whose role was limited to methodological input and ensuring alignment with the parent study; they had no role in data collection, analysis, or interpretation. UNC researchers independently added questions on xylazine. No data ownership or sharing agreements with the FDA were established; research outputs will be made publicly available, subject to participant confidentiality protections. Community advisory board members from the PA site (all of whom have lived or living experience of substance use) reviewed the interview guide and provided suggestions on question wording and additional probes. Participants were asked about xylazine to begin interviews (e.g., "Just to get started, we're asking folks about xylazine – if that's something you've seen around and what your thoughts on that are"), with additional prompts added as relevant themes emerged in early interviews.

Interviews averaged 45 min and were incentivized with $50 cash. All interviews were audio-recorded and transcribed with the *whisper* package in Python 3.9 then manually corrected by co-author ALS. The study was approved by the University of North Carolina-Chapel Hill Institutional Review Board (#24-0265). Drug checking data analyses were deemed exempt as anonymized secondary data research (#22-2714). A waiver of written informed consent for interviews was approved by the UNC IRB for interview participants to minimize risks associated with creating signed records of sensitive information. Verbal consent was obtained and documented by interviewers, with no signatures or identifying information collected.

Data analysis

ALS performed a close reading and memoing of the interview data; the analysis team (ALS, CWM, ND) then met to discuss the data, noting salience of xylazine to drug consumption behaviors among participants and setting the research question:

> *How (if at all) have participant drug consumption behaviors shifted in light of xylazine, and what factors may explain these shifts?*

Data were analyzed using the RADaR (rigorous and accelerated data reduction) approach (Watkins, 2017). Transcript excerpts were

imported into an all-inclusive data table in Microsoft Excel then reduced (i.e., shortening or removing excerpts) and analyzed across three phases. In phase one, we memoed on potential themes and divided the data into separate tables by topic (changes in use, feelings toward xylazine, learning about xylazine). In phase two, we open-coded the excerpts in each table and reduced the data further. In phase three, we refined our open codes into a final (mixed inductive-deductive) thematic codebook which were then applied to each table. Excerpts were collated into code reports and interpreted by the analysis team to determine initial themes; code reports and thematic conceptual models were then reviewed by remaining team members and themes were finalized.

Theoretical framework

Our analysis was framed by Protection Motivation Theory (PMT), which is suited to understanding how individuals adapt in response to emerging health threats (Boer & Seydel, 1996). Like many theories of health behavior, PMT is an expectancy-value model: Individuals make behavioral changes based on the expectation that the behavior will lead to a desired outcome (e.g., risk reduction) and the value they place on the outcome (Wigfield & Cambria, 2010). According to PMT, people may be motivated by fear to adopt adaptive responses to health threats. Specifically, one performs an appraisal based on perceived severity of the threat (e.g., how harmful are the effects of xylazine consumption?) and perceived vulnerability to the threat (e.g., how likely am I to experience these effects given my current consumption patterns?). This is coupled with a coping appraisal based on perceived response efficacy (e.g., how likely is a change in behavior, like using less often, to mitigate these risks?), self-efficacy (e.g., how confident do I feel that I can make this behavior change?), and response costs (e.g., what are the drawbacks of adopting this behavior?). One's protection motivation – their intention to perform the behavior – reflects these appraisals (Boer & Seydel, 1996). PMT has been used previously to understand harm reduction behaviors, including overdose prevention intentions and hepatitis C risk reduction strategies, making it well-suited to examine behavioral responses to xylazine adulteration (Lambers et al., 2018; Latkin et al., 2019; Macmadu et al., 2022).

We selected PMT over alternative frameworks like risk environment theory (Rhodes, 2009) because our data highlighted participants' active, individual-level adaptations to perceived xylazine threats, which aligns with PMT's focus on cognitive appraisal and protective behaviors. We take the structural constraints of illicit drug markets as a given—recognizing that individuals cannot control supply composition and face competing risks—but our interest was in understanding how people make decisions and enact harm reduction strategies within those constraints. While PMT was developed for general health threats and does not fully account for structural vulnerability, it provided the most appropriate lens for capturing the fear-motivated behavioral changes described by participants. Below, we report new patterns of use in the wake of xylazine and motivations for these changes.

Results

Xylazine was entrenched in the drug supply in both regions. Of 641 fentanyl samples analyzed (April 2023 to November 2024), the unadjusted presence of xylazine across both sites was 53.4 % (n 246/515, 47.8 % in MI and n 96/126, 76.2 % in PA).

Participants were largely familiar with xylazine's effects and presence in unregulated opioid markets, having learned about the adulterant from harm reduction and treatment providers or through the news. Many experienced xylazine's effects before putting a name to it ("Before I knew what it was, I was already seeing the effects, mostly just in abscesses that were happening," Emma, MI). No one shared positive perceptions of xylazine, which participants characterized as "scary," "terrible," "absolutely horrible," "evil," and "not normal." Many bemoaned an evolving supply that was becoming "scarier and more synthetic" after years of relative stability ("We got used to [fentanyl] a long time ago, still not what we'd prefer over actual heroin, but it is what it is," Emma, MI). For some, the adulterant and its effects were unprecedented:

> I've never had anything like it before … That particular drug, just everything about it irritates me. (Peter, MI)

> Like I already had bad anxiety and then it's like times ten. (Kelsey, PA)

> I've seen some of the worst wounds that I've ever seen in my life. (Kurt, MI)

Many commented on the pervasiveness of xylazine in the supply, sharing that it had become effectively unavoidable:

> I would say like middle to the end of like last winter is when it really started hitting. And now like you pretty much, you can't find anything without it. And it definitely changes the game. (Mikey, PA)

> Yeah, it's in pretty much every bag, I believe. I don't like it. Yeah. I'm 40. I came from like tar heroin, regular heroin. And it's just like, it's just whack. Like, I don't like it at all. (Travis, PA)

Participants overwhelmingly noted that the presence of xylazine had driven their fentanyl consumption lower. We categorized three predominant consumption patterns in the wake of xylazine:

1. using less in amount or frequency;
2. using differently (alternating use or changing route of administration);
3. quitting or seeking treatment.

Although most participants reported less fentanyl use, there were exceptions. Two participants reported using more in recent months, one due to increased tolerance to fentanyl, and the other due to perceived shorter duration or "legs" of tranq dope; two reported no change in use; and two shared a general feeling that some people are seeking out xylazine.

Changes in use

Using less

Most participants who reported modifying opioid consumption discussed using less frequently ("At least every two hours" to "three times a day," Angie, MI), in smaller amounts ("You only need like a half of a stamp bag," Devon, PA), or with periods of temporary abstinence:

> I'm to the point where I'm like, in 30 years, I have not been able to quit doing dope. But I have days where I don't do it. And that's never happened. Never happened out of rehab, for 30 years. I've been a hardcore addict for about 30 years. And xylazine scares the fuck out of me. (Kurt, MI)

For participants reporting amount, reductions were substantial: Several in Pennsylvania quantified their use as shrinking from a brick (50 0.1 g bags) to a bundle (10 0.1 g bags) daily. Participants had mixed feelings about these changes: While they bemoaned an increasingly unfulfilling and dangerous drug supply, many saw their reduction in use as an unlikely "bonus."

Using differently

Many participants discussed recent transitions from injecting to smoking, snorting, or boofing (i.e., ingesting rectally). Some believed that alternative routes could reduce the risk of lesions or prevent injection complications:

> It's also like been shutting down veins … It'd be like fucking hours of just sitting there trying to hit … I mean, look what it does to your fucking, IM [skin pop] it, when you miss. Like, what it does to your

tissue. Like, imagine what it's doing to the inside of your fucking veins. (Mikey, PA)

Others felt that changing the route of administration to snorting, smoking, or boofing helped them better control their dose to avoid sedation:

Like I never knew hardly anyone that smoked it a couple of years ago. And now I know a lot of people…I've even snorted…Like I try to, like, sometimes I don't want to just be out. Nodding out. I like to be there. (Ben, PA)

Though most participants described finding unadulterated opioids as extremely difficult, a few reported occasional access to ostensibly xylazine-free substances, which they identified through test strips, experimentation, or distinct packaging ('[Xylazine-free opioids] don't come in stamp bags…They'll put it like in a corner of a plastic bag and put it in a balloon,' Devon, PA)." Among these participants, some continued use but alternated between xylazine-positive and xylazine-negative bags. One participant, for instance, used adulterated bags only to induce sleep at night, while another alternated to alleviate xylazine withdrawal symptoms ("I feel sick now from…and I want the ones *with* xylazine. So, how I would do it, would be like, one with xylazine and one without xylazine, you know? I would, like, alternate," Jackie, PA).

Quitting or seeking treatment

Several participants reported stopping opioid use because of xylazine ("It scared me to the point where I knew I had to get clean," Trip, PA). Some described the cons of continued use outweighing the pros, concluding "It ain't worth it" or "It's a lot easier to stop because of that." Quitting was often facilitated by medications for opioid use disorder ("[Xylazine's] what made me get on Subs [buprenorphine]," Carly, PA). For others who continued use, methadone or buprenorphine were accessed to moderate consumption of xylazine-adulterated street drugs and reduce the risk of harm. Finally, some participants not yet in treatment reported a newfound desire to discontinue use ("It's been getting to the point where, if everything is going to have so much xylazine in it, it's making us want to just not use at all," Emma, MI), although they had not taken steps to do so.

Motivation for changes in consumption

Participants shared multiple reasons for reducing, stopping, or altering use. Generally, xylazine elicited emotions ranging from intense fear to exasperation, with some reaching a breaking point after years of unfulfilling use:

There's a lot of things that you will accept, if it was going to be as good as it was when you first started. You'll go through a lot of bullshit to get there, but if it's not even going to be that, then you're kind of done. (Emma, MI)

One participant shared a more optimistic perspective. Roger attributes his irregular heartbeat and kidney problems to xylazine, a belief that is motivating his recovery efforts: "In a way, I'm kind of trying to look at it as a blessing now. I'm at the point, I've tried going through rehab several times, but I know this is the time, you know what I mean?" (Roger, MI). Still, despite attempting to reframe his experience positively, Roger acknowledges the serious harms of xylazine, noting that his extensive scars are likely permanent.

The manifestations of xylazine adulteration were well-known to participants, almost all of whom reported witnessing or personally experiencing its effects. These impacts were often pronounced, e.g., necrotizing flesh, burning pain from injection, and cognitive impairment ("the xylazine daze"). Participants shared four factors that precipitated changes in use:

1. not experiencing intended effects;
2. physical health risks;
3. functional impacts;
4. overdose beliefs.

Not experiencing intended effects

Participants bemoaned no longer feeling the desired psychoactive effects of opioids ("When you do heroin, it feels good. Obviously. That's why we do it. But that shit [xylazine], it doesn't," Austin, PA). While participants reported missing expected sensations like euphoria and pain relief, some also yearned for the emotional numbing they sought in drug use. Kurt described using opioids to forget about the physical and sexual abuse he experienced as a child. Tranq dope does not provide the same reprieve:

I was self-medicating. But it's not working anymore. Like, the medication that people are whipping up in their kitchen right now isn't heroin. And it's not even real opiate. You know, it's a fucking tranquilizer. I don't want to go to sleep. I want the chemicals in my brain to make me feel better. And it's not happening. (Kurt, MI)

More immediately, participants reported tranq dope failed to curb opioid withdrawal symptoms, a primary driver of continued use ("It's not even making me right anymore, so I got back into the methadone clinic" Roger, MI).

Physical health risks

Skin and soft tissue damage commonly motivated those who reduced their use ("Breakfast, lunch, and dinner, I try to do three shots a day and just leave it at that because I don't like having abscesses all over…It makes me not want to leave my house," Angie, MI). Wounds were especially worrisome as they might take months to heal, if at all, a phenomenon that many participants had not experienced in years of drug use. Limb loss was a visceral fear for many who had heard about or witnessed xylazine-associated amputations:

The other people I know…a lot of people, I know their arms are about to fall off. (Mikey, PA)

Xylazine scares the fuck out of me. I don't want to lose limbs. (Kurt, MI)

If something like that happens and [my wife] has to get her leg amputated or her arm amputated…I feel like it would be my fault. (Austin, PA)

Like, it's eating my skin. Hell no, it ain't worth it. (Roger, MI)

Additional health risks participants hoped to avoid that were presumed due to xylazine included hallucinations and injection site complications ("Typically if you missed [a vein], it would get itchy and, like, red and bumpy. This one [xylazine], as soon as you missed, it was like lightning under your skin," Trip, PA).

Functional impacts

Xylazine can induce hours of unconsciousness or a dissociative state to the frustration, embarrassment, or bewilderment of many participants ("I even taped myself because I had to see how this was happening," Roger, MI). Undesired and unintended sedation hindered many from achieving an expected level of functionality and productivity ("I use a lot less, that's for sure. If you do too much of it, you're just going straight to sleep. You waste the whole day," Shawn, MI). Participants who used opioids for emotional numbing often found xylazine's tranquilizing effects too extreme:

The tranq, it's like, you just fall asleep…But personally, what started my use back up in the beginning, and this time, is just my anxiety. So, I don't really want to be sleeping. I just don't want to be constantly freaking out. (Linda, PA/)

Overdose beliefs

Some participants contended tranq dope was "stronger," potentiating overdose risk ("I've almost died off one bag, and I'm a veteran with this shit." Mikey, PA), or made overdoses more difficult to reverse with naloxone ("They don't pop out of it like a Pop-Tart anymore," Trip, PA). The consequent fear of mortality drove some participants to reduce or discontinue use:

> I've done an awful lot of reversals, and I know [xylazine] affects your central nervous system and keeps you—Narcan doesn't help reviving the respiratory part of it. So I had began using less and less until I had an intervention, essentially. (Peter, MI)

> When I came back [from overdosing], when I woke up…dude was telling me what happened, but all I was thinking about was, I still had the other half of that bag in my pocket. It's like, what are you going to do? You know, go out and, go buy yourself, overdose again? Like, what the fuck? I gave him the rest of that bag. (Trip, PA)

Discussion

In this qualitative study, we explored changes in drug consumption behaviors in the wake of xylazine's appearance in the unregulated drug supply. With few exceptions, participants described recent attempts at safer use – using less, changing route of administration, or abstaining entirely. Participants with decades of experience recalled adapting to previous supply transitions, including fentanyl. Xylazine, however, represented a novel inflection point, with some resigned that the current supply is no longer worth the pleasures of use, nor the pains of dependence.

While the human health risks of xylazine consumption – long-lasting wounds, deep sedation, and others – are well-documented, participants' accounts indicated that xylazine in the unregulated drug supply may play a role in individual decisions to reduce consumption. Findings are consistent elsewhere. Reduced self-administration has been documented in rodent models, where xylazine coadministration suppresses fentanyl consumption (Bedard et al., 2024; Khatri et al., 2024; Sadek et al., 2024); observational clinical research shows xylazine is associated with reduced cardiac arrest, oxygen distress, and fatality in fentanyl poisonings (Hays et al., 2024; Love et al., 2023); and similar shifts in perception and behavior have been discussed by Reddit users (Heidari et al., 2024). Collectively, these lines of evidence start to build the case for a paradoxical association between xylazine and reduced risk of overdose along multiple causal pathways, both physiological and behavioral.

Xylazine's appearance is qualitatively different from other major supply transitions of the overdose epidemic. The predominant opioid of each generation – from prescription pills, to heroin, to fentanyl, and perhaps next to nitazenes (Lassi & Jiang, n.d.) – has differed mainly in pharmacokinetics, e.g., potency, onset, and duration. The market shift toward xylazine and xylazine-adulterated opioids has brought with it new risks and largely replaced expected psychoactive effects with undesirable ones (Hochheimer et al., 2024; Michaels et al., 2024; Salwan et al., 2025). Our study suggests that behavioral responses to this most recent shift may be qualitatively different, as well.

Fear was a predominant emotion shared by participants. According to PMT, behavioral responses to health threats are most likely to occur when a threat is appraised as both severe and likely. Severity was evident in participants' responses. Almost all had experienced or witnessed xylazine-related wounds, which they described as unprecedented – slow to heal, necrotic, and ending in limb loss. There was also a widespread belief that xylazine-involved overdoses are more difficult – or impossible – to reverse. Susceptibility was apparent in the seeming unavoidability of xylazine and its effects. Most participants described not being able to find drugs without the adulterant, while personal or witnessed experiences of skin and soft tissue damage, unwelcome sedation, and intractable overdoses were nearly universal. Taken together, it seems reasonable that people at risk for xylazine exposure might be motivated to adapt their drug use to mitigate these tangible risks.

Yet, per PMT, behavioral adaptation also depends on how confident one feels to perform the behavior and the drawbacks of adapting. The desired effects of substance use – pain relief, euphoria, emotional numbing, withdrawal avoidance – are a clear opportunity cost of abstaining. But participants described diminishing returns as the drug supply has become more and more adulterated, believing that the benefits of use have largely been eroded. Still, even for those motivated for change, abstinence can be an unrealistic goal, given the immense physical and psychological toll of detoxification and recovery, as well as social-structural barriers to treatment access (Cernasev et al., 2021). It is unsurprising, then, that while some participants reported discontinuing entirely, most engaged in more achievable harm reduction behaviors – using less, changing route of administration, or balancing ongoing use with prescribed medications. Although research is nascent, one small study found a moderate positive association between xylazine severity beliefs (risk of overdose) and harm reduction behaviors (e.g., carrying naloxone, not using alone) (Salwan et al., 2025).

While our participants expressed widespread dissatisfaction with xylazine, prior research has documented that some individuals actively seek out xylazine, particularly in Puerto Rico and Philadelphia, where it was described as desirable for extending the short duration of fentanyl's effects (Friedman et al., 2022). Our findings, collected more recently, may reflect a shift in user perceptions over time as xylazine has lost some of its initial novelty and its harms have become more widely recognized. Another important contextual difference is that our study does not quantify xylazine concentrations; it is possible that contemporary street formulations contain higher and more variable levels of xylazine compared to earlier markets. In Puerto Rico, for example, xylazine was originally sold in separate bundles alongside heroin rather than pre-mixed, allowing users to titrate their dose to preference (Torruella, 2011). In contrast, current drug supplies in the United States often contain xylazine mixed at unknown concentrations, reducing user control and increasing the likelihood of unwanted effects. Taken together, these findings underscore the dynamic nature of drug preferences, which can shift as new psychoactive profiles emerge, evolve, and saturate local markets, and highlight the need for harm reduction interventions that are adaptive to shifts in user attitudes.

A key area of future investigation pertains to how xylazine-related behavioral shifts may influence population-level overdose mortality. In mid-2023, overdose deaths in the United States started decreasing, with annualized mortality dropping 30 % from 2023–2024 in some states (Dyer, 2024). The east-to-west pattern of overdose declines parallels the spread of xylazine in the unregulated drug supply (Dyer, 2024). However, the declines in overdose rates are surely more complex than the emergence of a single adulterant (Dyer, 2024). We can only conclude from our study that xylazine may have changed people's use of drugs sold as fentanyl in the sites we investigated, often in compensatory ways to decrease risk of severe skin wounds and overdose fatality. If indeed people exposed to xylazine are engaging in safer consumption behaviors (Heidari et al., 2024), then harm reduction interventions focused on safer use should be redoubled while risk salience is high and supply satisfaction remains at its nadir. Such interventions should, at a minimum, empower informed consumption decisions (e.g., access to xylazine test strips and drug checking services) and minimize the adulterant's physical harms (e.g., education on early wound detection and wound care). As importantly, people disillusioned by the supply should have adequate opportunity to reduce or eliminate use through low threshold methadone and buprenorphine treatment, whether or not abstinence is a goal (Jakubowski & Fox, 2020).

From a policy perspective, legislative measures to reduce supply of and demand for xylazine should be evaluated in light of these findings and with regard to potential unintended consequences. As of April 2024, 58 relevant state or federal policy initiatives had been proposed or

enacted, with most designed to schedule xylazine and create stiffer possession penalties (Sugarman et al., 2024). Most recently, the Combating Illicit Xylazine Act, introduced by bipartisan Congressional sponsors, would classify xylazine as a federal Schedule III substance while empowering the U.S. Drug Enforcement Agency to track and interdict upon illicit xylazine supply chains (Combating Illicit Xylazine Act, 2025). Though well-intentioned, drug enforcement initiatives often destabilize local markets and increase drug-related harms (Carroll et al., 2020; Ray et al., 2023; Zolopa et al., 2021). For instance, heroin shortages in five countries over 15 years had consistent population-level outcomes: increases in adulteration, transitions to polydrug use, and compensatory risk behaviors, like receptive syringe sharing (Zolopa et al., 2021). In the U.S., recent local and regional law enforcement seizures have been linked with subsequent fatal and non-fatal overdose spikes (Mohler et al., 2021; Ray et al., 2023; Zibbell et al., 2019).

We urge caution against reactive policy measures that interrupt the unregulated supply of xylazine. Our data, contextualized in this literature, suggest that the abrupt disappearance of these additives has the potential to reverse the observed behavioral changes described above, and lead to a rebound in street fentanyl or polydrug consumption. We also cannot disregard the inevitable appearance of new – and potentially more dangerous – adulterants filling the hole left in the supply. Medetomidine, a related and more potent alpha-2 adrenergic agonist, has supplemented or displaced xylazine in many markets (Palamar & Krotulski, 2024). While research is still emerging on its risk profile, early evidence highlights that medetomidine withdrawal syndrome is life-threatening and unresponsive to opioid and xylazine withdrawal medications (Huo, 2025; Ostrowski, 2025).

From a practical perspective, Protection Motivation Theory provides a template for encouraging behavior change. Point-of-care drug checking supplies (i.e., xylazine test strips) and – when possible – laboratory-confirmed drug checking services, can be educational tools to highlight xylazine's local prevalence and raise perceived vulnerability. Education should also center the unprecedented nature of xylazine's risks – from recalcitrant wounds to atypical overdose reversals – to raise perceived severity. People with low self-efficacy for change can be offered achievable steps, like reduced use, different routes of administration, or balanced consumption of street drugs with medications like buprenorphine or methadone. And while recovery is not and should not be a requisite endpoint of harm reduction services, the xylazine era presents a unique opportunity for practitioners to engage those whose motivation has peaked to start conversations about more elusive changes – including treatment.

We acknowledge an important ethical tension in our findings and recommendations. While we document that xylazine's harmful effects motivated safer consumption practices among our participants, we do not suggest that maintaining a toxic drug supply is an acceptable harm reduction strategy. Nor do we condone reactive enforcement measures (e.g., reclassifying xylazine) or abrupt supply interventions that may increase harm through market destabilization, rebound consumption, and the emergence of more dangerous adulterants.

Instead, we support supply-side alternatives that respect the dignity and agency of people who use drugs while addressing the harms of an unpredictable, adulterated market. While all drug use carries inherent risks, these risks can be mitigated through appropriate regulation and access models—much as medical professionals do when prescribing and monitoring medications like fentanyl. The critical question is not whether drugs are inherently dangerous, but how their use is managed to optimize the balance of benefit and risk (Rieder, 2025). Policy interventions can range from more regulated models like heroin-assisted treatment programs, which have demonstrated success in reducing illicit drug use in Europe and Canada (McNair et al., 2023), to less restrictive approaches such as prescribed safer supply programs that provide pharmaceutical opioids through integrated medical or harm reduction settings (Ivsins et al., 2020; Klaire et al., 2022). These initiatives recognize that many people will continue using drugs regardless of market conditions, and that access to a predictable, regulated supply can prevent the harms associated with toxic adulterants like xylazine. Rather than accepting a toxic supply as inevitable or relying on enforcement-based disruption, these models provide dignified alternatives that align with both public health goals and harm reduction principles. Expanding such programs along this continuum of regulation represents a critical long-term strategy for addressing not only the current xylazine crisis but future adulterant-related harms that will inevitably emerge in unregulated markets.

Our findings may not generalize to other geographic locations where the unregulated supply looks different, nor to people who do not access harm reduction. That almost all of our participants actively sought harm reduction services suggests that they may be more amenable to practice safer use in light of xylazine compared with other people who use drugs. Participants were also recruited from two sites that both offer on-site and lab-based drug checking, meaning they were possibly more sensitized to supply adulteration. Lack of demographic analysis also precludes insights into the role of social identity in behavioral responses, particularly race and gender. Additionally, while participants focused on physical and psychological motivations for behavioral change, we did not systematically explore the economic and social dimensions that may influence responses to xylazine. Future research should examine how xylazine affects social relationships and drug-sharing networks, economic factors such as changes in drug purchasing patterns or costs associated with wound care, and how these social and economic considerations interact with health concerns to shape consumption decisions.

In addition to restricted generalizability, a limitation of this study is that we cannot assess whether the behavioral adaptations participants described will be sustained over time, particularly as tolerance develops or if market conditions change. Nor can we explain the sustained proliferation of an additive that customers strongly view as undesirable, though there are other ongoing examples (Shover et al., 2024). The presence of xylazine in the unregulated drug supply does not conform to our understanding of previous drug outbreaks, requiring more nuanced investigation.

Conclusion

Our findings should not be interpreted as endorsing xylazine's presence in the drug supply. Rather, they underscore the resilience and agency of people who use drugs in adapting to dangerous market conditions and highlight the urgent need for interventions that support safer choices in unpredictable markets. The current moment demands bold harm reduction initiatives that address the immediate crisis of xylazine adulteration and the broader structural factors that create vulnerability to drug-related harm.

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CRediT authorship contribution statement

Adams L. Sibley: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Colin W. Miller:** Writing – review & editing, Investigation, Conceptualization. **Elizabeth Joniak-Grant:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Alice Bell:** Writing – review & editing, Validation, Conceptualization. **Malcolm Visnich:** Writing – review & editing, Validation, Conceptualization. **Steve Alsum:** Writing – review & editing, Validation, Conceptualization. **Nabarun Dasgupta:** Writing – review & editing, Methodology, Funding acquisition,

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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CLINICAL RESEARCH

Opioid overdoses involving xylazine in emergency department patients: a multicenter study

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ABSTRACT

Introduction: Illicit opioids, consisting largely of fentanyl, novel synthetic opioids, and adulterants, are the primary cause of drug overdose fatality in the United States. Xylazine, an alpha-2 adrenergic agonist and veterinary tranquilizer, is being increasingly detected among decedents following illicit opioid overdose. Clinical outcomes in non-fatal overdose involving xylazine are unexplored. Therefore, among emergency department patients with illicit opioid overdose, we evaluated clinical outcome differences for patients with and without xylazine exposures.

Methods: This multicenter, prospective cohort study enrolled adult patients with opioid overdose who presented to one of nine United States emergency departments between 21 September 2020, and 17 August 2021. Patients with opioid overdose were screened and included if they tested positive for an illicit opioid (heroin, fentanyl, fentanyl analog, or novel synthetic opioid) or xylazine. Patient serum was analyzed *via* liquid chromatography quadrupole time-of-flight mass spectroscopy to detect current illicit opioids, novel synthetic opioids, xylazine and adulterants. Overdose severity surrogate outcomes were: (a) cardiac arrest requiring cardiopulmonary resuscitation (primary); and (b) coma within 4 h of arrival (secondary).

Results: Three hundred and twenty-one patients met inclusion criteria: 90 tested positive for xylazine and 231 were negative. The primary outcome occurred in 37 patients, and the secondary outcome occurred in 111 patients. Using multivariable regression analysis, patients positive for xylazine had significantly lower adjusted odds of cardiac arrest (adjusted OR 0.30, 95% CI 0.10–0.92) and coma (adjusted OR 0.52, 95% CI 0.29–0.94).

Conclusions: In this large multicenter cohort, cardiac arrest and coma in emergency department patients with illicit opioid overdose were significantly less severe in those testing positive for xylazine.

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Introduction

An unprecedented increase in United States (US) opioid overdose mortality has been observed since 2014, driven by the near ubiquitous presence of synthetic opioids in the illicit opioid supply [1–4]. Polypharmacy implicated deaths, which include combinations of opioids, stimulants, and benzodiazepines, have also surged [5–8]. Recently, xylazine has been reported in drug materials and overdose deaths linked to illicit fentanyl proliferation [9]. However, patient clinical outcomes following non-fatal illicit opioid overdose with the presence of xylazine have not been described.

Xylazine, a potent central alpha-2 adrenergic agonist used in veterinary medicine with ketamine or opioids, is used for large-animal anesthesia or pain management [10]. Xylazine is structurally related to clonidine (Figure 1), resulting in central nervous system (CNS) depressant effects (sedation) and cardiovascular side effects (bradycardia, hypotention, and cardiac arrest) [10]. By bolstering alpha-2 adrenergic receptor activity, xylazine decreases norepinephrine presynaptic release, subsequently decreasing an adrenergic physiologic response [10]. Animal studies using a mouse model have also demonstrated xylazine activity at mu-opioid receptors [11].

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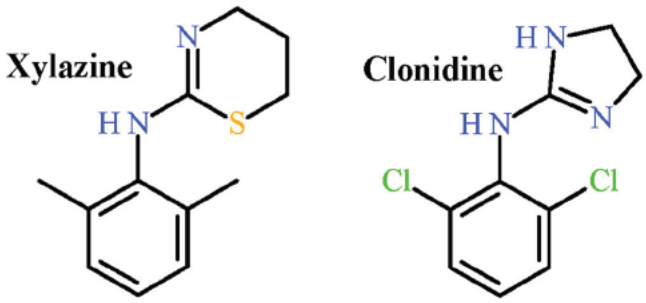

Figure 1. Chemical structures of xylazine and clonidine.

Over the last two decades, xylazine has emerged as an adulterant in the recreational drug supply (e.g., fentanyl, metamfetamine) [9,12]. Early xylazine detection in Puerto Rico describes patients using xylazine in combination with opioids or cocaine [13,14]. Recently, xylazine, known by its street-name "tranq," has been detected in urine, drug products and syringes with fentanyl and metamfetamine [15–17]. Xylazine has also been increasingly detected among overdose fatalities in post-mortem studies [18–22]. However, no studies have described clinical characteristics and outcomes for a prospective patient cohort exposed to opioids and xylazine.

Here, we investigate the effect of xylazine on clinical outcomes of emergency department (ED) patients who presented with suspected illicit opioid overdose. We performed blinded toxicological analyses and compared clinical outcomes *via* medical chart abstraction. We hypothesized that xylazine would be associated with worse clinical outcomes, most importantly cardiac arrest, and coma.

Methods

This multicenter, prospective cohort study enrolled consecutive patients with suspected opioid overdose who presented to a participating ED between 21 September 2020 and 17 August 2021. Participating institutions were a subset of the Toxicology Investigators Consortium (ToxIC), which is an existing network of 48 US hospitals in 30 US cities [23]. Nine EDs participated across 7 states: California, Oregon, Michigan, Missouri, Pennsylvania, New York, and New Jersey. A central institutional review board (Western IRB) provided approval and a waiver of informed consent.

Inclusion/exclusion criteria

Patients at least 18 years old and who presented to the ED with suspected opioid overdose between 21 September 2020 and 17 August 2021 were screened for study eligibility. Patients were eligible for study inclusion if they (1) had opioid toxicity based on chief complaint or discharge diagnosis; (2) received naloxone for overdose treatment in the ED; or (3) had self-reported opioid use resulting in an ED visit for an overdose. Patients who presented with trauma, in custody of law enforcement, or without waste specimens were excluded. Of those eligible for study inclusion, only patients testing positive for illicit opioids or xylazine were included in the final cohort. An illicit opioid included heroin, fentanyl, fentanyl analogs, nitazene analogs, or other new synthetic opioids.

Toxicological analyses

Waste clinical specimens were collected as directed by site investigators and ToxIC staff. Serum and/or blood samples drawn in heparinized tubes obtained as part of routine clinical care were collected, de-identified, and stored at −80 °C until sent to the Center for Forensic Science Research and Education (CFSRE) for analysis. Qualitative molecular identification consisted of liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) analysis with secondary analysis by liquid chromatography tandem quadrupole mass spectrometry (LC-QqQ-MS), when necessary. Current CFSRE toxicology testing contains over 900 drugs, including therapeutics, traditional illicit drugs, novel psychoactive substances, adulterants, and other compounds. This methodology has been previously validated [24] and the molecular battery is frequently updated, as drugs in this dynamic market change frequently. Illicit opioids of interest were fentanyl, fentanyl analogs (e.g., acetylfentanyl, furanylfentanyl, carfentanil, para-fluorofentanyl), nitazene analogs (e.g., isotonitazene, metonitazene), and other new synthetic opioids (e.g., brorphine, 2-methyl AP-237), as well as previously prevalent synthetic opioids (e.g., AH-7921, MT-45, U-47700) [5]. The limit of detection for both xylazine and fentanyl was 0.1 µg/L.

Biological samples were de-identified with a code linking the patient's sample to the corresponding ToxIC site clinical data entry. Toxicological analyses were blinded to clinical outcomes. Results were summarized and sent to the principal investigator for linkage to clinical data for analysis. Patients were then categorized into those testing positive (i.e., xylazine group) or negative (i.e., controls) for xylazine based on LC-QTOF-MS and/or LC-QqQ-MS.

Definitions

An illicit opioid was defined as heroin, fentanyl, fentanyl analogs, nitazene analogs, or other new synthetic opioids. Patients testing positive for prescription opioids (e.g., oxycodone, methadone) without xylazine were not included in the study cohort.

Cardiovascular adverse events were defined as a ventricular arrhythmia, intraventricular conduction delay, QT prolongation, documented cardiac arrest, elevated troponin, or bradycardia (<50 beats per minute at any time). Troponin was considered elevated if above the upper limit of normal for the given hospital's reference range.

Individual sites were grouped into three regions: West (California, Oregon), Central (Michigan, Missouri), and East (Pennsylvania, New York, New Jersey).

Data collection

Medical record data included age, sex, past medical and psychiatric comorbidities, suspected opioid name, treatment rendered (including dose, amount, route, and duration of

naloxone administration), and outcome, including the presence or absence of any organ system toxicity. Data were collected and entered in a secure, web-based software platform (Research Electronic Data Capture [RedCap]) by a trained research assistant or site investigator/toxicologist.

Outcomes

The primary outcome of cardiac arrest was defined as loss of pulse requiring cardiopulmonary resuscitation (CPR), as documented in the medical chart. The secondary outcome of coma was defined as unarousable unresponsiveness or the phrase "coma" at any time within the first 4 h of ED arrival based on medical chart documentation. Adjudication of outcomes was performed independently by each ToxIC site investigator.

Data analysis

Descriptive statistics are reported as medians with interquartile ranges and percentages. Categorical variables were evaluated using the Chi-squared test and Fisher's exact test (when appropriate). Continuous variables were compared *via* Student's *T*-test. Clinical variables included age, sex, race/ethnicity, psychiatric history, initial blood pressure, total naloxone dose administered, and the presence of xylazine. Multivariable logistic regression analysis was used to estimate the association between the explanatory variable (xylazine) and study outcomes when controlling for confounders. Data are reported as point estimates with corresponding 95% confidence intervals. Data analysis was performed on Stata/SE (version 16.1; College Station, TX).

Data management and quality

Site-specific medical record data were abstracted into a RedCap data collection platform without patient identifiers. Patient data were linked to corresponding biological specimens. ToxIC registry data quality assurance is maintained in accordance with current best-practices [25] including database logical checks, pilot testing, procedure manuals, quality assurance personnel, paperless e-forms, automated data cleaning, data tracking, secure encryption, and data abstractor training [26]. RedCap platform quality assurance confirmed that >90% of pertinent data fields were completed.

Results

Figure 2 shows study patient selection. During the study period, 1,006 patients were screened for eligibility and 395 patients were enrolled. 321 patients (81.3%) were identified with at least one illicit opioid of interest or xylazine present in toxicology samples. Of these patients, 90 patients (28.0%) tested positive for xylazine and 231(72.0%) tested positive for an illicit opioid without xylazine. Among patients without xylazine, 16% had heroin detected, 93.5% had fentanyl detected, 13.9% had other fentanyl analogs detected and 3.0% had a novel synthetic opioid detected. Among patients with xylazine, 25.5% had heroin detected, 98.9% had fentanyl detected, 32.2% had other fentanyl analogs detected and 2.2% had a novel synthetic opioid detected (Table 1). Only one patient tested positive for xylazine without an illicit opioid. This patient tested positive for a prescription opioid (methadone).

Overall, most patients were male (69.5%). The median (IQR) age was 39 (30–50) years. Psychiatric illness was prevalent and relatively evenly distributed among patients with and without xylazine. Baseline characteristics were similar

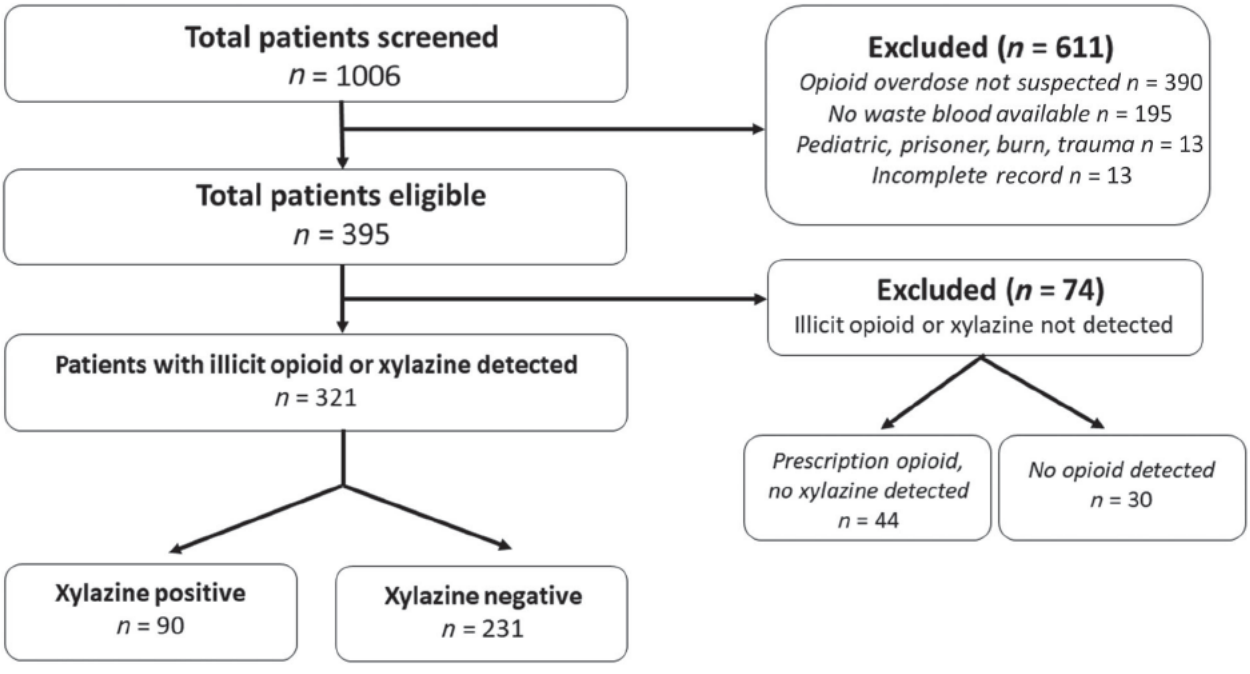

Figure 2. Patient eligibility and enrollment.

Table 1. Demographic characteristics of xylazine and control cohorts.

Demographic variables	Xylazine (*n* 90)	Xylazine absent (*n* 231)
Male (%)	69 (76.7%)	154 (66.7%)
Age; median (IQR)	41 (32 53)	38 (30 50)
Psychiatric history		
Any	58 (64.4%)	138 (59.7%)
Anxiety	19 (21.1%)	34 (14.7%)
Attention deficit hyperactivity disorder	4 (4.4%)	10 (4.3%)
Bipolar	9 (10%)	25 (10.8%)
Depression	17 (18.9%)	55 (23.9%)
Post traumatic stress disorder	4 (4.4%)	12 (5.2%)
Schizophrenia	4 (4.4%)	10 (4.3%)
Geographic Region		
East (PA, NY, NJ)	63	127
Central (MI, MO)	26	74
West (CA, OR)	1	30
Naloxone		
Received any naloxone (%)	70 (77.8%)	195 (84.4%)
Initial naloxone dose mg; median (IQR)	2 (0.875 4)	2 (2 4)
Total naloxone dose mg; median (IQR)	3.6 (1.3 4.1)	2.8 (2 4.1)
Number of naloxone doses; median (IQR)	2 (1 3); range 1 5	1 (1 2); range 1 9
Repeat naloxone received (%)*	39 (43.3%)	96 (41.5%)
Initial ED vital signs		
SBP; median (IQR)	132 (114 150)	130 (118 145)
DBP; median (IQR)	84 (68 98)	84 (70 95)
HR ED; median (IQR)	95 (81 108)	98 (84 112)
RR ED; median (IQR)	18 (14 20)	18 (15 20)
Opioid analytes detected **		
Heroin	23 (25.5%)	37 (16%)
Fentanyl	89 (98.9%)	216 (93.5%)
Other fentanyl analogs	29 (32.2%)	32 (13.9%)
Novel synthetic opioids	2 (2.2%)	7 (3.0%)

Abbreviations. IQR, interquartile range; PA, Pennsylvania; NY, New York; NJ, New Jersey; MI, Michigan; MO, Missouri; CA, California; OR, Oregon; ED, emergency department; DBP, diastolic blood pressure; SBP, systolic blood pressure; HR, heart rate; RR, respiratory rate.
*Percentage of entire cohort.
**Samples tested for all potential analytes. Single sample may have multiple analytes and percent totals may exceed 100%.

between groups, but xylazine was more prevalent in samples from the East (Table 1).

Most patients (82.6%) were treated with naloxone and received a median initial 2 mg dose. Table 1 describes naloxone administration in patients with and without xylazine detected. A large patient minority (42.1%) in both groups required multiple doses of naloxone.

Cardiovascular-related clinical outcomes were uncommon and did not differ between patients who did and did not have xylazine detected (Table 2). Xylazine-negative patients were more likely to have cardiac arrest compared to xylazine-positive patients: 33 patients (14.3%) without xylazine compared to four patients with xylazine [(4.4%), $P = 0.013$; 95% CI −0.16, 0.036)]. The 95% confidence interval is –0.16 to –0.036.

Coma was documented in 24 (26.7%) xylazine-positive patients within 4 h and persisted in 12 patients (13.3%) beyond 4 h. In contrast, coma was documented in 87 (37.7%) xylazine-negative patients within 4 h and persisted beyond 4 h in 35 patients (15.2%). However, there was no significant difference in early or late coma rates among those with and without xylazine (Table 2).

Most patients were discharged from the ED (59 [65.5%] xylazine-positive, vs. 147 [63.6%] xylazine-negative patients). One xylazine-positive patient (1.1%) died, compared with five (2.16%) xylazine-negative patients. The proportion of patients discharged from the ED, admitted patient average length-of-stay, and mortality rates were not significantly different between the xylazine-positive and xylazine-negative groups.

Table 3 shows multivariate logistic regression modeling results for patients developing coma within 4 h of ED arrival. After controlling for age group, sex, race, prior psychiatric history, initial blood pressure and naloxone administration, xylazine exposure was associated with a significantly lower odds of developing coma within 4 h of ED arrival (OR = 0.52, 95% confidence interval: 0.29 − 0.94). Blacks/African Americans (OR = 1.95, CI: 1.01–3.74), unknown race (OR = 3.64, CI: 1.63–8.16), and receiving naloxone (OR = 2.48, CI: 1.29–4.79) were associated with significantly higher odds of coma within 4 h of ED arrival.

Table 4 shows multivariate logistic regression modeling results for patients with cardiac arrest. After controlling for age group, sex, race, prior psychiatric history, initial blood pressure and administration of naloxone, xylazine exposure was associated with a significantly lower odds of cardiac arrest (OR = 0.30, 95% confidence interval: 0.10 − 0.92). Black/African American race (OR = 0.23, CI: 0.06–0.84) was also associated with lower odds of cardiac arrest.

Discussion

In this large multicenter study analyzing xylazine overdose severity in ED patients, our primary finding was that clinical

Table 2. Clinical outcomes in xylazine vs. control patients.

Clinical outcome variables	Xylazine (*n* 90)	Xylazine absent (*n* 231)	*P* Value
Cardiovascular outcomes			
Received CPR	4 (4.4%)	33 (14.3%)	**0.013**
Bradycardia	2 (2.2%)	4 (1.7%)	0.77
Pulmonary outcomes			
Intubated within 4 h	2 (2.2%)	13 (5.6%)	0.193
Non invasive positive pressure within 4 h	1 (1.1%)	4 (1.7%)	0.689
Any ventilatory support within 4 h	3 (3.3%)	17 (7.4%)	0.182
Intubated after 4 h	2 (2.2%)	11 (4.8%)	0.298
Non invasive positive pressure after 4 h	2 (2.2%)	2 (0.9%)	0.327
Any ventilatory support after 4 h	4 (4.4%)	13 (5.6%)	0.67
Central nervous system outcomes			
Coma within 4 h	24 (26.7%)	87 (37.7%)	0.063
Coma after 4 h	12 (13.3%)	35 (15.2%)	0.682
Overall outcomes			
Death	1 (1.1%)	5 (2.16%)	0.528
Discharged from the ED	59 (65.6%)	147 (63.6%)	0.528
ICU Admissions	11 (12.2%)	39 (16.9%)	0.30
Miscellaneous			
Length of hospitalization (h); median (IQR)	10 (5 28)	9 (5 36)	0.806
Total naloxone dose (mg)	3.68 (1.3 4.05)	2.8 (2 4.1)	0.448

Abbreviations: IQR, interquartile range; CPR, cardiopulmonary resuscitation; ED, emergency department; ICU, intensive care unit. The bold values indicate variables that are statistically significant ($P < 0.05$).
*Percentage of entire cohort.

Table 3. Modelling xylazine as an independent predictor of coma.

Variable name	aOR	95% CI
Xylazine	**0.52**	**0.29 0.94**
Age category		
18 29 years old	REF	REF
30 39 years old	1.52	0.73 3.17
40 50 years old	0.92	0.41 2.05
50+ years old	1.54	0.69 3.45
Sex		
Female	REF	REF
Male	1.49	0.84 2.64
Race category		
Non Hispanic White	REF	REF
Black/African American	**1.95**	**1.01 3.74**
Asian	1.00	
Hispanic	0.51	0.15 1.67
Other/Native American/Hawaiian/mixed race	2.54	0.72 8.91
Race unknown	**3.64**	**1.63 8.16**
Prior psychiatric history	0.87	0.49 1.56
Initial ED blood pressure	0.99	0.97 1.00
Received naloxone	**2.48**	**1.29 4.79**

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ED, emergency department; REF, reference category. Variables in **bold** were statistically significant.

Table 4. Modelling xylazine as an independent predictor of cardiac arrest.

Variable name	aOR	95% CI
Xylazine	**0.30**	**0.10 0.92**
Age category		
18 29 years old	REF	REF
30 39 years old	1.41	0.57 3.50
40 50 years old	0.78	0.26 2.35
50+ years old	0.56	0.15 2.03
Sex		
Female	REF	REF
Male	0.68	0.32 1.44
Race category		
Non Hispanic White	REF	REF
Black/African American	**0.23**	**0.06 0.84**
Asian	1.00	
Hispanic	1.63	0.51 5.23
Other/Native American/Hawaiian/mixed race	1.10	0.21 5.69
Race unknown	0.80	0.24 2.67
Prior psychiatric history	1.93	0.92 4.05
Received naloxone	1.37	0.52 3.61

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ED, emergency department; REF, reference category. Variables in **bold** were statistically significant.

outcomes for ED patients with illicit opioid overdose were significantly less severe in those testing positive for xylazine compared to those testing negative for xylazine. Additionally, high rates of cardiac arrest (11.5% of patients analyzed) and high total naloxone requirements (3.68 mg xylazine vs. 2.8 mg non-xylazine) were observed. Importantly, almost all xylazine patients had fentanyl/fentanyl analogs detected rather than heroin. These findings are consistent with recent reports describing a strong association between xylazine detection and fentanyl analogs in the illicit drug supply [9,17,21,22].

Our findings of lower odds of cardiac arrest and coma among xylazine-adulterated opioid overdoses are consistent with and build upon prior studies. Previously, commonly described xylazine overdose clinical effects included CNS depression, bradycardia, and hypotension [10,27,28]. Xylazine overdose case reports have described respiratory depression, hyperglycemia, and hypotonia [27,29]. With supportive treatment, most patients recover from xylazine intoxication [27]. In our study, the mortality rate overall was low, and most patients in both groups were discharged from the ED. Both groups had similar initial ED vital signs, and there was no difference in rates of bradycardia. These findings may be explained by the increasing presence of adulterants, contaminants, and other substances in illicit opioids.

In the present study, there remains a question of whether xylazine was an adulterant or desired component of the illicit opioid supply. Adulterants are pharmacologically active substances added to mirror or enhance specific drug effects [30] and have been well-described in illicit drug supply studies. Adulterants in heroin have included scopolamine [31] and quinine [32,33], and more recently clenbuterol [34,35] and

novel synthetic opioids [36,37]. Recent reports have described the adulterant role of xylazine as one that improves and prolongs opioid-associated euphoria [9].

The explanation for the findings associated with xylazine-adulterated opioids remains elusive. Xylazine does not cause the same degree of respiratory depression as opioids, especially fentanyl. It is possible that a drug sample containing both xylazine and an opioid may result in exposure to a lower opioid concentration. Alternatively, other adulterants, contaminants, or novel psychoactive substances in patients' illicit opioid products may account for lower cardiac arrest and high ED discharge rates. Finally, it is possible that patients without xylazine exposure were exposed to higher total opioid amounts.

Despite similar mortality rates between groups, the xylazine group had significantly lower adjusted odds of cardiac arrest. Cardiac arrest following opioid overdose is mechanistically preceded by respiratory arrest, leading to hypercarbia, respiratory acidosis, and cardiovascular collapse. In pre-hospital settings, CPR initiation may be triggered by bystanders or emergency medical services for an apneic patient. Respiratory depression from xylazine is markedly less severe than that from opioids. Thus, the xylazine group may have had decreased risk of severe respiratory depression, and account for the lower odds of cardiac arrest.

Patients with detectable xylazine and an illicit opioid had approximately half the rate of coma within 4 h of ED arrival. Due to the alpha-2 adrenergic agonist effects of xylazine, we hypothesized that the xylazine group would have a higher likelihood of developing early coma. Several factors may contribute to these results. The amount of xylazine contained in a sample may cause mild clinical CNS effects. Most case reports of xylazine exposure associated with hemodynamic or severe CNS depression/coma have described large, single-agent exposures. Also, the combination of insufficient xylazine and decreased total opioid concentration may have led to lower overall rates of coma.

Interestingly, all patients had relatively high total naloxone requirements (3.68 mg xylazine vs. 2.8 mg non-xylazine), but there was no significant difference in initial or total naloxone doses received between the groups. We hypothesized that patients in the illicit opioid only group might receive a higher total naloxone dose or more frequent repeat naloxone dosing, due to the opioid dose received or high potency of fentanyl/nitazene analogs. Again, the presence of other adulterants or contaminants may have limited the patient's total opioid exposure. Alternatively, patients in the xylazine-opioid group may have received more naloxone due to mild xylazine-related CNS depression, which could be mistaken for opioid-related CNS depression. If ED clinicians are titrating naloxone to reverse CNS depression, frequent repeat dosing may result.

Finally, there was no association between the xylazine group and ED length-of-stay or hospital admission. Most patients in both groups were discharged from the ED. Several clinical care factors may explain this finding. The relative concentration of xylazine in a drug sample and subsequently small hemodynamic or CNS changes are easily managed with ED resuscitation, such as intravenous fluids, and standard ED observation times. Also, because xylazine is an increasingly prevalent adulterant, ED clinician disposition decision-making is likely guided by opioid and naloxone pharmacokinetic knowledge, and without consideration to monitor for the potential clinical effects of xylazine. Because the human half-life of xylazine is not known, it is difficult to assess if the pharmacokinetics are related to patient length-of-stay.

Limitations of the present study require some consideration. Waste clinical specimens were not available for a large proportion of patients screened, leading to a large number of exclusions; this likely contributed to a higher overall overdose severity for patients included. Many screened patients did not have blood samples obtained in the ED, and patients who had blood work performed may represent a skewed overdose population. Blood sampling provided qualitative detection only; because quantitative serum concentrations were not measured, and opioid concentrations were not adjusted for, it is fraught to infer causality. Additionally, we do not know the relative timing of substance use; therefore, it is possible, though unlikely, that the presence of xylazine represented a prior drug exposure.

Because this study focused on ED patients, pre-hospital fatalities which were pronounced in the field were not examined; however, there were many cardiac arrests in the field which were successfully resuscitated and survived to hospital discharge. Lastly, given the severity of the US opioid epidemic, the study regions may limit generalizability especially to international locations. All participating ToxIC sites were located in large cities, and findings may not be applicable to rural communities.

Future studies should focus on measuring illicit opioid and xylazine serum concentrations to evaluate if relative serum concentrations of opioids, xylazine or other adulterants predict clinical effects and patient outcomes. Additionally, antidotal naloxone use to reverse xylazine toxicity is theoretically plausible [38] but its efficacy is understudied.

Conclusions

In summary, in this large multicenter cohort study, ED patients with illicit opioid overdose testing positive for xylazine had significantly lower odds of cardiac arrest and coma. Confirmed illicit opioids consisted mostly of fentanyl and fentanyl analogs, rather than heroin. Overall rates of cardiac arrest and total naloxone dosing following acute opioid overdose were relatively high, consistent with the high prevalence of potent fentanyl and fentanyl analogs detected.

Author contributions

AFM, ML, KA, JB, AJK, BKL and PW conceptualized the study. AFM was primarily responsible for funding acquisition. AJK, BKL and SEW were responsible for toxicologic specimen data analysis and acquisition, while KA, AFM and the ToxIC study group were responsible for clinical data acquisition. JSL, ML, CVT and AFM conducted formal data analysis. JSL and ML wrote the original manuscript draft, and all authors were responsible for manuscript review and editing.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Xylazine is an agonist at kappa opioid receptors and exhibits sex-specific responses to opioid antagonism

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ABSTRACT

Xylazine is in the unregulated drug supply at increasing rates, usually combined with fentanyl, necessitating understanding of its pharmacology. Despite commentary from politicians, and public health officials, it is unknown how xylazine impacts naloxone efficacy, and. few studies have examined it alone. Here, we examine the impact of xylazine alone and in combination with fentanyl on several behaviors in mice. Surprisingly, naloxone precipitates withdrawal from xylazine and fentanyl/xylazine coadministration, with enhanced sensitivity in females. Further, xylazine is a full agonist at kappa opioid receptors, a potential mechanism for its naloxone sensitivity. Finally, we demonstrate surprising effects of xylazine to kappa opioid antagonism, which are relevant for public health considerations. These data address an ongoing health crisis and will help inform critical policy and healthcare decisions.

One-sentence summary: We present surprising new insights into xylazine and fentanyl pharmacology with immediate implications for clinical practice and frontline public health.

Introduction

Human exposure to the veterinary anesthetic xylazine has been reported intermittently in Spain [1], Germany [2], Canada [3], and the United States [4,5] since the 1970s, often associated with occupational exposure or intentional self-administration. Sustained use of the liquid veterinary formulation for euphoric effect was documented in Puerto Rico starting around 2001 [6], with sporadic detection in seized street drugs first on the east coast of the United States mainland from 2006 onwards, and in California for at least the last 4 years [7,8]. The complex interplay between illicitly manufactured xylazine, heroin, fentanyl, and methamphetamine supply can be traced to power shifts among drug trafficking organizations, exacerbated by international drug control policies; overseas chemical manufacturers have responded to demand for fentanyl alternatives driven by consumer dissatisfaction with the potent opioid [1,6,7,9,10]. Currently, xylazine is predominantly found in powder forms of unregulated street drugs in many (but not all) regions of the United States, and mostly (but not exclusively) with illicitly manufactured fentanyl [6,7,11]. In recognition, the federal government designated "fentanyl adulterated or associated with xylazine" as an emerging drug threat in April 2023 [7]. However, xylazine and fentanyl co-exposure is not an exclusively American phenomenon: the earliest documented xylazine-fentanyl co-ingestion was accidental in a farmworker in New Zealand in 1984 [12], and a xylazine-fentanyl-heroin overdose death was reported in the United Kingdom in 2023 [13]. Clinical management of human xylazine exposure is made difficult by

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disfiguring and lingering skin ulcers, a distinctive agitated withdrawal syndrome, and lack of approved antidote or withdrawal support medications [14,15]. Ultimately, the limited pharmacological understanding of xylazine, in conjunction with the lack of an approved antidote, has hampered effective clinical responses to this emerging threat [16].

Despite having similar sedative effects, fentanyl and xylazine previously have been thought to act on distinct G protein-coupled receptors (GPCRs). Xylazine purportedly acts on the alpha-2-adrenergic receptor (α_2-AR) whereas fentanyl engages mu, kappa, and delta opioid receptors (μOR, κOR, δOR respectively). As xylazine has been increasingly found in the unregulated drug supply, there have been reports of worsened overdoses attributed to mixtures of fentanyl and xylazine [17–19]. A general assumption has been that due to the presence of xylazine, these overdoses are not as responsive to naloxone [10,20], an opioid receptor antagonist used to alleviate respiratory depression induced by opioids. Some evidence has indicated, however, that xylazine may also act on other receptors [21], though it has not been thoroughly tested *in vitro* nor *in vivo* until now.

Preclinical veterinary research has largely focused on xylazine's sedative effects in combination with ketamine [22,23], and few studies have investigated xylazine alone or in the context of reward learning [24–26]. Additionally, these studies did not account for locomotor effects and the potential sedation induced by α_2-AR agonists which could impede learning mechanisms in rodent models. Recently, Khatri et al. found that xylazine depressed fentanyl self-administration in male and female rats [27]. However, α_2-AR agonists (e.g. clonidine), despite being commonly used to treat opioid withdrawal, may have reinforcing potential themselves [28–36]. Here, we sought to better understand the effects of xylazine alone and determine if it alters the fentanyl-withdrawal experience in both male and female C57BL/6J mice.

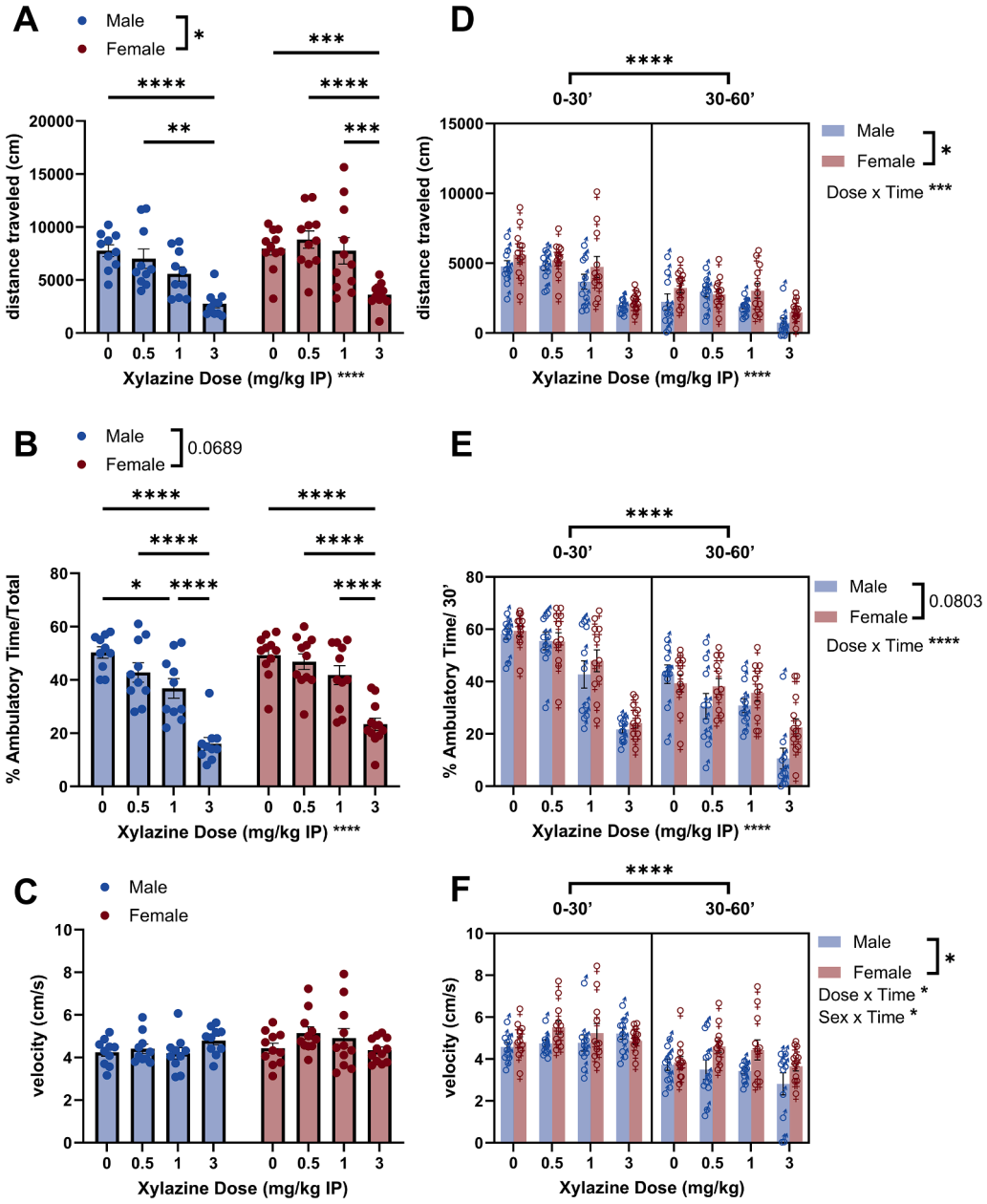

Fig. 1. Effect of acute IP xylazine administration on locomotor activity. (A) Cumulative distance traveled, (B) % ambulatory time, and (C) average velocity of male and female mice administered saline or xylazine (0.5, 1.0, or 3.0 mg/kg). (D) Distance traveled, (E) % ambulatory time, and (F) velocity split into 30 min bins. (D-F) 3-way ANOVAs (Time x Sex x Dose).

Results

Identification of non-sedative doses of xylazine

Few studies in mice have investigated the sedative effects of xylazine administered alone (i.e., without the addition of ketamine or other anesthetics) [24]. Because sedation alters locomotor activity and learning, it is necessary to determine a non-sedative dose for use in behavioral experiments. Typically, a 10 mg/kg IP dose of xylazine is used with ketamine for anesthesia [22,23]. Previous studies have tested doses as low as 2.5–3 mg/kg IP [24,25] We tested a lower range of 0, 0.5, 1, and 3 mg/kg xylazine on locomotor behaviors. We found that 3 mg/kg IP xylazine resulted in decreased distance traveled in both males and females compared to saline (males: $p < 0.0001$; females: p 0.0003) and 0.5 mg/kg (males: p 0.0011; females: $p < 0.0001$), and in females compared to 1 mg/kg (p 0.0006; Fig. 1A). A dose of 3 mg/kg IP also decreased the % ambulatory time compared to the other three doses in both males (3 vs. 0: $p < 0.0001$; 3 vs. 0.5: $p < 0.0001$; 3 vs. 1: $p < 0.0001$) and females (3 vs. 0: $p < 0.0001$; 3 vs. 0.5: $p < 0.0001$; 3 vs. 1: $p < 0.0001$; Fig. 1B). In males but not females, the 1 mg/kg dose decreased % time ambulating compared to saline (p 0.012; Fig. 1B). Additionally, none of the doses resulted in a significant reduction in the average velocity for either sex across the full 60 min trial, although there is a trend for interaction between sex and dosage (p 0.0915).

Xylazine's onset of action is estimated to be about 10–15 min and exploratory behavior naturally declines over time due to intrasession habituation. To examine the temporal effects of xylazine on locomotor activity, we further analyzed the data in both 30 min (Fig. 1D–F) and 10 min time bins (Fig. S1). As expected, distance traveled, % time ambulatory, and velocity generally declined across time for both male and female mice at all doses (male: $F_{(3.439,\ 123.8)}$ 86.89 $p < 0.0001$; female: $F_{(3.878,\ 159.0)}$ 82.40 $p < 0.0001$; Fig. S1A–C). Males and females differed in distance traveled and velocity (Fig 1D and F), possibly due to an interaction among time, sex, and dosage in the % ambulatory time ($F_{(3,\ 77)}$ 2.310 p 0.0829). Males were more sensitive to the sedative effects of xylazine as their locomotor activity took longer to recover to control levels compared to their female counterparts (S1 A-C). These data confirm that xylazine can exert sedative effects at doses as low as 1 mg/kg in male mice and 3 mg/kg in female mice. Our results reveal sex differences in the time course and recovery from the sedative effects of xylazine. In subsequent experiments, we chose to proceed with 0.5 mg/kg xylazine because it was non-sedative in all measures of both sexes (Fig. 1).

Naloxone- and atipamezole-precipitated withdrawal

Withdrawal from reinforcing substances is a critical component of the addiction cycle [37–39] and xylazine withdrawal has been reported to be particularly severe [14,15]. Previously, we and others have used repeated precipitated morphine withdrawal models to demonstrate that somatic symptoms exacerbate across withdrawal sessions and that interrupted opioid exposure drives behavioral and physiological correlates of addiction [40–45]. Our model emphasizes that the experience of exacerbated withdrawal from low to moderate doses of drug promotes physiological and behavioral adaptations. We have shown that this model results in sleep disturbances, and promotes long-lasting sex-dependent behavioral adaptations in both male and female mice over six weeks into forced abstinence [40,46]. Here we adapted our withdrawal model to fentanyl withdrawal and explored if fentanyl/xylazine co-administration would impact the development and severity of the withdrawal syndrome. We hypothesized that xylazine could potentiate withdrawal from fentanyl and thus we chose doses of fentanyl and xylazine that we did not anticipate would result in maximal withdrawal responsivity in an effort to capture potential synergism. Male and female mice were administered (IP) either saline (equivolume), fentanyl (0.1 mg/kg), xylazine (0.5 mg/kg), or a coadministration of fentanyl/xylazine (0.1 and 0.5 mg/kg respectively). Two hours later, mice received an injection of either naloxone (1 mg/kg SC) or atipamezole (1 mg/kg SC, an α_2-AR antagonist used by veterinarians to reverse xylazine anesthesia; Fig. 2A). We report our data both as z-scores (Fig. 2, S2) of withdrawal symptoms to eliminate the weighting of one symptom over others, and as individual behaviors (Fig. S7)

Surprisingly, and in contrast to the conventional concept that 'xylazine is not affected by naloxone', we found that female mice treated exclusively with xylazine demonstrated significant global somatic withdrawal scores (shown as z-scores, $F_{(1,36)}$ 10.80, p 0.0023, individual withdrawal behaviors Fig. S7 [47]) following naloxone administration, which sensitized over three days (Fig. 2B and C). Indeed, across the 3-day paradigm, xylazine withdrawal was of equal severity to fentanyl withdrawal in females (Day 1: $p > 0.9999$, Day 2: p 0.9948, Day 3: p 0.9622; Fig. 2B). Compellingly, female mice showed the most exacerbated somatic withdrawal when fentanyl and xylazine were combined (Day 3: FX vs. F p 0.0925, FX vs. X p 0.0652, FX vs. S $p <$ 0.0001; Fig. 2B). Male mice, however, demonstrated the highest withdrawal scores to fentanyl alone (Day 3: F vs. X p 0.0026, F vs. S p 0.0002), and the fentanyl/xylazine coadministration did not alter the degree of withdrawal experienced (F vs. FX p 0.9948; Fig. 2). We also considered that the sexes and treatment groups might experience different types of somatic withdrawal symptoms. To assess this, we plotted the average z-score for each individual behavior on withdrawal day 3 (Fig. 2, individual scores Fig. S7). Interestingly, the most robust withdrawal symptom for both sexes observed was paw tremors in the fentanyl/xylazine coadministration group. Regardless, females exhibited multiple withdrawal behaviors that were enhanced in the fentanyl/xylazine coadministration group as compared to either the fentanyl or xylazine groups. In both sexes, the addition of xylazine decreased the fecal boli count relative to the fentanyl group (Female FN vs XN p 0.0258, Male FN vs. XN p 0.0028; Fig. 2C). Males displayed a more robust increase in escape jumps due to the fentanyl/xylazine coadministration than females (Female FXN vs XN p 0.7992 and vs. SN p 0.6186, Male FXN vs. XN or SN p 0.0160), but females saw increases in wet dog shakes and abnormal posture between fentanyl/xylazine and fentanyl (Female FN vs XN p 0.0258, Male FN vs. XN p 0.0028; Fig. 2C).

We were surprised to observe that atipamezole was able to induce precipitated withdrawal behaviors from animals exposed to fentanyl alone although without significant sensitization across days (Males-Day 1 vs Day 3: p 0.0829; Females-Day 1 vs. Day 3: p 0.2232). Females exhibited similar levels of withdrawal in fentanyl, xylazine, and fentanyl/xylazine groups in response to atipamezole (Fig. 2D). Males showed reduced atipamezole-induced withdrawal overall compared to females. Interestingly males responded similarly to xylazine and fentanyl (Day 3: $p > 0.9999$), but the coadministration of the two attenuated the effects. Finally, female mice, but not males showed withdrawal symptom sensitization to saline-atipamezole over the three days (Fig. 2D).

These data indicate a hyposensitivity of males to xylazine compared to females (at this dose) and that female responses to fentanyl withdrawal can be enhanced by the addition of xylazine. Further, female mice exhibited increased sensitivity to the α_2-AR antagonist in comparison to males, indicating a sex difference in adrenergic systems. Importantly, the atipamezole data did not replicate the results we observed with naloxone (especially in female mice) suggesting that the naloxone mediated effects were not due to displacement of xylazine from α_2-ARs.

Male and female mice exhibit differential c-Fos expression following naloxone-precipitated withdrawal

To begin to probe which brain regions may be differentially activated in the male and female mice following naloxone precipitated withdrawal, we focused on nodes that have been implicated in reward/habit, withdrawal related behaviors, negative reinforcement, and those that

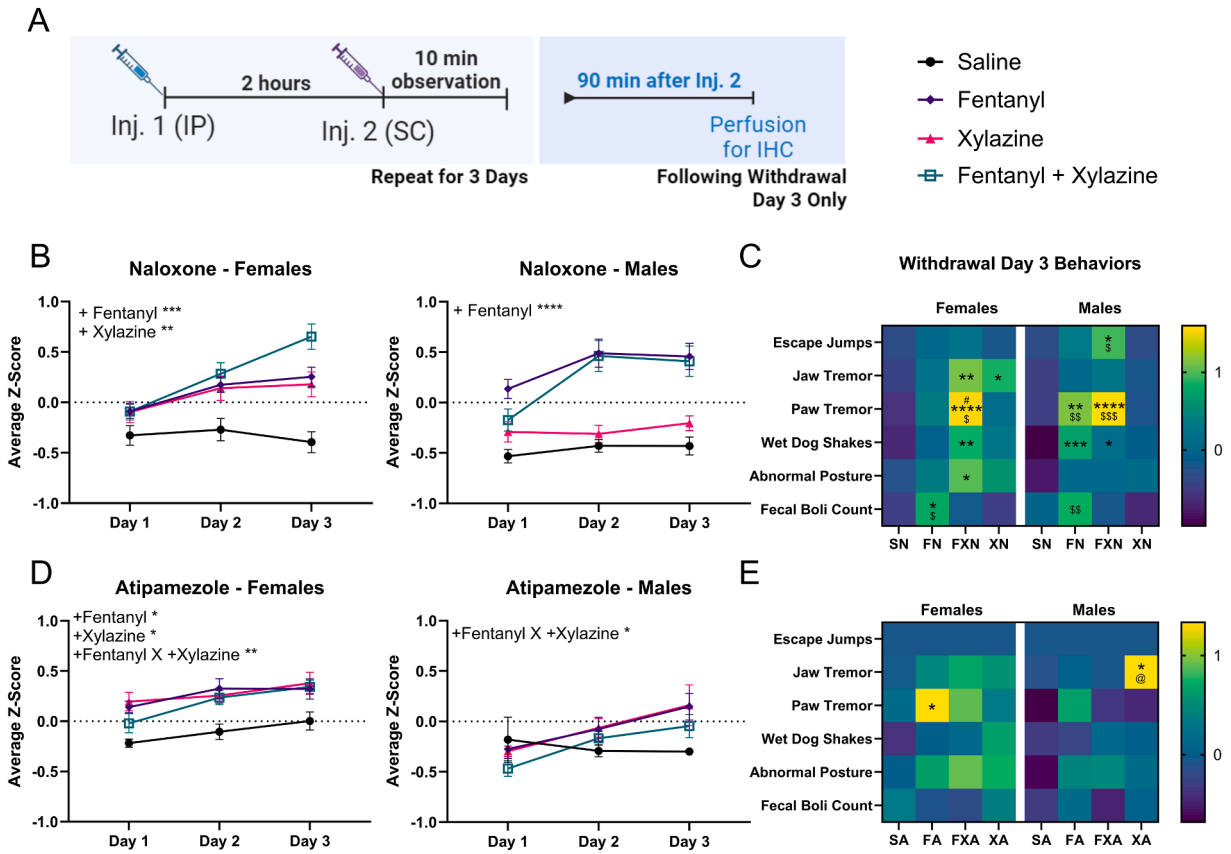

Fig. 2. Naloxone- and atipamezole-precipitated withdrawal. (A) 3-day precipitated withdrawal paradigm. Global scores are shown as average z-score ± SEM. (B) Average z-scores of female and male mice over three days of naloxone-precipitated withdrawal. (C) Heatmap of average z-scores on day three of withdrawal for individual behaviors. (D) Average z-scores of female and male mice over three days of atipamezole-precipitated withdrawal. (E) Heatmap of average z-scores on day three of atipamezole-precipitated withdrawal for individual behaviors. (B&D) 3-way ANOVAs (Day X Addition of Fentanyl X Addition of Xylazine) $P = 0.05$*, 0.01**, 0.001***, 0.0001****. Main effects p-values and Tukey's post-hoc shown in Fig. S2. (C&E) 2-way ANOVAs (Tx Group X Behavior) with Tukey's post-hoc, $P = 0.05$ where * (vs. saline), # (vs. fentanyl), @ (vs. fentanyl/xylazine), and $ (vs. xylazine). SN=saline-naloxone; FN=fentanyl-naloxone; FXN=fentanyl/xylazine-naloxone; XN=xylazine-naloxone; SA=saline-atipamezole; FA=fentanyl-atipamezole; FXA=fentanyl/xylazine-atipamezole; XA=xylazine-atipamezole.

contain norepinephrine or receive dense norepinephrine innervation [37]. 75–90 min following naloxone administration on the final day of withdrawal, mice were perfused for immunohistochemistry. Expression of the immediate early gene, c-Fos was indexed as a measure of activity [48,49]. We analyzed c-Fos levels in brain regions implicated in opioid use disorder that receive input from the locus coeruleus, one of the largest sources of noradrenaline in the brain[50]. Within the regions analyzed, significant differences between treatment groups were observed in the pontine locus coeruleus (LC) region, dorsal bed nucleus of the stria terminalis (dBNST), dorsal medial striatum (DMS), and lateral central nucleus of the amygdala (lCeA) in females, but only in the LC region, DMS, and basolateral amygdala (BLA) in males (Fig. 3).

LC regional c-Fos expression was significantly higher in female mice that received fentanyl alone and xylazine alone compared to female mice that received saline (Fig. 3A). Intriguingly, male mice that received xylazine alone and the fentanyl/xylazine coadministration had significantly higher c-Fos expression than the male mice that received only fentanyl (Fig. 3A). In both sexes, the three treatment groups exhibited significantly higher c-Fos expression than the mice that received saline (Fig. 3).

Female mice displayed significant c-Fos expression differences in a few additional regions of interest. In the dBNST, the female mice that received the coadministration had significantly higher c-Fos expression compared to the female mice that received fentanyl alone. Interestingly, no differences were observed between the saline mice and those that received xylazine, suggesting a dBNST effect that is driven primarily by fentanyl administration (Fig. 3A). Differences in c-Fos expression within the lCeA were also observed in female mice, wherein the coadministration displayed significantly greater c-Fos expression than saline and xylazine groups. In the DMS, the coadministration resulted in increased c-Fos compared to all other female treatment groups and compared to the male coadministration group (Fig. 3A).

In the BLA, males that received fentanyl alone displayed significantly greater c-Fos expression than those that received any other treatment and the coadministration group reduced c-Fos expression to saline levels (Fig. 3A). Fentanyl also increased c-Fos in the DMS of males compared to saline.

Characterization of xylazine pharmacology

Xylazine is canonically believed to be an α_2-AR agonist, though its binding and functional activity at different receptors have not been systematically tested. Because our withdrawal data suggested that xylazine may be targeting other receptors we tested xylazine (10 μM) across a host of common drug targets for radioligand binding activities. Xylazine inhibits radioligand binding by 50 % or more at α_2-ARs, as well as 5-HT_7 serotonin receptor (5-HT_{7A}R), kappa opioid receptor (κOR), sigma 1 receptor (σ1R), and sigma 2 receptors (σ2R) (Fig. S3). We also tested xylazine in the PRESTO-tango GPCRome screen for potential agonist activity at 320+ human GPCRs. These data indicated xylazine (10 μM) activates α_2-ARs as expected, κOR as well as D2 dopamine receptor (Fig. S4). These binding and functional results at the κOR were validated in additional assays. Xylazine was able to completely displace a radiolabeled κOR agonist ^{3}H-U69593 with a submicromolar binding

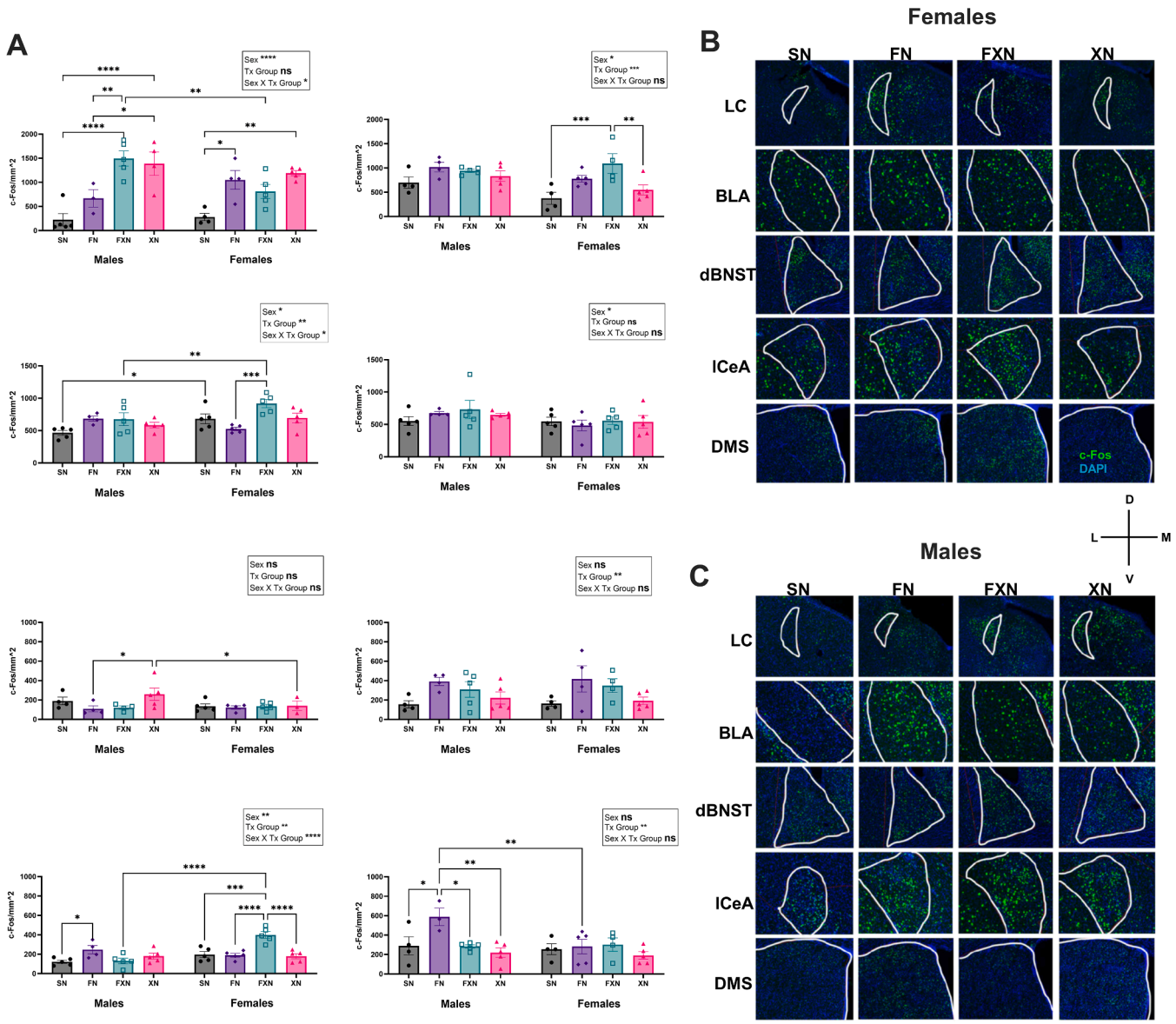

Fig. 3. Quantification of c-Fos expression following naloxone-precipitated withdrawal. (A) Female and male c-Fos expression displayed as number of positive cells per mm2 in various regions of interest. (B) Representative images of female regions of interest. (C) Representative images of male regions of interests. (A) 2-way ANOVAs (Tx group X Sex) with Tukey's post-hoc. $P = 0.05$*, 0.01**, 0.001***, 0.0001****.

affinity (Fig. 4A, pK_i 6.33 ± 0.02, K_i 0.47 μM). Xylazine showed agonist activity only at the κOR, not the μOR or δOR opioid receptors as shown in concentration response curves (Fig. S4 D–F). A Gi-GloSensor assay demonstrated that xylazine acts as a full agonist at the κOR with a potency of 1.4 μM (pEC_{50} of 5.86) and was as efficacious (although less potent) as the naturally occurring κOR agonist, salvinorin A (Fig. 4C), as well as a full agonist with a potency of 34 nM at α_{2A}-AR as expected (Fig. 4D: pEC_{50} of 7.47). The pK_i values for all competition binding assays can be found in Supplemental Table 1. Potency and efficacy values can be found in Supplemental Table 2. Xylazine was also screened against 97 human kinases in the KINOMEScan™ profiling assays (Eurofins) and results showed that at 10 uM it had little or no inhibitory activity at any tested kinases (supplementary excel sheet).

The major metabolites of xylazine, 3-hydroxy- and 4-hydroxy-xylazine [51,52], were also tested for activity in GPCRome agonist activity screening, and at μOR, δOR, κOR, nociception receptor, and D2R (Figs. 4 and S4,5). Xylazine and both metabolites showed Gi agonist activity at κOR but not the other opioid receptors in these assays. 3-hydroxy-xylazine was as efficacious, though less potent, as xylazine and salvinorin A. 4-hydroxy-xylazine was less efficacious at κOR overall. As these functional assays could over-estimate agonist activity due to the signal amplification nature of the assays, we turned to Bioluminescence Resonance Energy Transfer 2 (BRET2) assays (TRUPATH [53]) to identify potential bias activity among inhibitory G proteins (G_{i1}, G_{oA} and G_z) and β-arrestin signaling pathways by xylazine and the metabolites. Xylazine and 3-hydroxy-xylazine showed similar activation of κOR, G_{i1} and G_{oA}, G_z pathways while 4-hydroxy showed no activity (Fig. 4E, G, I). Xylazine, its metabolites, as well as other relevant adrenergic agonists exhibited agonist activity at α_{2A}-AR G_{i1}, G_{oA}, and G_z (Fig. 4F, H, J). Interestingly, xylazine and the metabolites showed no activity in ß-arrestin 1 (Fig. S5G) or ß-arrestin 2 recruitment (Fig. 4K). Xylazine and the metabolites also had minimal α_{2A}-AR ß-arrestin 2 recruitment activity, though slightly more efficacious than at κOR (Fig. 4L). Importantly, these are the first findings to our knowledge indicating xylazine and 3-hydroxy-xylazine are both G protein biased agonists at κOR and α_{2A}-AR.

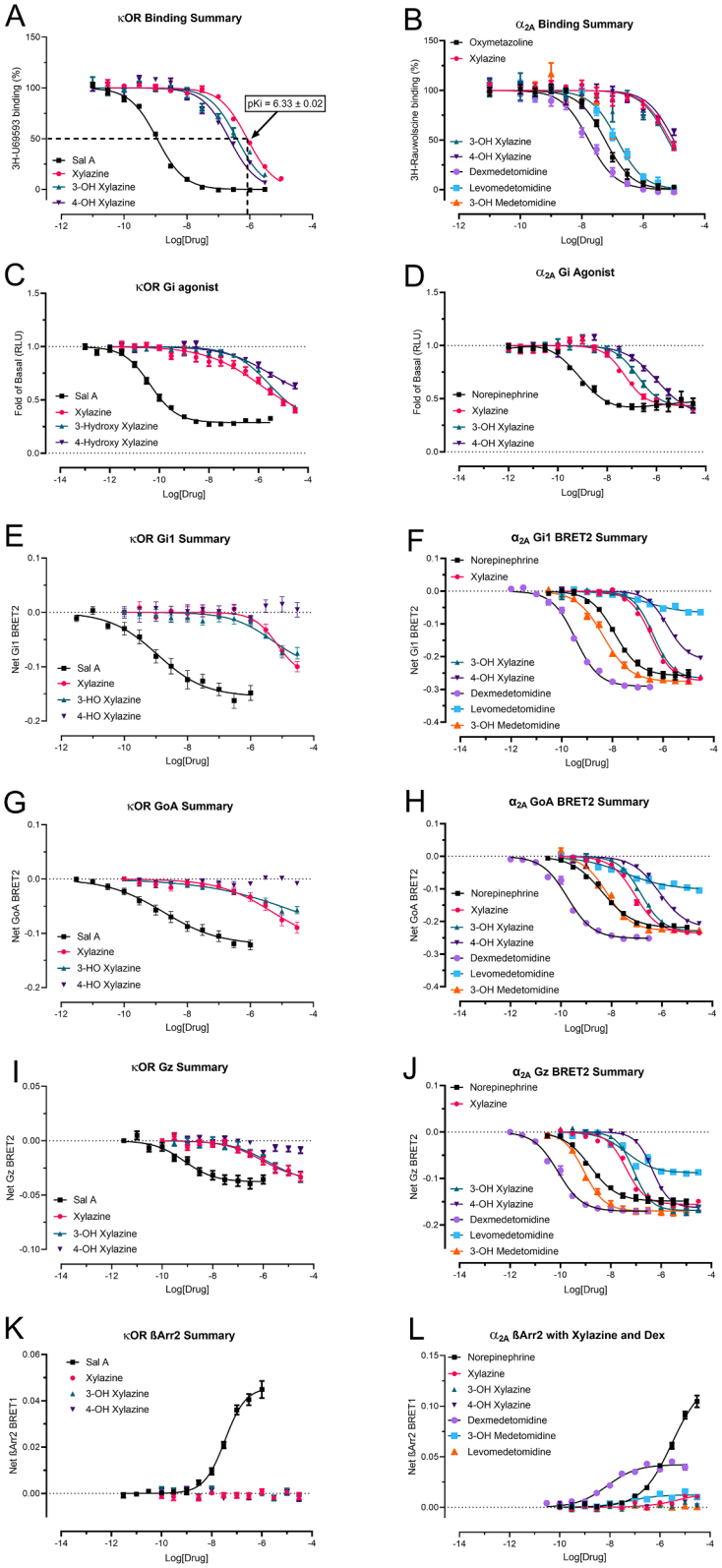

Fig. 4. Xylazine acts as a G-protein biased agonist at κOR and α_{2A}-AR. (A-B) Radioligand competitive binding assay confirms xylazine activity at κOR (A) and α_2-AR (B), shown with known reference agonists. (C-D) Gi-GloSensor cAMP assays at κOR (C) and α_2-AR (D). (E-L) TRUPATH BRET2 assays for Gi1 (κOR (E) and α_2-AR (F)), GoA (κOR (G) and α_2-AR (H)), Gz (κOR (I) and α_2-AR (J)), and Barr2 (κOR (K) and α_2-AR (L)).

Assessment of potential for therapeutic benefit of κOR-antagonism

Following identification of xylazine as an agonist at the κOR, we tested the ability of the κOR-selective antagonist nor-binaltorphimine (nor-BNI) to mitigate withdrawal symptoms. Given nor-BNI's long lasting effects due to receptor modification/inactivation [54–56], mice were injected with fentanyl, xylazine, the combination, or saline for three consecutive days. On the third day only, mice were injected with nor-BNI and withdrawal was scored for the next 10 min (Fig. 5A). There was a main effect of treatment group regardless of sex ($F_{(3,112)}$ 3.614, p 0.0155; Fig. 5C). Additionally, there was a main effect of sex in which female mice exhibited increased withdrawal z-scores compared to males ($F_{(1,112)}$ 38.79, $p < 0.0001$; Fig. 5C). These differences were significant in the saline (p 0.0019), fentanyl (p 0.0004), and fentanyl/xylazine (p 0.0001) conditions, but only trending in the xylazine condition (p 0.0988; Fig. 5C). Female fentanyl mice demonstrated a range of different withdrawal behaviors but exhibited increased instances of abnormal posture compared to the xylazine alone females (p 0.0262; Fig. 5D).

Given the sex differences in nor-BNI-precipitated withdrawal, we also investigated the ability of nor-BNI to alter the naloxone-precipitated withdrawal experience (Fig. 5B). We hypothesized that pretreatment with nor-BNI 7-days prior to drug exposure might mitigate the severity of xylazine withdrawal we previously saw in female mice. Both sexes showed a main effect of day (Females: $F_{(1.563, 26.56)}$ 4.738, p 0.0242; Males: $F_{(1.436, 25.85)}$ 47.05, $p < 0.0001$), while males also showed an interaction of day and pretreatment group ($F_{(2, 36)}$ 3.823, p 0.0312; Fig. 5E). Surprisingly, female mice who received nor-BNI 7 days prior to the withdrawal paradigm had higher withdrawal z-scores by day 3 than mice who were pretreated with saline (p 0.0389; Fig. 5E). Despite showing cumulative differences in withdrawal z-scores, there were no post-hoc differences between pretreatments in specific behaviors (Fig. 5F).

Discussion

Cycles of drug exposure and withdrawal are critical to the development of substance use disorders [37,38]. The increase of xylazine in the North American drug supply in recent years prompts the need to understand how xylazine may interact both alone and in conjunction with fentanyl to alter behavioral and physiological responses. Here, we report the first xylazine dose-response locomotor study in male and female mice as well as the first assessment of adrenergic- and opioid-receptor antagonist-precipitated withdrawal symptoms following, xylazine, fentanyl, and xylazine/fentanyl administration in mice. These experiments

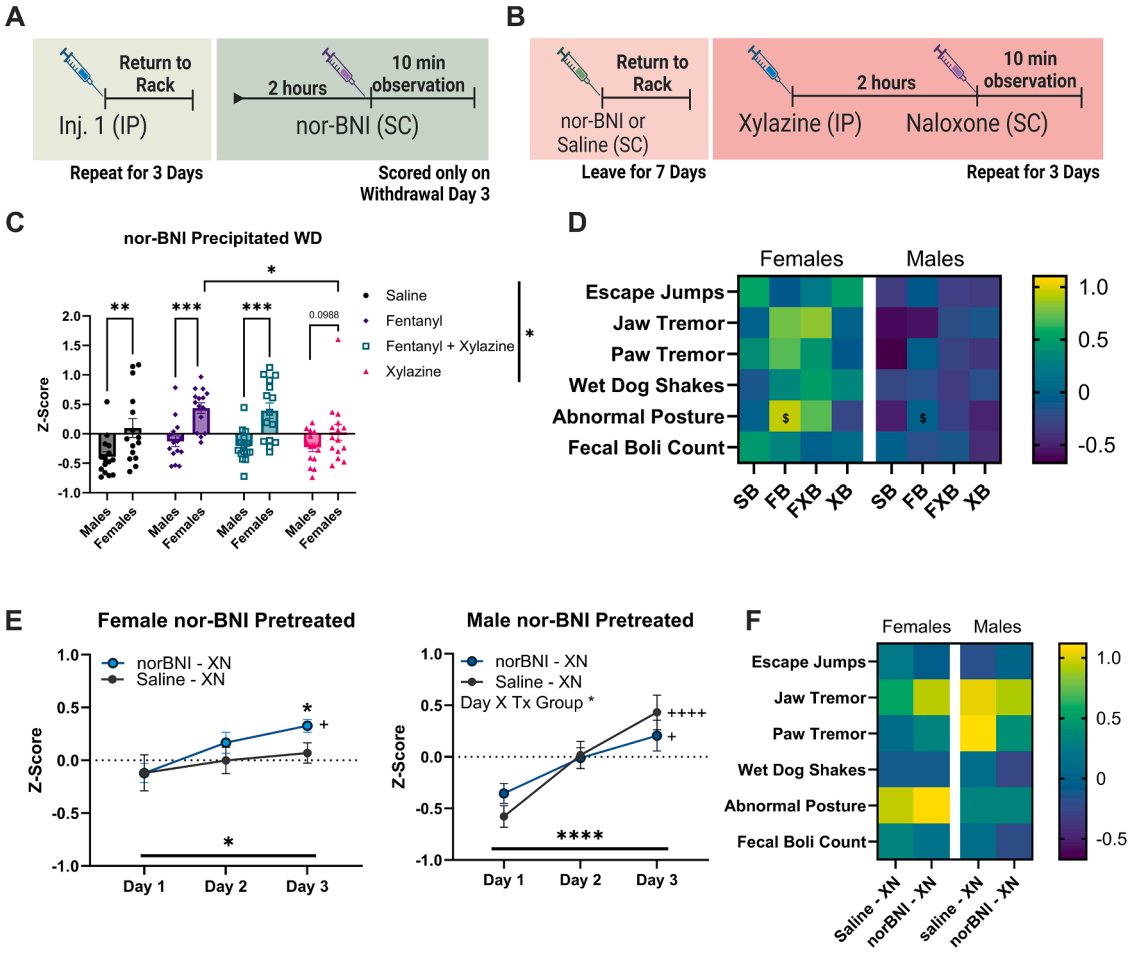

Fig. 5. Female mice exhibit increased responses to kOR antagonism. (A) nor-BNI-precipitated withdrawal paradigm. Mice received agonist injections for 3 days and nor-BNI 2 h later only on the 3rd day. (B) nor-BNI pretreated withdrawal paradigm. Mice received nor-BNI or saline 7 days prior to xylazine and naloxone-precipitated withdrawal. (C) Average z-score of nor-BNI precipitated withdrawal for female and male mice. 2-way ANOVA (Treatment Group X Sex) (D) Average z-score of nor-BNI pretreated naloxone withdrawal for individual behaviors. (E) Average z-score of nor-BNI pretreated naloxone withdrawal for female and male mice across 3 days. 2-way ANOVAs (Day X Pretreatment Condition). Tukey's post-hoc Day 1 vs Day 3: $P = P = 0.05^{+}$, 0.01^{++}, 0.001^{+++}, 0.0001^{++++}. (F) Average z-score of nor-BNI pretreated naloxone withdrawal for individual behaviors on day 3. $P = 0.05$*, 0.01**, 0.001***, 0.0001****. Main effects p-values and Tukey's post-hoc shown in Fig. S6. (D & F) 2-way ANOVAs (Tx Group X Behavior) with Tukey's post-hoc, $P = 0.05$ where * (vs. saline), # (vs. fentanyl), @ (vs. fentanyl/xylazine), and $ (vs. xylazine). XN=xylazine-naloxone; SB=saline-nor-BNI; FB=fentanyl-nor-BNI; FXB=fentanyl/xylazine-nor-BNI; XB=xylazine-nor-BNI.

show that male and female mice are differentially sensitive to xylazine. We find female mice are less sensitive to the motor-suppressing effects of xylazine contrary to the recent findings in rats reported by Khatri et al. (2023), potentially due to their use of repeated dosing of xylazine or species differences [27]. Using a modified version of our 3-day precipitated withdrawal model [40,41,46], we show xylazine is indeed responsive to naloxone, contrary to common assumptions made by both health professionals and in the media [7]. Both sexes exhibited some level of somatic withdrawal behaviors to xylazine and naloxone, though females showed sensitized behavioral responding. Indeed, females appear to be as sensitive, if not more sensitive to xylazine withdrawal than fentanyl withdrawal at tested doses, while males remain much more responsive to fentanyl withdrawal conditions. At the doses tested in our study, the effect of naloxone precipitated withdrawal on xylazine/fentanyl combination was synergistic as compared to each drug in isolation. This was especially apparent when examining increased bouts of paw tremors, which may represent a more passive coping behavior that we have previously observed is sexually dimorphic in opioid withdrawal [41]. In contrast, we did not observe similar findings when withdrawal was precipitated by atipamezole, an α_2-AR antagonist used anesthesia reversal in veterinary medicine. These intriguing findings led us to consider the possibility of direct xylazine activity on opioid receptors. Previous studies have shown that xylazine is antinociceptive, results in a cross-tolerance to some mechanisms of opioid induced antinociception, and that these effects are naloxone-sensitive, but surprisingly not sensitive to the κOR selective antagonist nor-BNI [57–60]. Congruent with this data, we did not observe significant expression of withdrawal behavior to nor-BNI precipitated withdrawal, and pretreatment with nor-BNI exacerbated naloxone precipitated withdrawal in female mice. Until now, xylazine was thought to exert these effects through promotion of endogenous opioid release and xylazine has not been directly tested as a potential opioid agonist. We are the first to report definitive evidence that xylazine acts as a full agonist at κOR and is biased towards G-protein signaling pathways.

Xylazine has complex pharmacological targets

The synergism of xylazine and fentanyl on withdrawal behavior in female mice is intriguing also, because we and others have previously shown that α_2-ARs are subject to dysregulation by opioid administration [42,61]. As norepinephrine (NE) in the ventral noradrenergic bundle is critical for opioid reward learning [62], the activation of these critical circuits by both opioids and xylazine are targets for future experiments. These data, along with others [61,63], strongly suggest that there is extensive crosstalk between the α_2-AR and opioid receptor systems [42]. Because of this, it is critical to understand how, and if, effects are compounded when agonists target both α_2-AR and opioid receptors simultaneously. Indeed, recent studies examining hypoxia have demonstrated that combined treatment with atipamezole and naloxone reduces the prolonged oxygen deprivation induced by xylazine/fentanyl administration [64]. In contrast, only naloxone, and not the α_2-AR antagonist yohimbine, prevented fatal overdose by the combination [65]. Furthermore, we identified that sigma receptors are also impacted by xylazine. These intracellular receptors are known to complex with both opioid receptors and the dopamine transporter. Understanding how sigma receptors may compound with κORs in critical brain circuits for reward and withdrawal will be important to understand the impact of xylazine on addictive behaviors. When we tested the ability of atipamezole to evoke somatic withdrawal behaviors akin to precipitated opioid withdrawal, we found that again females were more responsive this manipulation, even showing withdrawal sensitization over days to saline-atipamezole alone. Despite potential differences in responsivity, we found that neither sex was sedated or showed decreased ambulatory activity at the selected dose of 0.5 mg/kg xylazine. Given evidence in the human population that women experience exacerbated withdrawal symptoms [66], and that female rats self-administer higher levels of fentanyl [67], future studies should consider the influence of sex differences on adrenergic and opioid system interactions.

Sex as a biological variable in adrenergic and opioid systems

Both the adrenergic systems and the κOR system are known to have sex differences in rodent models [68–71]. In our study we found sex differences in locomotion, precipitated withdrawal behavior, and in immediate early gene activation by withdrawal. Female rats are less sensitive to the depressive effects, and show differential c-Fos activation in the dBNST to κOR agonism when compared with male rats [72]. Here we also found that withdrawal from fentanyl/xylazine coadministration increased c-Fos in the dBNST of female but not male mice. It would be interesting to know which cell types in the dBNST were activated by each of these treatments. In clinical reports, women tend to report enhanced analgesia from mixed κOR/μOR agonists, while rodent models show males with enhanced analgesia to κOR agonism [73,74]. These differences may be partially explained by the melanocortin 1 receptor gene and sex differences as related to α-melanocyte-stimulating--hormone (α-MSH) release via κOR dependent mechanisms [75,76]. Here we demonstrated sex differences in responsivity to the κOR-antagonist, nor-BNI. Females showed significant withdrawal symptoms following nor-BNI injections under multiple treatment conditions, indicating an engagement of the kappa system that was not seen in males to the same degree. Pretreatment with nor-BNI resulted in exacerbated naloxone-precipitated withdrawal from xylazine in females, but not males. These results indicate that κOR-antagonism might be a beneficial addition to overdose and/or recovery treatments for some people, but could make withdrawal worse in others, promoting increased opioid administration due to negative reinforcement. Future studies will need to examine this circuitry with a more focused lens to determine the role of κOR and the adrenergic systems in mediating the response to fentanyl, xylazine and in combination.

Contextualizing our findings in the current public health emergency

Our findings carry important clinical and public health implications. Considering that xylazine is a full κOR agonist, we note two prominent historical and international examples of non-medical use of the κOR agonist pentazocine: the "Ts and Blues" (pentazocine and tripelennamine) outbreak in the midwestern United States from 1977 to 1981 [77–79], and pentazocine injection in Nigeria [80] and India [81–84]. In both settings, characteristic skin lesions beyond the site of injection, eschar formation, and wound cratering were observed [85–90], with morphological similarity [91] to reports involving xylazine from Puerto Rico [92], the Philadelphia area [9,93], and New Haven, Connecticut [94]. κOR distribution in human skin has led to its study as a therapeutic target [95–97], suggesting new directions for research into wound etiology. Separately, withdrawal symptoms specific to pentazocine include heightened anxiety, agitation, and paranoia [98]; these are also cited by clinicians and people who use drugs to be distinguishing presentations of xylazine withdrawal, increasing the difficulty of initiating medication assisted therapy for opioid dependence [14,99,100]. Further investigations are needed to establish if similarities to skin ulcers and withdrawal are coincidental or may be mediated in part by κOR. It is also worth noting that pentazocine, akin to xylazine, also targets sigma receptors. In addition, existing human pharmaceutical κOR agonists (pentazocine, butorphanol, nalbuphine) could be investigated immediately to alleviate xylazine withdrawal, which is difficult to manage in clinical settings [7]. Dexmedetomidine, another α_2-AR agonist approved for human use for other indications in the United States, could logically be considered a candidate medication to be investigated for its potentialto manage xylazine withdrawal, although it would be considered off-label at the current time. (Note: we are not endorsing off-label use.) Current public health and harm reduction messaging makes claims that naloxone is ineffective in reversing the effects of xylazine [7,101]. This

is problematic because this messaging may lead people to not use naloxone in an overdose scenario when xylazine is suspected in conjunction with fentanyl. In mice, we found that xylazine is responsive to naloxone both in cases where xylazine is administered alone, and in combination with fentanyl. While our findings do not address if xylazine impacts opioid-induced respiratory depression, nor if the presence of xylazine mediates naloxone's ability to rescue opioid-induced respiratory depression, they do suggest that more nuanced health messaging is warranted in community-based naloxone distribution settings. Opioid-induced respiratory depression is thought to be due to activity at μOR [102]. Our current data suggest a lack of direct xylazine activity at μOR, however, it is possible that although it has no direct effect on opioid-induced respiratory depression, crosstalk between the two systems or allosteric modulation of μOR might still play a role. The U.S. has seen a recent increase of overdose deaths in which xylazine was identified as contributory to death [103]; however attribution of causation by medical examiners is inconsistent in practice, and many states do not assay for or report xylazine when present in overdose [18]. Our findings suggest the urgent need to understand the mechanisms by which xylazine may be implicated in opioid-related overdose, with implications for reporting by forensic medical toxicologists. Our work, and others, seeks to bridge the gap in translatability to continue to provide meaningful animal models of contaminants in the drug supply, providing physicians and regulatory agencies with data to make rapid and effective decisions for public health.

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CRediT authorship contribution statement

Madigan L. Bedard: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Xi-Ping Huang:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jackson G. Murray:** Writing – review & editing, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Alexandra C. Nowlan:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Sara Y. Conley:** Writing – review & editing, Conceptualization. **Sarah E. Mott:** Validation, Methodology, Conceptualization. **Samuel J. Loyack:** Validation, Investigation. **Calista A. Cline:** Validation, Investigation. **Caroline G. Clodfelter:** Validation, Investigation. **Nabarun Dasgupta:** Writing – review & editing, Writing – original draft, Conceptualization. **Brian Krumm:** Conceptualization. **Bryan L. Roth:** Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Zoe A. McElligott:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

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Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.addicn.2024.100155.

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Drug and Alcohol Review

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ORIGINAL PAPER OPEN ACCESS

Emergence of Medetomidine in the Unregulated Drug Supply and Its Association With Hallucinogenic Effects

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ABSTRACT

Introduction: The unregulated drug supply in the United States is rapidly evolving, and veterinary tranquillisers have emerged as adulterants of concern, especially in illicitly-manufactured fentanyl. Following the proliferation of xylazine, medetomidine, a more potent sedative, has recently appeared in multiple US states. This study describes the characteristics of medetomidine samples from a national mail-based drug checking program and aims to determine whether medetomidine is associated with hallucinogenic effects.

Methods: We conducted a retrospective analysis of 11,363 drug samples between December 2022 and April 2025. Samples were sent voluntarily by people who use drugs. Participant-reported sensations and sample characteristics (e.g., colour, texture) were gathered at point-of-contact. Composition was analysed using gas-chromatography mass spectrometry. We estimated adjusted prevalence ratios for hallucinations in medetomidine-containing samples using generalised estimating equations.

Results: Medetomidine was identified in 278 samples (2.4%), with pronounced growth beginning June 2024. Medetomidine commonly appeared with fentanyl (58.8%) and/or xylazine (55.9%). Most samples were powders (85.3%). Among all 11,363 samples, those containing medetomidine in primary abundance ($n = 136$) were more likely to be associated with reported hallucinations (17.6%) compared to all other samples (1.2%; adjusted prevalence ratio: 11.95, 95% confidence interval 6.36, 22.44).

Discussion and Conclusions: Medetomidine is an emerging adulterant, although its risk profile is under-described. Our findings suggest medetomidine may cause hallucinogenic effects, contradicting clinical use for preventing delirium in postsurgical settings. Unexpected hallucinations may serve as a sentinel signal for medetomidine's presence in local drug markets. Education is needed for people who use drugs and clinicians about novel adverse effects of medetomidine.

1 | Introduction

The United States is experiencing a rapidly evolving unregulated drug supply, complicating efforts to protect people who use drugs from overdose and other health sequelae of substance use. Recent trends include the introduction of new psychoactive substances (e.g., nitazenes and synthetic cannabanoids), nontherapeutic fillers with uncertain safety profiles (e.g., bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate [BTMPS]), and of particular concern, xylazine, a veterinary tranquilliser

Summary

- Medetomidine, a potent veterinary tranquilliser and human sedative, is emerging as a new adulterant in the unregulated drug supply in the United States.
- We analysed 11,363 drug samples through a national mail-based drug checking program from December 2022 to April 2025.
- A total of 278 samples contained medetomidine, which commonly co-occurred with fentanyl (58.8%) and/or xylazine (55.9%).
- Samples containing medetomidine were 12 times as likely to include reported hallucinations than other samples; contradicting clinical expectations.
- Hallucinations may be one signal of medetomidine's presence in local markets; education is needed for people who use drugs and providers about distinct presentations of this adulterant.

co-occurring with—and sometimes supplanting—fentanyl and other opioids in illicit drug markets [1–3].

There is an urgent need to identify and characterise new constituents of the unregulated supply in a timely manner in order to inform harm reduction practice and policy. In particular, people who use drugs should be adequately informed to assess the risk of substances they may knowingly or unknowingly ingest. Unfortunately, efforts to educate substance-using communities often fail to keep pace with supply trends, owing in part to the mercurial nature of drug markets and, as importantly, the inertia of research dissemination pipelines [4, 5]. Xylazine presents one example: Although the adulterant had appeared in 38 states by 2019, its association with severe skin ulceration was not reported in the research literature, to our knowledge, until 2022 (cf. two studies identified skin ulcers as an adverse reaction shortly after xylazine's introduction to Puerto Rico in the late 2000s) [6–9]. As laboratory-based drug checking becomes formalised as an accessible harm reduction strategy—and prolific data source—it is incumbent upon researchers to characterise new drugs of consumption before they saturate markets and cause preventable harm.

One emerging substance of concern is medetomidine, a racemic mixture of levo- and dex-medetomidine [10]. First identified in the unregulated supply in Maryland in mid-2022 [11], medetomidine, like xylazine, is a potent veterinary tranquilliser; unlike xylazine, its active enantiomer (dexmedetomidine, commonly delivered as injectable Precedex, Pfizer, New York, USA) is an FDA-approved α2-adrenergic agonist used as a sedative, analgesic and anxiolytic in humans. Dexmedetomidine is widely used in hospital settings because it is not a controlled substance and is also used in veterinary medicine and biopharmaceutical research in animal models. Sublingual dexmedetomidine (Igalmi, BioXcel Therapeutics, New Haven, CT, USA) is additionally used in humans for management of agitation among adult patients with agitation due to schizophrenia or bipolar disorder.

Dexmedetomidine was developed to be a safer human sedative due to its purported lack of respiratory depressive effect and increased selectivity for the alpha-adrenergic receptors. Interestingly, dexmedetomidine and xylazine were both developed in a cascade of medicinal chemistry attempts to improve on the sedative and addiction therapy potential of clonidine, an earlier α2-adrenergic agonist [12]. Xylazine and dexmedetomidine have both been touted as selective α2-adrenergic agonists, but this has recently been refuted for xylazine [13, 14]. In fact, xylazine has now been reported to have agonist activity at the kappa opioid receptor, 5-HT_7 serotonin receptor, sigma 1 and 2 receptors, as well as the 3 α2-adrenergic receptor subtypes [13, 14]. Current literature does not report any indications that dexmedetomidine is not selective for the alpha-adrenergic system.

Given the complexity of xylazine's pharmacology, and growing concerns about prospective harms of medetomidine to human health alone or in combination with opioids [15, 16], there is a need for further validation of medetomidine's profile of effects and its presentation in community settings. The purpose of this study, therefore, is to characterise medetomidine and reported effects using data from a national drug checking service.

1.1 | Study Rationale and Hypothesis

In October–November 2024, our team attended two harm reduction programs in Pennsylvania and Michigan to conduct a qualitative study of naloxone administration and overdose reversal behaviours in people who use drugs [17]. Several interview participants discussed a new constituent of the local drug supply, sometimes called 'trippy dope', that was described as inducing severe and troublesome visual hallucinations. These participants noted that 'trippy dope' was a relatively new phenomenon, appearing within the previous several months. This timeline roughly aligned with the proliferation of medetomidine in drug checking samples from both states. In consultation with harm reduction partners at both programs, we therefore formulated the following hypothesis:

Hypothesis. *Drug checking samples containing medetomidine are more likely to include reports of hallucinations than samples not containing medetomidine.*

2 | Methods

2.1 | Study Design and Data Source

We conducted a retrospective analysis using data from a public drug checking service, the UNC Street Drug Analysis Lab. Analysis was restricted to samples with complete analysis by the lab between 7 December 2022, the first date of a positive medetomidine sample, and 11 April 2025, with at least one substance positively identified, comprising a total of 11,363 samples. The dataset included qualitative sample composition profiles identified using gas chromatography mass spectrometry (GCMS); all detected substances were positively identified using reference standards. Participant-reported data included geographic location, collection method, expected substance and sample characteristics (sensations, colour and texture) recorded on a standardised data card filled out by program staff. Hallucinations were one of 12 closed-ended response options for

the sensation field on the data card and participants could expand on their selection(s) in a free text field (Appendix A) [18].

Because GCMS cannot distinguish between medetomidine and its individual enantiomers, the term *medetomidine* is used throughout this manuscript to refer to the compound as a whole.

2.2 | Data Collection

Samples were submitted by health-serving organisations including harm reduction programs, drug user unions, public health agencies and universities. Samples were collected as powders, pill fragments, swabs or used cottons, dissolved in acetonitrile solution and shipped to the drug checking lab with a prepaid return envelope. Sample collection and shipping followed established harm reduction exemptions under state-controlled substance laws and federal regulations for small quantity hazardous materials.

Samples were prepared then analysed on a Thermo Scientific Q Exactive GC Orbitrap GC–MS System with a TriPlus RSH Autosampler with electron ionisation. Xcalibur Qual Browser Version 4.5.445.18 (ThermoFisher, Bremen, Germany) was used to analyse raw GCMS output. Substances were identified using mass spectral libraries and classified as 'primary' or 'trace' in abundance. Trace substances were defined as those with $\geq 5\%$ peak height area relative to the most abundant substance. Complete lab analysis methods, including reference libraries, are described elsewhere [19].

2.3 | Measures

The unit of analysis was a drug sample. The primary outcome was participant-reported hallucinations. The primary exposure of interest was the positive identification of medetomidine in abundance per sample.

2.4 | Covariates

Substance covariates were selected using a model-driven approach: Substances were included if they were associated with both medetomidine presence and independently associated with hallucinations in preliminary bivariate analyses. Substances were then grouped based on pharmacological class and/or to address sparse data bias based on an a priori threshold of ≥ 5 co-occurrences of hallucinations with medetomidine. Among 410 unique substances identified in the dataset, 23 co-occurred with medetomidine in a reported hallucination. Only one substance (bromazolam, a benzodiazepine) was excluded, as it did not meet the a priori threshold and could not be grouped pharmacologically. Substance covariates selected for the model were: xylazine, fentanyl, fentanyl precursors/impurities (4-ANPP, 1,3-diacetin, despropionyl p-fulorofentanyl), other opioids (buprenorphine, heroin, 6-monoacetylmorphine, N-phenethyl-N-phenylpropionamide, p-fluorofentanyl), local anaesthetics (procaine, lidocaine, tetracaine, bupivacaine), stimulants (methamphetamine, cocaine, caffeine) and nonpsychoactive fillers (quinine, acetaminophen, dimethyl sulfone, BTMPS).

Additional covariates were considered for the model using forward variable selection and the quasi-information criterion. These variables were the number of substances per sample (including abundant and trace, to account for polysubstance complexity), region (Northeast, Midwest, South, West) and time (i.e., year). The number of substances and region improved model fit and were included. Year was excluded as only one medetomidine-associated hallucination occurred prior to 2024.

2.5 | Statistical Analysis

We used generalised estimating equations with a log link and Poisson distribution to estimate adjusted prevalence ratios (aPR). The model accounted for clustering by county using an exchangeable correlation structure. All hypothesis tests were two-sided. Statistical significance was assessed at the $p < 0.05$ level. Multicollinearity was assessed using variance inflation factors; no covariates exceeded a variance inflation factor of 5. All analyses were conducted in Python 3.10 using the statsmodels, pandas and mlxtend packages in a Deepnote environment.

2.6 | Sensitivity Analysis

Participant-reported sensations were recorded on 52.2% of data cards. Because it was unclear whether blanks indicated the substance was not consumed, there was a lack of sensations, or the question was not asked, a sensitivity analysis was conducted, including only samples with any recorded sensations (hallucinations or otherwise).

2.7 | Preregistration

The study protocol was preregistered at https://osf.io/4agfx.

3 | Results

Between 7 December 2022 and 11 April 2025, 11,363 samples were analysed by GCMS. Primary collection methods were spatula (56.3%), swab (10.9%), pill (8.3%), scoop (5.4%) or cotton (3.8%). Medetomidine was identified in 278 samples (2.4%), including 136 in primary abundance (1.2%). Pronounced growth in the prevalence of positive samples began around June 2024 (Figure 1, xylazine as comparator molecule).

Medetomidine was identified in primary abundance in seven US states during the analysis period (New York, Pennsylvania, North Carolina, Michigan, Ohio, Florida, Virginia) (Appendix B). Medetomidine-containing samples were most often white and in powder form (Table 1). Commonly endorsed sensations included 'sedating' (32.4%), 'stronger' (25.0%), 'unpleasant' (16.9%), 'weird' (13.2%) and 'more down' (11.0%). Sample donors most often expected samples to contain fentanyl (86.9%), xylazine (42.3%) and/or heroin (23.1%).

Most medetomidine-positive samples also contained fentanyl (58.8%) and/or xylazine (55.9%) (Table 2). Including trace substances, GCMS identified a median of eight substances in

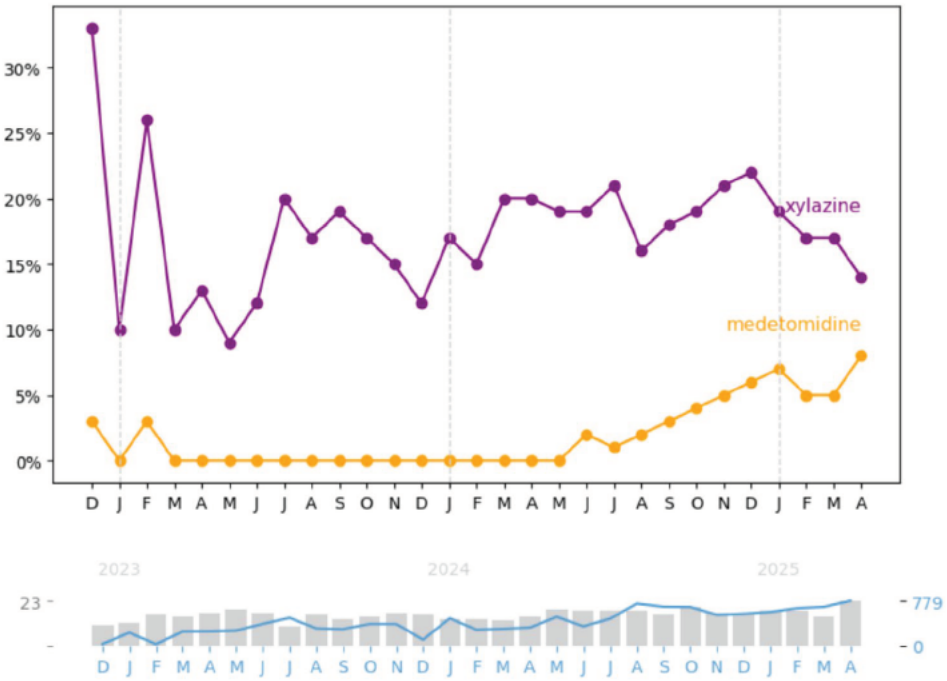

FIGURE 1 | Top: Percentage of samples containing xylazine and medetomidine, December 2022–April 2025. Bottom: Total samples received (blue line) and number of originating state (grey bars) per month.

medetomidine-containing samples (range: 2–17) compared with a median of three substances in all other samples (range: 1–19) (Table 3).

Hallucinations were reported in 17.6% of samples containing medetomidine overall ($n = 24$) and 25.0% of such samples with recorded sensation data, as compared with 1.2% and 2.3% in the overall dataset. Adjusting for covariates, samples containing medetomidine were significantly more likely to be associated with hallucinations compared with other samples, with an aPR of 11.95 (95% confidence interval [CI] 6.36, 22.44) (Table 4). Among covariates, selected nonpsychoactive fillers (aPR 0.41, 95% CI 0.24, 0.70) and fentanyl precursors and impurities (aPR 0.46, 95% CI 0.22, 0.96) were associated with lower prevalence of hallucinations. Hallucinations were significantly more common overall in the Northeast, South and Midwest compared with the West during the study period. Model results were robust to sensitivity analysis, though attenuated (aPR 9.11, 95% CI 4.81, 17.23) (Appendix C). In free response, participants described medetomidine-related hallucinations as 'intense', 'trippie [sic] like DMT', 'psychedelic' and 'dissociative seeming' (Appendix D).

4 | Discussion

In this paper we characterise the increasing presence of an emerging tranquilliser adulterant in the unregulated drug supply in multiple regions of the United States. We identified 278 samples containing medetomidine, including 136 in primary abundance. Medetomidine was found to co-occur with multiple substances, most commonly fentanyl, 4-ANPP (a fentanyl by-product), xylazine, local anaesthetics (e.g., procaine) and various nonpsychoactive cuts.

Participants commonly reported that medetomidine-containing samples induced sedation, which aligns with its pharmacodynamic profile [20]. However, reports of hallucinations—which were common in these samples but rare in the broader dataset—belie clinical expectations. Psychosis is not a documented adverse effect in the FDA labelling for Precedex [21]. In fact, dexmedetomidine may be administered perioperatively to reduce risk of postoperative delirium during cardiac and noncardiac surgery [20, 22–25]. Nonetheless, the effects of dexmedetomidine on postoperative delirium remain a subject of debate, with at least one retrospective study suggesting increased, rather than decreased, postoperative risk [26]. Notably, in one case report of a woman with polysubstance use, dexmedetomidine was determined to induce delirium and agitation in an increasing dose–response manner, and symptoms only ceased after discontinuation [27].

Though our results suggest medetomidine is a likely culprit behind reported hallucinations, the mechanism is unclear given the relative absence of these effects in clinical safety profiles or the medical literature. It is possible that the side effects of unregulated medetomidine arise from the racemic mixture where clinical populations are only exposed to dexmedetomidine. Though classified as pharmacologically inactive, levomedetomidine in high doses has been demonstrated in animal studies to attenuate the sedative and analgesic effects of dexmedetomidine and enhance bradycardia [28]. It is possible that levomedetomidine may also have psychoactive side effects in humans, although the drug has not been adequately clinically evaluated. Related α2-adrenergic agonists such as clonidine and guanfacine have been associated with hallucinations and delirium in multiple case studies and clinical trials [29–34]. To further complicate matters, clonidine has also been successfully used to treat hallucinations in patients

TABLE 1 | Characteristics of samples containing medetomidine in primary abundance ($n = 136$).

	n (%)
Sensations[a]	
Sedating	44 (32.4)
Stronger	34 (25.0)
Hallucinations	24 (17.6)
Unpleasant	23 (16.9)
Weird	18 (13.2)
More down	15 (11.0)
Normal	8 (5.9)
Long	6 (4.4)
Weaker	5 (3.7)
Other	10 (7.4)
Unknown/not specified	40 (29.4)
Textures[a]	
Powder	116 (85.3)
Chunky	24 (17.6)
Dull	12 (8.8)
Flaky	9 (6.6)
Other	11 (8.1)
Unknown/not specified	17 (12.5)
Colour[a]	
White	47 (34.6)
Brown	13 (9.6)
Tan	10 (7.4)
Grey	7 (5.1)
Blue	7 (5.1)
Other	22 (16.2)
Unknown/not specified	45 (33.1)
Expected substance(s)	
Fentanyl	114 (83.8)
Xylazine	55 (40.4)
Heroin	31 (22.8)
Benzodiazepine	8 (5.9)
Ketamine	3 (2.2)
Medetomidine	3 (2.2)
BTMPS	2 (1.5)
Opioids (unspecified)	2 (1.5)
M30	1 (0.7)
Nitazene	1 (0.7)
Crack cocaine	1 (0.7)
Procaine	1 (0.7)
Methamphetamine	1 (0.7)
Cocaine	1 (0.7)
Unknown/not specified	13 (9.6)
Region	
Northeast	99 (72.8)
Midwest	20 (14.7)
South	17 (12.5)
West	0

[a]Includes values with count ≥ 5.

with schizophrenia [35, 36]. The potential for noradrenergic implication in medetomidine-induced hallucinations is clear but certainly requires more careful study.

It is also possible that hallucinations occur only at high doses. If illicit drug suppliers are replacing xylazine or supplementing fentanyl with medetomidine, then many people who use drugs may be purchasing and ingesting supratherapeutic doses of medetomidine, perhaps in amounts that are orders of magnitude greater than clinically indicated. As opioids and α2-adrenergic agonists exhibit cross-tolerance to sedation, it is possible that people who use fentanyl are desensitised to sedation from medetomidine while still predisposed to other known or unknown adverse effects [37, 38]. Future studies should investigate how the pharmacology of medetomidine might contribute to hallucinogenic effects, particularly given that reports of hallucinations associated with xylazine—a pharmacologically related adulterant—were rare in our sample.

Importantly, hallucinations were not reported in most medetomidine samples, suggesting that pharmacology alone cannot explain these adverse reactions. More research would be needed to determine how various factors contribute to differential risk, including individual characteristics (e.g., neurobiological vulnerability, substance use history) and/or drug-related factors (e.g., drug–drug interactions, route of administration).

Although medetomidine can be identified by technicians using specialised equipment (e.g., GCMS, infrared absorption spectroscopy) or by harm reduction participants using test strips, these technologies are not readily available to every person who uses drugs. Sensation data may provide a useful proxy indicator of drug adulteration in a constantly evolving unregulated supply. We found that hallucinations were reported in 17.6% of medetomidine-containing samples but only 1.2% of samples overall. Hallucination reports could be one sentinel signal of medetomidine's introduction into local markets, just as pervasive and enduring wounds, often of the extremities, are among

TABLE 2 | Co-occurring substances found in primary abundance in medetomidine-positive samples ($n = 136$).

Substance[a]	*n* (%)
Fentanyl	80 (58.8)
Xylazine	76 (55.9)
4-ANPP	55 (40.4)
Procaine	55 (40.4)
Lidocaine	42 (30.9)
BTMPS	34 (25.0)
Caffeine	34 (25.0)
Heroin	30 (22.1)
Tetracaine	27 (19.9)
Acetaminophen	25 (18.4)
Diphenhydramine	16 (11.8)
6-monoacetylmorphine	12 (8.8)
Dimethyl sulfone	11 (8.1)
Bromazolam	9 (6.6)
Cocaine	8 (5.9)
Bupivacaine	8 (5.9)
Despropionyl p-fluorofentanyl	8 (5.9)
1,3-Diacetin	7 (5.1)
P-fluorofentanyl	7 (5.1)
Promethazine	6 (4.4)
Quinine	5 (3.7)
Methamphetamine	5 (3.7)
All others	35 (25.7)

[a]Includes values with count ≥ 5.

TABLE 3 | Measures of central tendency for number of unique substances identified per sample ($N = 11{,}363$).

	Median (range)	Mean (SD)
Including abundant substances only		
Medetomidine-positive samples	5 (2–14)	5.38 (2.12)
Medetomidine-negative samples	2 (1–13)	2.34 (1.76)
Including trace and abundant substances		
Medetomidine-positive samples	8 (2–17)	8.24 (2.89)
Medetomidine-negative samples	3 (1–19)	3.53 (2.92)

Note: p values for group comparisons were calculated using permutation tests (50,000 iterations) for median and mean differences. All comparisons yielded $p < 0.001$.

TABLE 4 | Adjusted prevalence ratios of hallucination reports by sample characteristics.

Covariate	aPR	95% CI
Substance(s)		
Medetomidine	11.95*	(6.36, 22.44)
Fentanyl	0.78	(0.48, 1.27)
Xylazine	1.41	(0.81, 2.45)
Nonpsychoactive fillers	0.41*	(0.24, 0.70)
Local anaesthetics	1.59	(0.90, 2.79)
Other opioids	1.00	(0.56, 1.79)
Stimulants	0.76	(0.47, 1.22)
Fentanyl precursors/impurities	0.46*	(0.22, 0.96)
Number of substances	0.96	(0.90, 1.02)
Region (Ref: West)		
Northeast	2.02*	(1.00, 4.08)
South	5.44*	(2.94, 10.08)
Midwest	3.87*	(1.72, 8.71)

Abbreviations: aPR, adjusted prevalence ratio; CI, confidence interval.
*$p < 0.05$.

the first indicators of xylazine adulteration in an area [3, 39, 40]. Zibbell et al. argued for 'sensory discernment strategies' during the market transition from heroin to fentanyl [41]. The authors found that people who use opioids were able to discern fentanyl from heroin based on appearance, psychoactive effects (e.g., shorter time to withdrawal) and sensations (e.g., pins and needles) [41]. In the absence of drug checking technology, such inferential strategies may be necessary to keep people who use drugs educated about the potential presence of novel adulterants in local supplies.

Much remains unknown about the potential harms of medetomidine to the health of people who use drugs. Preliminary evidence suggests that bradycardia and hypertension are common sequelae of street medetomidine consumption [10], and repeated use may lead to severe withdrawal symptoms, including tachycardia, hypertension, agitation, tremor and vomiting [42, 43]. As with xylazine-adulterated fentanyl, medetomidine-involved overdoses and medetomidine-induced withdrawal may present with different symptoms than those involving opioids alone. And as with xylazine, it is still unclear how responsive medetomidine will be to opioid overdose antagonists. Nonetheless, current clinical practice dictates naloxone should be administered in any suspected opioid overdose in community settings, and rescue breathing should be especially emphasised where α2-adrenergic agonists may be involved [44]. Medical providers, first responders, harm reduction practitioners and people who use drugs should be educated about signs of medetomidine involvement, as optimal responses to overdose and/or withdrawal may differ from fentanyl and other opioids [44].

Our study has some limitations. Findings pertaining to prevalence should be interpreted with caution. Samples are submitted

voluntarily, and it is possible that substances with unique appearances, tastes and/or sensations are more preferentially submitted for testing. The drug checking service also receives more samples from certain states (e.g., Washington, New York and North Carolina) than others (Appendix E); our results are not indicative of geographical trends. Sensations are presented as closed-response options on the sample data card and are likely inexhaustive. Relatedly, hallucinations are also not defined for participants, and so the construct validity of this variable is unclear, specifically the lack of detail on visual versus auditory hallucination. However, notes on cards and common usage of the word *hallucination* in the context of our service users strongly favours semantic usage to mean visual hallucinations; several participants characterised reactions as visual hallucinations or psychedelic effects.

Our cross-sectional design precludes causal inferences about the relationship between medetomidine and hallucinations. The temporal relationship between substance use and reported effects cannot be confirmed from our data, and individual factors such as tolerance, concurrent substance use or underlying medical conditions may influence the occurrence of hallucinations.

Regarding laboratory analysis, quantitative results are not available, and the threshold for primary abundance ($\geq 5\%$ peak) may have influenced results. Relatedly, our model cannot account for the dosage of drug consumed by sample donors. Finally, it cannot be inferred from GCMS alone whether positive samples contained a racemic mixture of medetomidine or its active enantiomer, dexmedetomidine. An answer to this question will be necessary to determine whether hallucinations are an under-described sequela of dexmedetomidine administration, or whether these findings present insight into the human impacts of veterinary formulations.

5 | Conclusion

In this study, we describe characteristics of a novel α2-adrenergic agonist in the unregulated drug supply in the United States. We find that medetomidine is significantly associated with reported hallucinations, a finding at odds with clinical and pharmacological expectations. Hallucinogenic effects, along with the sedation typical of α2-adrenergic agonists, may be unique signals of trends in local markets toward medetomidine adulteration. Resources permitting, harm reduction providers and participants should continue to use drug checking technologies to empower informed consumption decisions, and medical providers should remain alert to the presentation of medetomidine-involved overdose and withdrawal as more is learned about this new adulterant.

Author Contributions

Each author certifies that their contribution to this work meets the standards of the International Committee of Medical Journal Editors. **Adams L. Sibley:** conceptualisation, methodology, formal analysis, writing – original draft. **Madigan L. Bedard:** conceptualisation, writing – original draft, writing – reviewing and editing. **Samuel Tobias:** conceptualisation, methodology, writing – reviewing and editing. **Brooke A. Chidgey:** conceptualisation, writing – reviewing and editing. **Irina G. Phillips:** conceptualisation, writing – reviewing and editing. **Alice Bell:** conceptualisation, writing – reviewing and editing. **Nabarun Dasgupta:** conceptualisation, methodology, formal analysis, data curation, writing – reviewing and editing.

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Ethics Statement

This investigation was reviewed by the UNC Office of Human Research Ethics and deemed exempt from human subjects research.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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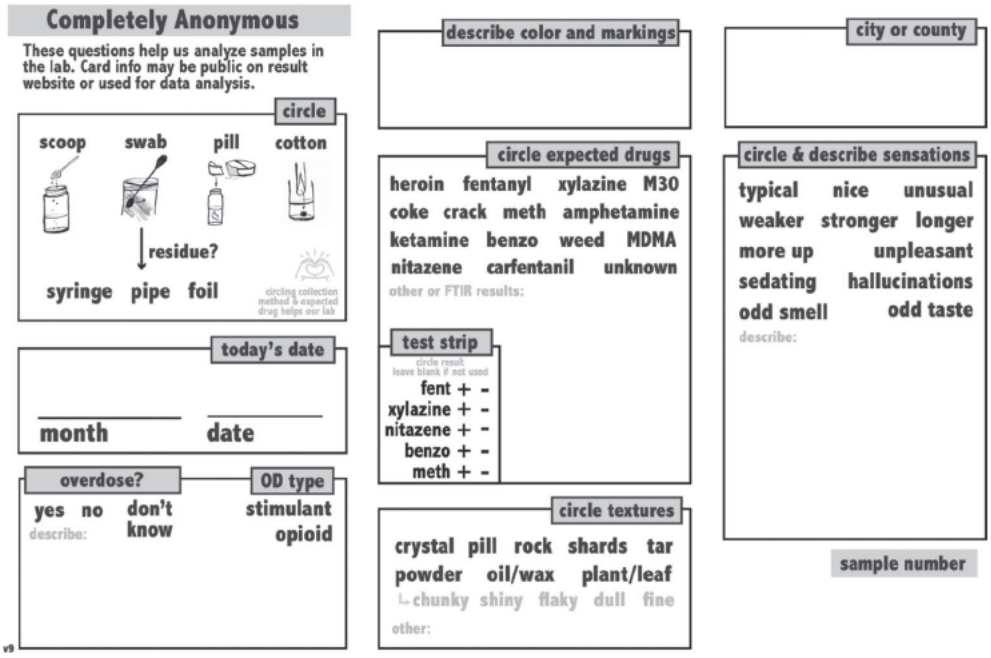
Appendix A

Sample Collection Data Card



Appendix B

Medetomidine-Positive Samples Received by State, 11 December 2022–1 April 2025

State	Trace and primary abundance	Primary abundance only	Total samples received
New York	140	65	2058
Pennsylvania	50	34	321
North Carolina	36	14	1600
Michigan	20	7	913
Ohio	19	13	147
Florida	6	2	261
Virginia	3	1	52
Oregon	1	0	623
Colorado	1	0	589
Wisconsin	1	0	124
New Mexico	1	0	433
Total	278	136	7121

Appendix C

Sensitivity Model

Covariate	aPR	95% CI
Substance(s)		
Medetomidine	9.11*	(4.81, 17.23)
Fentanyl	0.75	(0.48, 1.17)
Xylazine	1.25	(0.74, 2.10)
Nonpsychoactive fillers	0.37*	(0.21, 0.65)
Local anaesthetics	1.49	(0.87, 2.57)
Other opioids	0.96	(0.55, 1.67)
Stimulants	0.67	(0.41, 1.10)
Fentanyl precursors/impurities	0.44*	(0.21, 0.93)
Number of substances	0.95	(0.89, 1.01)
Region (Ref: West)		
Northeast	1.97	(0.91, 4.28)
South	3.57*	(2.07, 6.17)
Midwest	3.10*	(1.55, 6.23)

Abbreviations: aPR, adjusted prevalence ratios; CI, confidence interval.
* $p < 0.05$.

Appendix D

Free Text Sensation Descriptions in Samples With Medetomidine in Primary Abundance

1. Made dizzy and felt weird like not right for dope feelings
2. [Blank]
3. Paralysis, doesn't seem like opioid
4. Person was very tired for days, trippie like DMT; incoherent for hours. was with several peers and they all were very scared
5. Bad
6. Like being really drunk + speedy, auditory and visual hallucinations then pass out
7. Knocked out
8. Very strong
9. Lethargic, dissociative seeming, long lasting down
10. Burned when injecting, black out
11. Sleepy
12. Numb lips and hands anxiety, heart rate up, chest hurt
13. Head tingle, low blood pressure, upset diarrhoea, restless legs (body), headache
14. Dissociative, tranq
15. Felt like a bad anxiety attack
16. Weird
17. Lots of sweating
18. Less opioid, more tired, knocked out
19. Visual hallucinations then passed out quickly
20. Trippy
21. Foggy, rooted in place
22. Bad reaction
23. Tranq/hallucinate, weakness
24. After 15 min hits hard. Vivid nightmares for 8 h
25. Fainting, shortness of breath, paralysis, hearing in and out
26. Blood pressure spiked
27. Shitty
28. DK
29. High lasted 24 h., out of it, felt psychedelic
30. Head is in the dirt
31. Knocking people out
32. Odd smell, heavily sedating
33. Unusual. Hallucinations when sniffed
34. Heavy sedation, no rush
35. Stroke like symptoms
36. Nausea, dizziness, sweat, intense hallucinations. Did not feel like opiate

Appendix E

Summary of Coverage of UNC Drug Checking Services

State	Programs	Samples	Counties	Earliest sample	Latest sample
Washington	14	3946	13	17-Nov-22	5-May-25
New York	29	2058	44	27-Jan-22	2-May-25
North Carolina	43	1600	56	26-Jan-22	5-May-25
Michigan	8	913	15	11-Oct-22	29-Apr-25
California	17	800	13	9-Jan-23	5-May-25
Oregon	5	623	8	30-Aug-22	30-Apr-25
Colorado	4	589	5	19-Jul-23	5-May-25
New Mexico	6	433	11	22-Nov-22	5-May-25
Pennsylvania	9	321	10	11-Feb-22	22-Apr-25
Florida	10	261	15	7-Jun-23	30-Apr-25
Texas	7	180	13	27-May-22	28-Apr-25
Ohio	9	147	10	3-Jan-23	22-Apr-25
Tennessee	6	141	13	17-Jul-22	9-May-24
Wisconsin	6	124	8	18-Apr-23	28-Apr-25
Minnesota	1	74	4	6-Nov-24	2-May-25
Virginia	5	52	3	21-Apr-23	25-Apr-25
Maine	3	46	5	3-Feb-23	28-Apr-25
Arizona	6	44	6	18-Jul-22	3-Apr-24
Nevada	1	35	1	26-Jan-23	29-Apr-25
South Carolina	7	24	4	11-Feb-22	11-Oct-24
Indiana	2	24	5	16-Mar-23	24-Jul-24
Georgia	7	14	6	21-Apr-22	14-Apr-25
Massachusetts	4	14	4	28-Aug-23	15-Nov-24
Illinois	3	13	1	27-Mar-23	2-May-25
New Jersey	3	9	3	12-Jun-23	6-Feb-25
Missouri	1	8	1	27-Aug-24	10-Mar-25
Connecticut	1	8	2	28-Aug-23	7-Nov-24
Alabama	1	5	1	26-Aug-24	26-Aug-24
Hawaii	1	5	1	28-Apr-25	28-Apr-25
Montana	2	4	2	28-Nov-22	4-Feb-25
Delaware	1	4	1	20-Aug-24	22-Aug-24
Oklahoma	1	3	2	17-Jul-23	8-Sep-23
District of Columbia	1	2	1	1-May-25	2-May-25
Mississippi	1	2	1	23-Apr-23	23-Apr-23
Vermont	1	2	1	25-Feb-25	25-Feb-25
West Virginia	1	2	1	21-Apr-23	21-Apr-23
Kentucky	1	1	1	28-Oct-24	28-Oct-24
New Hampshire	1	1	1	19-Feb-25	19-Feb-25
Idaho	1	1	1	3-Jan-24	3-Jan-24
Louisiana	1	1	1	10-Nov-23	10-Nov-23
Rhode Island	1	1	1	21-Apr-23	21-Apr-23

RESEARCH ARTICLE

Trends and characteristics during 17 years of naloxone distribution and administration through an overdose prevention program in Pittsburgh, Pennsylvania

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Data availability statement: Data are released by permission of Prevention Point Pittsburgh. The datasets have been uploaded here: https://osf.io/e8bqa/. In addition, we have also placed

Abstract

Objective

Describe time trends during 17.5 years of community-based naloxone distribution

Methods

Analysis of administrative records from a harm reduction program in Pittsburgh, Pennsylvania, USA, collected during encounters for overdose education, naloxone dispensing and refills. Monthly time trends were analyzed using segmented regression. Programmatic context aided interpretation of quantitative findings. We also evaluated impacts of 2014 state legislation loosening naloxone prescribing requirements and providing Good Samaritan protections.

Results

From July 2005 to January 2023 there were 16,904 service encounters by 7,582 unique participants, resulting in 70,234 naloxone doses dispensed, with 5,521 overdose response events (OREs), utilizing 8,756 naloxone doses. After legislation, new participants increased from 10.4 to 65.9 per month. New participants tended to be older (46 vs. 37 years), female (58% to 35%), White race, and more likely to be family/friends as opposed to people who use drugs themselves. Consequently, ORE per participant fell from 1.46 to 0.47 in the year after enactment. On average, 1.63 (95% CI: 1.60, 1.65) naloxone doses were administered per ORE, which did not change substantially over 17 years ($\chi^2 = 0.28$, 3 df, $p = 0.60$) during evolution from prescription opioids, to heroin, to illicitly manufactured fentanyl. In 98.0% of OREs the person who

Stata analytic code, and Jupyter notebooks with code, data, and output in the project repository: https://osf.io/sq5d6/.

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Competing interests: ND is on the Board of Directors, and EJW and MDS are employees of Remedy Alliance For The People, a non-profit wholesale distributor which provides bulk, free and low-cost naloxone to harm reduction programs and health departments. AB ad MV are staff at Prevention Point Pittsburgh. This does not alter our adherence to PLOS ONE policies on sharing data and materials.".

experienced overdose "was okay", i.e., survived. Emergency medical services were called in 16% of OREs overall, but <7% since 2019. There were 106 more emesis events per 1,000 OREs with 4 mg nasal spray compared to intramuscular injection; and 48 per 1,000 more reports of anger. Titration of intramuscular naloxone was associated with lower rates of adverse events.

Conclusions

While state legislation created the environment for expansion, reaching previously underserved communities required intentional new programmatic development and outreach. Long-term consistency of <2 doses per ORE, high survival rate, and robust utilization all lend confidence in prioritizing naloxone distribution directly to people who use drugs and their social networks.

Trial registration: This investigation was pre-registered https://osf.io/b2f4h

Introduction

In the United States (US), fatal overdose rates have increased over the past four decades. The characteristics have changed from heroin dominance in the early 1990s to prescription opioids in the late 1990s and 2000s, to heroin again around 2013 [1,2]. By 2015, the emergence of non-pharmaceutical fentanyl and analogues played the most prominent role in fatal overdoses, and currently stimulant-opioid fatal overdoses are increasing [3,4]. After many years of unrelenting increases, the national data show decline in annual overdose deaths in 2023 and 2024 [5,6]. However, at the state level the results are heterogeneous, with states having different rates of overdose decline.

Community-based distribution of the opioid overdose reversal agent, naloxone, has expanded considerably since federal funding support in 2018 and is a critical strategy for preventing fatalities [7]. Harm reduction programs train people who use drugs to recognize and respond to opioid-induced respiratory depression. People who access these services, by the nature of their ongoing drug use, are at the highest risk of overdose [8], yet there is a paucity of quantitative data characterizing peer reversal behaviors, particularly as the drug supply landscape has evolved. Specifically, in the context of community-based naloxone distribution, there are few published studies detailing time trends of adverse events, formulation effects, titration practices, changes during the COVID-19 pandemic, and infiltration of xylazine in the unregulated drug supply. Over the last two decades, state laws have also evolved to reduce barriers to community-based naloxone distribution. In the scientific literature, policy analyses of state laws have lent support for this continued practice [9], localized evaluations have been published [10–13], as have evaluations of barriers [14,15]. What has been not been adequately described is the longitudinal evolution of harm reduction programs themselves. As harm reduction programs become enduring and institutionalized amid fluctuating public health investment, it is imperative to understand long-term programmatic trajectories, which can, in turn, inform future policy decisions.

Specifically, there is limited documentation of how harm reduction programs adapt to changing drug supply, laws, pharmaceutical formulations, and societal norms over an extended time. Herein we describe trends and experiences over 17 years from one of the longest continuously operating overdose prevention programs in the world, at Prevention Point Pittsburgh, a harm reduction and syringe services program. With continuous data collection [16], this setting offers a unique opportunity to understand long-term time trends in both community practice and individual responses simultaneously.

Applying the Evidence-Making Intervention framework [17], this comprehensive manuscript balances programmatic context with quantitative findings. The authors come from three professional domains: harm reduction program staff, government and academic scientists, and public health advocates. Some of the authors were the earliest innovators and implementors of community-based naloxone distribution in the US [18–21]. Of note, Prevention Point Pittsburgh has maintained institutional memory via staff retention; one co-author (AB) has been directing the program in Pittsburgh for the entirety of the observation period and provided invaluable canonical information on changes in service delivery. The length of the manuscript reflects aspects that are of relevance to each of the three professional domains, and we encourage readers to make use of section headings to follow the storyline that is of greatest interest.

About naloxone

Naloxone was first synthesized in 1961 by Jack Fishman and Harold Blumberg and was approved by the US Food and Drug Administration (FDA) in 1971 as a human prescription medication for the reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids ("overdose") [22]. Naloxone is approved to be administered intravenously (IV), intranasally (IN), or by intramuscular or subcutaneous injection (IM/SC). Naloxone for injection is currently available in the US under many approved generic versions. Additionally, many naloxone-containing drug-device products delivering a range of doses have been approved by the FDA since 2014 (Table S1 of Supplemental Material in S1 File) and are available by prescription or nonprescription. These product approvals have relied upon data derived from healthy subjects, in accordance with the 505(b)(2) pathway outlined in the Federal Food, Drug, and Cosmetic Act of 1938 [23].

The pharmacological action of naloxone [24] is primarily via antagonism at the mu-opioid receptor, with additional antagonist ability at the kappa- and sigma-opioid receptors. Naloxone's strong attraction to opioid receptors displaces and prevents the binding of opioid agonists such as heroin, fentanyl, and morphine in the central nervous system. Intravenous administration of naloxone leads to rapid redistribution in the body, including crossing the placenta (teratogenicity category C). Naloxone administered intramuscularly and intranasally reach a maximum concentration at 10–30 min and 5–30 min, respectively [25]. The nasal and oral bioavailabilities of naloxone are approximately 50% and 1%, respectively. The serum half-life of naloxone ranges from 30–81 min in adults. Naloxone is primarily excreted via the kidneys after glucuronide conjugation in the liver.

Adolescents (those ≥12 years of age) through adults experiencing opioid overdose can receive an initial dose of 0.4 mg to 2 mg IV, which can be repeated at 2-to-3-minute intervals as needed to reverse respiratory depression; intranasal and IM/SC products follow a similar frequency of dosing. Additional doses may need to be administered every one to two hours or given as an infusion for extended-release opioids or opioids with long durations of action (e.g., methadone, buprenorphine). Caregivers are encouraged to keep patients under surveillance to guard against the chance of renarcotization and return of respiratory depression. There is no maximum dose of naloxone, and very high exposures have been reported in the literature [26]. However, the FDA Prescribing Information cautions clinicians to consider an alternative cause of the patient's presentation if 10 mg of naloxone has been given IV without an improvement in the patient's condition [24].

Adults with opioid dependence who receive naloxone can develop an opioid withdrawal syndrome, characterized by body aches, abdominal cramping, nausea, vomiting, diarrhea, rhinorrhea, sneezing, diaphoresis, tremulousness or shivering, anxiety or agitation, piloerection, and yawning. The severity and duration of the precipitated withdrawal is related

to the dose of naloxone and to the degree of opioid dependence. Other adverse reactions include tachycardia, increased blood pressure, and rarely, seizures. A rare but serious adverse reaction to naloxone is noncardiogenic pulmonary edema. The risk of naloxone-induced pulmonary edema also appears to be dose-dependent [27].

Naloxone is on the World Health Organization's List of Essential Medicines [28]. It reverses opioid-induced respiratory depression rapidly but may also precipitate withdrawal in people who have opioid tolerance. Community-based naloxone distribution has become widely accepted in the US as a means of secondary prevention of overdose deaths, albeit with heterogeneity in enabling state governmental laws and policies [29].

Brief history of community naloxone distribution

Prevention Point Pittsburgh started distributing naloxone in 2005, after being inspired by formative work by the Chicago Recovery Alliance. Previously naloxone had been used exclusively in hospitals for managing anesthesia and by pre-hospital emergency medical service providers to reverse opioid overdose. In 1996, fueled by rising fatal heroin overdose among participants and staff, the Chicago Recovery Alliance [30] began distributing naloxone via their syringe services program to people who use drugs and their immediate social networks, an innovation marking the first known formal overdose education and naloxone distribution program in the world [31,32].

For the first decade of operations, the naloxone distribution program at Prevention Point Pittsburgh operated within a broader national context, which evolved from an environment of little support to codified scientific and legal protections. Given limited funding during the first 18 years (1996–2014) of broader intervention evolution, the development and implementation of new naloxone distribution initiatives within syringe services programs nationally was primarily through peer-based mentoring and technical assistance between programs. This was the case with Prevention Point Pittsburgh. Naloxone was purchased using smaller value unrestricted funds from sources such as t-shirt sales and donations to memorial funds from families who had lost a loved one to overdose. The staff time and cost to implement and deliver the services was absorbed by syringe service programs, viewed as an ethical imperative regardless of funding. Using this unfunded interorganizational mentoring model, there were 48 programs in the US by 2010 [18], and 140 by 2014 [33]. Because naloxone was a prescription medication, these initiatives existed in a medico-legal gray area that generated onerous requirements on harm reduction programs. For example, from 2005 to 2014, a documented in-person medical encounter and individual prescription from a physician was required for Prevention Point Pittsburgh to dispense naloxone to a participant. After coordinated national advocacy by public health organizations, state level legislation, and accumulating scientific evidence, policies supporting naloxone distribution were established starting around 2014 nationally, and directly contributed to the expansion of the naloxone distribution initiative in Pittsburgh.

The advent of federal support for naloxone distribution also had an impact on Prevention Point Pittsburgh by creating an expanded community of harm reduction practice for innovation, diffusion, and communication. In 2014, a memo from the Substance Abuse and Mental Health Services Administration (SAMHSA) to the National Association of State and Territorial AIDS Directors (NASTAD) clarified that using federal funds for naloxone was an acceptable expenditure for state block grants [34]. The first new federal funding that explicitly allowed for naloxone distribution was the Health Resources and Services Administration (HRSA) 2015 Rural Opioid Overdose Reversal grant program [35]. Prior to federal funding, local governments and harm reduction programs used local and philanthropic funds to support naloxone distribution in Massachusetts [20], New York [14], New Mexico [36], San Francisco [37], Rhode Island [38], North Carolina [21], Baltimore [39], and Pittsburgh [19]. Prevention Point Pittsburgh operated within this community of practice, the activity of which centered around the listserv and monthly meetings of the Opioid Safety and Naloxone Network, facilitated for over a decade by co-author AB [40,41].

By the end of 2015, several key events paved the way for further development of Prevention Point Pittsburgh's naloxone distribution program. Research emerged confirming that naloxone distribution via syringe services programs was effective at reducing overdose mortality [42] and was cost-effective [43,44]. Laws were passed in 43 states to support

expansion [45,46]. Two new branded naloxone products (nasal spray and auto-injector) were approved for prescription use among lay persons [47] and heavily promoted by pharmaceutical manufacturers [48]. Harm reduction programs also created a Buyers Club to obtain low cost injectable naloxone directly from a different manufacturer [40]. The FDA supported development of nonprescription naloxone formulations by conducting studies of labeling instructions [49] and expediting review of new products [50]. Of direct relevance to Prevention Point Pittsburgh, Pennsylvania Act 139 was enacted on November 30, 2014, allowing standing orders and third-party naloxone prescriptions. Prevention Point Pittsburgh's Medical Director issued a standing order for the organization, enabling naloxone distribution without requiring individual prescriptions. Other relevant contextual dates are cataloged in Supplemental Material Table S2 in S1 File.

Research questions

Five research questions were specified in the public pre-registration [51].

1. Did the utilization rate of naloxone and demographics of participants change after enabling state legislation was enacted?
2. After enactment of state legislation, what actions did the program take to focus uptake of naloxone directly to networks of people who use drugs?
3. Were program adaptations (e.g., site expansion) effective in improving naloxone uptake among communities of color in Pittsburgh?
4. Has the average number of doses of naloxone administered during an overdose response event changed over time as the drug supply has changed? Specifically, was more naloxone needed for reversing overdoses during the era of illicitly manufactured fentanyl, compared to previous periods where overdoses were due to heroin [52]?
5. Is the number of doses administered per overdose response event impacted by type of naloxone formulation?

Three additional questions were developed by the co-authors during the iterative analysis process and evaluated in accordance with the Evidence-Making Intervention (EMI) framework (described in Methods).

6. Did enactment of the Pennsylvania "Good Samaritan" law impact the proportion of overdoses response events in which 911 was called?
7. What were the circumstances of deaths reported after administration of naloxone?
8. Did adverse events differ by formulation of naloxone? And did titration of naloxone have an impact on adverse event rates?

Methods

Conceptual framework

This study was based on the EMI framework [17,53]. This framework shifts the locus of evidence production away from universally generalizable knowledge, which is common in traditional biomedical research. Instead, EMI prioritizes a more contextualized scientific process in which data and conclusions are generated through localized public health interventions serving immediate, applied needs. Therefore, the purpose of this analysis is not to present the hypothetically universal experience of naloxone distribution, but rather to examine one location in-depth to understand the forces that directly impacted service delivery and naloxone utilization. The application of the framework to the current investigation can be summarized using the six central tenets of EMI. In applying these principles in the Results section, "Programmatic Context" follows "Quantitative Results" for each set of variables analyzed.

1. *Material-discursive Process*: Naloxone distribution in Pittsburgh is not expected to be the same as anywhere else, yet there is value in understanding the local context. State policies and local drug supply considerations are made when interpreting quantitative data.
2. *Emergent, Contingent, Multiple effects:* Applied to this study, participant behaviors were expected to change over time. Overdose response practices naturally evolved over a 17-year period, instead of assumed to be static, as in shorter studies.
3. *Practice-based Matter-of-concern:* Of central relevance is how the concept of naloxone distribution was interpreted by program staff and locally adapted. For example, the program adapted to the COVID pandemic, and as new naloxone products and street drugs shifted. Therefore, contemporaneous contextual details are provided allow quantitative data to be interpreted with fidelity.
4. *Practice of Implementation:* How the intervention was delivered is of equal importance to other outcomes (e.g., biomedical or pharmacological). Therefore, logistical considerations and site expansion rationales are provided in detail, especially in ways that impacted participant recruitment and training of participants, and ultimately, the quantitative data.
5. *Performative Work of Science:* Administrative data were collected first and foremost for service delivery, and the scientific knowledge generated from their review is an added benefit. While data were collected with the intention of analysis, the questions asked of participants were also designed to gather information on reversals that would reveal opportunities for counselling and behavior change at the point of care.
6. *Equality of Knowledge:* Program staff's experience of service delivery is of equal explanatory value as quantification of administrative records. Program staff were included in each step of the analysis process, and their experiences are recorded in the Results section, and they are co-authors of this manuscript.

The Equality of Knowledge principle, a recursive process for knowledge generation was applied, starting with whole-team generation of the research questions. The data analyst (ND) generated tabular and graphical representations of time trends for batches of variables. The team then assembled to discuss patterns, aberrations, policy impacts, public health implications, and topics for further investigation, including new research questions based on discussions of programmatic context. After the initial discussion, the analyst would prepare follow-up tables, developing statistical methods as the inquiry warranted, and refine time trend graphs, which were then presented at the following meeting. This recursive process was applied to each set of variables in the dataset until all variables had been analyzed and discussed. In addition to the five research questions elaborated in the pre-registration, the recursive process resulted in three additional research questions described above.

Data source

We analyzed naloxone dispensing records and participant intake forms from a multi-site comprehensive harm reduction program (e.g., syringe services provider) in Pittsburgh, Pennsylvania, US. Datasets were anonymized by Prevention Point Pittsburgh prior to analysis. Data were generated at either initial training encounters or refill requests by participants, the latter of which included questions about the overdose that the naloxone had been used during. Interviewers received training to ensure standardized data collection, and ongoing data quality assessments were conducted. These administrative records span July 24, 2005 to January 24, 2023; initial naloxone distribution started in late July 2005 and the first reversal was reported in August. Data were collected on standardized paper forms, with weekly manual data entry using an electronic record system. Keystroke entry and missing corrections for early years of data were necessary to standardize dates and syntactical conventions (e.g., comma versus semi-colon for list delimiting) using natural language processing (described in Supplemental Material).

Naloxone formulations

During the 210-month study period, three formulations of naloxone were predominantly distributed. For both vial sizes of the liquid injectable, following product labelling, participants were instructed that one dose is 1 mL administered intramuscularly. Intramuscular syringes (typically 25 gauge x 1" or 0.5 mm x 25 mm) were provided in the kit; intravenous delivery of naloxone was almost never reported. Patient counselling and graphical printed cards advised that intramuscular administration could be achieved directly through clothing, into the shoulder or buttocks. These instructions have long been standardized among harm reduction programs nationwide, with many reproducing the same graphic developed at Chicago Recovery Alliance, and were consistent at Prevention Point Pittsburgh for the entire 17.5 years. In earlier years, one 10 mL vial could have been used in more than one overdose response event; by contrast, even with fractional dosing, 1 mL vials were not reported to be reused. For the nasal spray, one dose was defined as one full actualization in one nostril.

Naloxone provided in each kit:

- One 10 mL vial of 0.4 mg/mL naloxone hydrochloride: 2005–2015
- Two 1 mL vials of 0.4 mg/mL naloxone hydrochloride: October 2012 to January 2023
- Two units of 4 mg naloxone hydrochloride nasal spray: August 2016 to January 2023

Additional formulations available indirectly or briefly during the study period:

- 2 mL pre-filled needleless syringes of 1 mg/mL naloxone hydrochloride with aftermarket nasal adaptor [20]. This combination was not distributed by Prevention Point Pittsburgh, but some participants had received it elsewhere and reported using it when presenting for refills.
- 2 mg naloxone in 400 μL autoinjector. The autoinjector was briefly available in 2016 through a small donation of demonstration units from the manufacturer (Kaléo, Richmond, Virginia, US).

Definitions

Dose was defined as the lowest single dose in approved labeling for overdose reversal. For 1 mL and 10 mL vials, a single dose was defined as 0.4 mg delivered intramuscularly, and 4 mg intranasally (in one nare) for the nasal spray.

Overdose response events (OREs) include any report of an attempted overdose reversal regardless of the outcome of the event (successful resuscitation, death, or unknown outcome) where naloxone was administered (or in one report attempted to be administered, see Death Case Review). While the term "reversals" is commonly used in the literature, "ORE" was considered a more accurate term in the context of these data.

ORE per 100 doses dispensed (as presented in Fig 2) is a novel surveillance metric developed for to aid localized overdose investigation based on syndromic surveillance. As detailed in the Methods section of Supplemental Material, this metric was calculated by taking the number of ORE in a month and dividing by the number of naloxone doses dispensed that month by Prevention Point Pittsburgh. For external validity, we compared the resulting time series with opioid-related hospital emergency department visit rates published in the Allegheny County dashboard, observing strong visual concordance. This previously undescribed metric from the harm reduction setting may have utility as an adjunct to syndromic surveillance. This metric also could help harm reduction programs with predicting stocking volume of naloxone during demand surges. A limitation of this metric is that naloxone obtained from other sources beyond Prevention Point would not be accounted for in the denominator, and OREs not reported to the program would not be accounted for in the numerator.

Cumulative utilization rates (as presented in Table 3) are a quantification of how many units of dispensed naloxone were administered to reverse an overdose, during a specified calendar time period. In contrast to the surveillance-based definition above, these definitions [54] were selected because they are commonly used in drug utilization studies in pharmacoepidemiology. They were calculated in two ways, both with the number of overdose response events as the

numerator. The two denominators were either the number of units dispensed or standardized across formulations by the number of doses in a packaged unit. While this provides a useful metric for programmatic and financial planning, and as an input in modeling studies, it only accounts for doses dispensed by and OREs reported to Prevention Point Pittsburgh. As above, naloxone obtained via pharmacy or other venues are not accounted for in utilization rate denominators, and OREs not resulting in an encounter at Prevention Point are not represented in the numerator.

"*Felt sick*" was understood by participants and staff to mean "dopesick" from precipitated opioid withdrawal. This is a different semantic meaning than generalized malaise recorded in spontaneous adverse event reporting systems.

Titration in the context of community distribution was the administration of fractional doses of liquid injectable naloxone, as reported by the respondent (e.g., "one and half doses"). Since only the total number of doses were recorded, there may have been instances of titration where two ½ doses were administered but would only appear as a single dose (1.0) in the data. Therefore, this metric should be considered to have high specificity, but with misclassification resulting in bias towards the null in adverse event analyses. Nasal spray and auto-injector formulations were not capable of delivering fractional doses in the manner dispensed.

Programmatic context

Programmatic context reflects co-authors AB's and MV's lived experience from years of direct service delivery, program coordination, and employee supervision. Other staff members were also available to supply extra details. Specific aspects of programmatic context were supported as needed by the organization's primary physical and electronic documentation: training, inventory, and purchasing logs, internal datasets, completed data collection forms, emails, meeting notes, and photographs, as well as material from conference presentations and proceedings, and published scientific studies conducted at Prevention Point. During full team meetings, relevant programmatic context was discussed, led by AB and ND, and recorded in meeting notes. Following the EMI principles of Equality of Knowledge and Practice Implementation, these conversations were often of the nature whereby program staff and advocates informed scientists and government officials about the nuance of service delivery. Consensus drawn from meeting notes are summarized in sections that follow each quantitative analysis.

Statistical analysis

In descriptive analyses, *t*-tests were used to assess between-group differences for continuous variables, with the Satterthwaite approximation for degrees of freedom [55] employed when unequal variance between groups was present, or Fisher's exact test for low cell counts. Two-tailed chi-square distributions were used.

Time-series modeling

Data were aggregated by calendar month. Changes over time were assessed in four ways. First, smoothed monthly time trends (details in Data Visualization) were plotted along with 95% confidence intervals of the mean. Second, record-level data were aggregated by calendar month for segmented regression, specifically piecewise linear regression, to identify abrupt changes in time trends empirically. The model optimized data fitting to a single breakpoint between two straight lines with differing slopes. It was implemented using 'nl hockey' in Stata MP version 17 (College Station, TX, USA). Results are summarized in Table 2 and detailed visualizations are in Supplemental Material. Third, to provide tangible public health interpretation of segmented regression results, we summarized macro time differences between the beginning and end of the observation period. To do we this calculated means within each level of categorical variables which compared the first 24 months to the last six months (Table 2). These timeframes were selected to balance the number of observations (e.g., sample size) at early and later time points, as volume in later years was considerably greater than at the start. Visual inspection of continuous plots from segmented regression modeling in Supplemental Material did not reveal major differences if these time windows were to be modified to be twice as long. Fourth, based on programmatic

context and policy implication discussions, further time-trend modeling used linear splines at pre-specified dates if a specific question about an expected changepoint was being evaluated, such as a law enacted on a certain date or a major change in service delivery. Splines were modeled using 'mkspline' and incorporated as mixed effects linear models using 'xtmixed' in Stata.

For time-series analysis of changes in naloxone dose, we used government data from Allegheny County to identify phases in fatal and non-fatal overdose, defined in three waves [56,57] per the national understanding long-term overdose trajectories: prescription opioids and heroin (2005–2011), mostly heroin (2012–2015), and mostly unregulated (illicitly manufactured) fentanyl (2016–2023). In addition to segmented regression as a continuous variable, we also summarize the arithmetic mean of average monthly naloxone doses per ORE during the three waves.

Relative dose

Relative dose was defined as a relative ratio of the number of doses of naloxone administered in an overdose response event, useful when comparing between formulations. First, average number of doses per ORE were calculated by formulation, reporting the arithmetic mean and 95% confidence interval of the mean. Consistently over 17.5 years, participants had been counselled that 1 mL equals one dose, regardless of whether it came from the 10 mL vial or 1 mL vial. Since the 1 mL vial had the lowest number of doses per ORE, it was selected as the reference group. Relative doses by formulation are reported as percent higher doses per ORE, and population averages calculated using scaled Poisson regression, assessed using two-tailed chi-square Wald tests.

Rate differences

To compare adverse event (AE) incidence rates (per 1,000 OREs), rate differences between formulations were also estimated using Poisson regression in Stata, adjusting for the number of doses as a linear continuous variable. Since the 1 mL vial had the lowest rates of adverse events, it was treated as the reference group; the rate difference represents the number of additional adverse events per 1,000 OREs that were observed with the 4 mg nasal spray or multiple formulations, relative to the number of AEs for the 1 mL vial. This metric provides a general measure of population level side effects for each of the major formulations; it is not meant to be interpreted as counterfactual inference as would result from a causal pharmacoepidemiology study where strength of conclusions could be drawn based on control for confounding by formulation.

Data visualization

In time series plots, calendar month is presented on the horizontal axis from July 2005 to January 2023 (n = 210 months), except for adverse events in Fig 11 which are aggregated by year (2017−22) due to lower incidence and not having been collected in earlier years. The vertical axes are monthly arithmetic means. Overlaid scatterplots represent unadjusted data points. Time series were smoothed with locally estimated scatterplot smoothing (LOESS) and 95% confidence internal, with a 6-month window. In Supplemental Material for segmented regression, the two linear segments intervals are visualized instead. Because denominators for time trends can be different across figures, sparklines below the main time trends panel are provided to visualize fluctuations in monthly counts of new participants (Figs 2 and 4), naloxone doses distributed (Fig 5) or administered (Fig 9), or number of ORE (Fig 10). For visualizing the number of doses per ORE by formulation in Fig 8, a Gaussian (three sigma) smoother was applied. Figures were generated using Python 3.7 'matplotlib' within a distributed Deepnote (deepnote.com) environment.

Death case review

Prevention Point Pittsburgh conducted a review of reports in which the person administered naloxone was reported to have died. Paper records (encounter notes and written program logs) with interview notes were retrieved for the 23 deaths

that were reported by participants who had been at the scene and who had administered naloxone (n = 1,909) from 2020 to 2023; only one of these records did not contain any additional contextual information, but circumstances of death were present in the 22 others. Narratives of each death were constructed based on available records and assessed on when naloxone was administered relative to likely time of death, evidence of other causes of death described by health professionals, or other circumstances.

Study conduct

Open science practices. Pre-registration: DOI osf.io/b2f4h. Anonymized datasets, data collection form, analytical code and results, and Jupyter notebooks have been placed in this public repository: DOI osf.io/sq5d6.

Institutional ethics review. This study was reviewed by the University of North Carolina-Chapel Hill Office of Human Research Ethics and deemed to be exempt, as anonymized secondary data research (22–2714).

Data access

Data from Prevention Point Pittsburgh were provided to analysts on January 30, 2023. Data were anonymized so no individually identifiable information was available to analysts.

Participation of people with lived experience

People with lived experience of drug use, naloxone distribution, and overdose reversal were involved in the design and conduct of the services provided by Prevention Point Pittsburgh, as well as study conceptualization and interpretation of results. Results were to be reported back to participants of Prevention Point Pittsburgh through posters at program sites, a dedicated website, and a community presentation.

Results

Overview

Descriptive quantitative results and time trend analysis are presented for each variable analyzed first. These are followed by programmatic context notes provided by Prevention Point Pittsburgh staff.

The first of five topic areas covers characteristics of participants receiving naloxone, which was deemed of high importance by harm reduction program co-authors. The subsequent four sections focus on biomedical and behavioral features: naloxone distribution, circumstances of overdose response events, response behaviors, and adverse events.

Trends in naloxone distribution and administration were examined from July 24, 2005 through January 24, 2023, comprising an observation period of 210 consecutive calendar months (inclusive), or 17.5 years. A total of 16,904 service encounters by 7,582 unique participants, resulted in 70,234 doses of naloxone dispensed, with 5,521 OREs reported, utilizing 8,756 doses of naloxone.

New participant volume

Quantitative results. After a decade of steady volume (Fig 1), unique new participant intakes increased sharply starting January 2015. Pennsylvania Act 139 allowed standing orders and third-party naloxone prescriptions, and Prevention Point Pittsburgh's Medical Director issued a standing order for the organization, enabling naloxone distribution without requiring individual prescriptions. Monthly new participant intakes increased from an average of 10.4 per month (95% CI: 9.4, 11.4) to 65.9 per month (95% CI: 60.7, 71.1) after the law was enacted, translating to 56.2 (95% CI: 46.5, 65.8; Wald χ^2 510, 3 df, $p < 0.001$) additional new participants per month (Fig S1 in S1 File).

However, despite the immediate increase in new participants, the utilization of naloxone was lower. Average ORE per new participant enrolled in 2014 was 1.46 (95% CI: 0.84, 2.1), but in 2015 after the law change, it fell to 0.47 (95% CI:

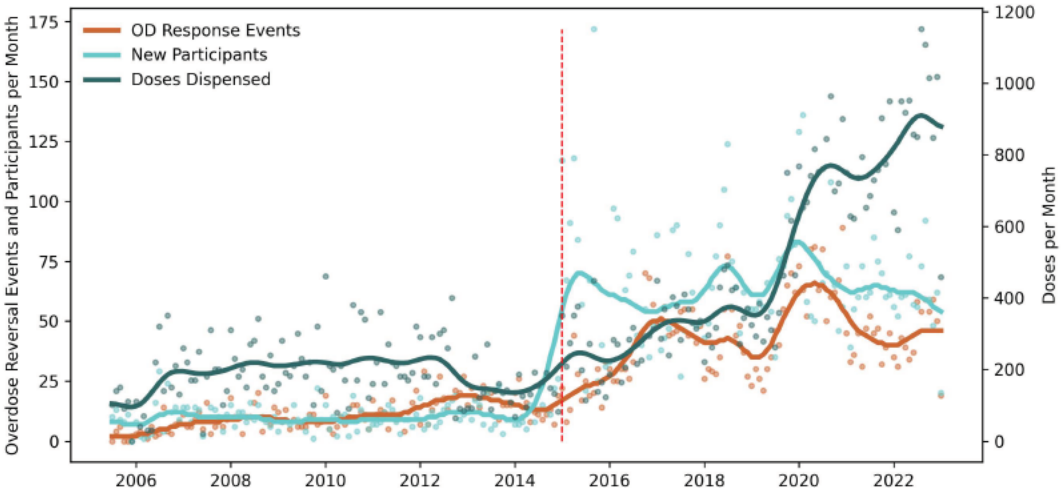

Fig 1. Monthly volume of new participants trained, naloxone dispensed, and overdose response events reported. Dots are raw monthly counts; lines are moving averages. Three time series are presented on two vertical axes. The left vertical axis is the number of new participants trained and the number of monthly overdose response events reported. The right vertical axis is the monthly count of doses of naloxone dispensed. The vertical red dashed line at December 2014 represents the change in state legislation.

https://doi.org/10.1371/journal.pone.0315026.g001

0.24, 0.70). This decrease mirrors, in part, a downward secular trend in OREs from 2013-2015 following the emergence of illicitly manufactured fentanyl in 2013, Fig 2. However, though a similar peak in overall OREs occurred in 2016–2017 as carfentanil was known to be circulating, no concurrent spike in new participant OREs occurred after enactment of state legislation. Overall, the trendline in OREs reported by new participants following the law change no longer mirrored the overall trendline, a decoupling that may suggest that new participants tended to be qualitatively different before and after the legislation.

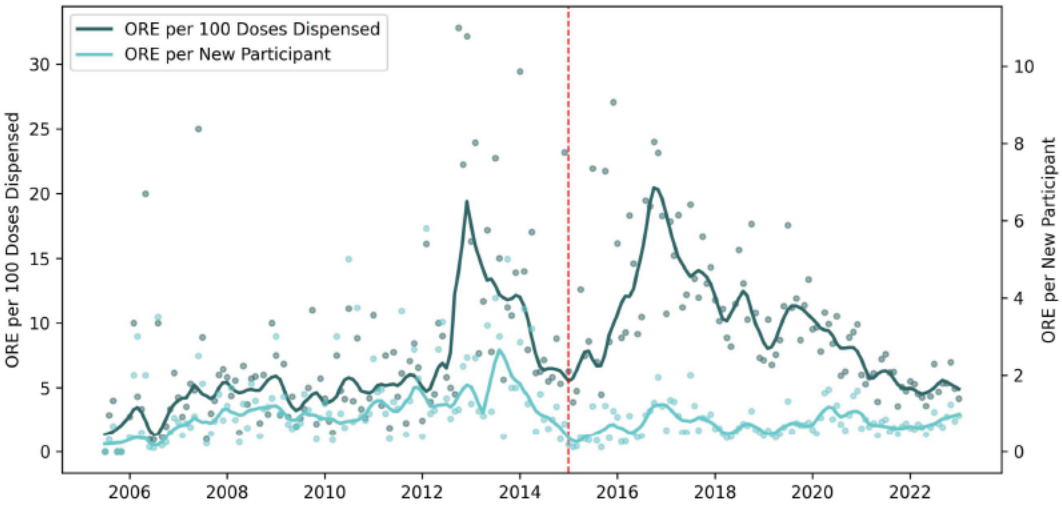

Fig 2. Monthly Rates of Overdose Response Events per 100 Doses of Naloxone Dispensed and New Participants. Dots are monthly rates; lines are moving averages. Monthly utilization rates of naloxone during overdose response events (ORE) are presented using doses dispensed and new participants as denominators. Red line at December 2014 represents the enactment of legislation enabling community based naloxone distribution. Study dates: July 2005 to January 2023.

https://doi.org/10.1371/journal.pone.0315026.g002

As suggested by the raw monthly counts of the two spikes in Fig 2, during sudden increases in overdose due to an unregulated drug supply, ORE per 100 doses dispensed can spike, remaining elevated for more than 6 months. This metric may help inform stocking by harm reduction programs during demand surges.

Programmatic context. Program staff verified the quantitative finding that the volume of new participants increased immediately after the law was enacted. However, they also provided context that, compared to previous years, new participants were demographically different: Increases were disproportionately in patients more likely to be older, female and of White race. In early 2015, the venues for overdose prevention trainings shifted from syringe services sites to fire houses and community centers, where audiences were exclusively constituted of the concerned general public, and not people who used drugs themselves. Program staff reported initial excitement at the broader reach of the intervention, but a few months later began to realize that the newly trained general community members were not reporting naloxone utilization or reversals. Accordingly, program staff felt that demographic changes after enactment of the law were crucial to document because they have direct implication on public health practice. Therefore, we proceeded to quantify the programmatic observation that the law led to a change in the underlying population receiving naloxone at Prevention Point Pittsburgh.

Participants: Age

Quantitative results. The median age at the initial training was 40 years (IQR: 31 years, 53 years), Table 1. Segmented regression (Table 2, Fig S3 in S1 File) identified a breakpoint in April 2015. From 2005 to 2015, average age increased in linear single-year increments during the first decade of naloxone distribution (Fig 3), so that the average age in 2005 was 31.6 years, and 41.5 in 2015, suggesting a possible birth-cohort influence if the source population is assumed to be stable without replenishment. Immediately following the enactment of the legislation, new participants were older: The average age increased from a baseline 37.0 years-old (95% CI: 36.3, 37.7) to 46.0 years-old (95% CI: 45.0, 46.9, *t*-test 14.9, 2048 df, $p < 0.001$) the following year.

Programmatic context. Program staff observations corroborated quantitative findings. The immediate increase in age during 2015 was due to large-audience naloxone training events hosted by Prevention Point Pittsburgh that attracted parents concerned about their children. These events were often held in venues outside of Pittsburgh city limits [58], including suburban and rural areas of western Pennsylvania. In a departure from traditional service delivery, these large-audience events attracted more family and friends than people who use drugs.

This increase in terms of age leveled out by the end of 2016 as Prevention Point Pittsburgh refocused outreach efforts to serve people who use drugs instead of concerned friends and family. This change in focus was made intentionally by program staff in early 2016 because there were fewer-than-expected ORE reports despite the large increase in new participants. Program staff believed that naloxone distributed in the mass training events to friends and family were less likely to be used, compared to when distributed directly to people who use drugs. In the most recent data years (2022−3), the downward age trend was explained as being due to programmatic expansion to mobile sites in previously underserved neighborhoods drawing younger populations.

Participants: Percent females

Quantitative results. Pursuant to Executive Order 14168 [59] by the President of the United States, full demographic distribution, as collected, is not provided. Although segmented regression did not identify a single breakpoint, visual inspection of the timeline and discussion with Prevention Point Pittsburgh staff suggested that the percent of new participants identifying as female increased in 2015−16, immediately following the enactment of the aforementioned naloxone law. The percent of female new participants increased from 34.6% (95% CI: 31.4%, 37.8%) to 58.1% (52.7%, 63.5%, *t*-test 8.0, 22 Satterthwaite df, $p < 0.001$) in the calendar year before and after the legislation.

Programmatic context. Prevention Point Pittsburgh staff noted that after the legislation there was increased representation of concerned mothers of children who use opioids who attended large training events. After 2016,

Table 1. Participant Characteristics, Behaviors, and Service Utilization.

PARTICIPANT CHARACTERISTICS		
Age at Intake		
Arithmetic mean (SD)	42 years (13.6)	
Median (IQR)	40 years (31, 53)	
Missing	119 (1.6%)	
Range	13 to 88 years	
Racial Identity	**N**	**%**
White	5,362	70.7%
Black	1,533	20.2%
Latinae	96	1.3%
Multi-racial	76	1.0%
Asian-American	26	0.34%
Native American	16	0.21%
Pacific Islander	3	0.04%
Other	46	0.61%
Missing	424	5.6%
Total Participants	7,582	100%
NALOXONE DISTRIBUTION		
Encounter Type		
Initial training	7,567	44.8%
Refill	9,337	55.2%
Total Encounters	16,904	100%
Naloxone Doses Dispensed by Encounter Type		
Initial training	27,279	38.8%
Refill	42,955	61.2%
Total Doses	70,234	100%
Reason(s) for Refill (multiple choice)		
Used it	5,521	57.5%
Need extra kit	2,307	24.0%
Gave it away	1,009	10.5%
Expired	375	3.9%
Lost	264	2.7%
Taken by law enforcement	37	0.4%
Other	89	0.9%
Total Refill Reasons	9,602	100%
OVERDOSE RESPONSE EVENTS REPORTED		
Who Administered Naloxone		
Person prescribed naloxone	4,374	79.2%
Someone else (bystander)	1,077	19.5%
Missing	70	1.3%
Total Reversals	5,521	100%
Naloxone Used On		
Friend	4,483	81.2%
You (person reporting)	491	8.89%
Family member	268	4.85%
Stranger	240	4.35%
Missing	39	0.71%

(Continued)

Table 1. (Continued)

PARTICIPANT CHARACTERISTICS		
Total Reversals	5,521	100%
Doses Administered per ORE		
Arithmetic mean (SD)	1.63 doses (0.99)	
Median (IQR)	1 dose (1, 2)	
Missing	133 (2.4%)	
Range	0.25 to 10 doses	
RESPONSE BEHAVIORS & SERVICE UTILIZATION		
Rescue Breathing		
No	2,768	50.1%
Yes	2,419	43.8%
Missing	334	6.0%
	0	0%
Total Reversals	5,521	100%
Chest Compressions*		
No	2,092	69.60%
Yes	711	23.70%
Missing	201	6.70%
Total Reversals	3,004	
Called 911		
No	4,530	82.0%
Yes	903	16.4%
Missing	88	1.6%
Total Reversals	5,521	100%
Ambulance Arrived After Calling 911		
No	456	50.5%
Yes	444	49.2%
Missing	3	0.33%
Total 911 Calls	903	100%
Hospital Transport		
No	5,209	94.3%
Yes	274	4.96%
Missing	38	0.69%
Total Reversals	5,521	100%

*Collected November 2015 to December 2020.

https://doi.org/10.1371/journal.pone.0315026.t001

Prevention Point Pittsburgh made the conscious decision to re-prioritize people who are actively using drugs for naloxone outreach, and the percent female new participants stabilized to around 40–50% per month. In recent years (2022–23), there was a noticeable uptick in the proportion of females to 50–60%, concurrent with the younger average age noted previously; additional demographic details are available elsewhere [60].

Participants: Racialized identity

Quantitative results. Self-reported racialized identity of participants was 70.7% White, 20.2% Black, 1.3% Latine, 1% multiracial, with less than 1% each of others, Table 1. The racial distribution mirrored the population of Allegheny County,

Table 2. Participant characteristics, behaviors, and adverse reactions in first 24 months and last 6 months, with segmented regression break-points (July 2005 to January 2023).

	First 24 months	Last 6 months	Segmented Regression				
	Percent	Percent	Break Month	95% CI	Test	Slope Before	Slope After
Participants							
Participant volume per month							
Average Age of Participants	31.6 years	41.5 years	Apr 2015	Oct 2008, Feb 2017	10.8, 3 df, p < 0.001	0.11	−0.01
Percent Non-White	11.3%	29.8%	Jan 2015	May 2012, Oct 2017	7.0, 3 df, p < 0.001	0.07	0.29
Perecnt Black race	4.9%	24.0%	Dec 2015	Feb 2014, Nov 2017	63.9, 3 df, p < 0.001	0.05	0.31
Refill Reason							
Percent of refills dispensed							
Expired	0.85%	1.1%	April 2010	Jul 2009, Jan 2011	12.7, 3 df, p < 0.001	0.39	−0.13
Used It	87.2%	36.9%	Aug 2017	Jul 2016, Sep 2018	22.5, 3 df, p < 0.001	0.01	−0.91
Gave Away	0%	28.9%	Jul 2018	Jan 2018, Dec 2018	58.1, 3 df, p < 0.001	0.004	0.35
Need Extra Kit	0%	32.3%	Jan 2012	Aug 2010, Jul 2013	8.8, 3 df, p < 0.001	0.015	0.21
Taken By Police*	3.4%	0.10%	Jun 2009	.	0.32, 3 df, p = 0.75	.	.
Other and Lost	8.5%	0.77%	*Not tested*				
Naloxone Used on Whom							
Percent of reversals reported							
Friend	74.8%	72.4%	Jun 2013	Aug 2011, May 2015	8.3, 3 df, p < 0.001	0.21	−0.15
You (person reporting)	7.6%	16.3%	May 2018	Dec 2016, Oct 2019	17.5, 3 df, p < 0.001	−0.04	0.32
Family member	1.4%	2.8%	Jul 2018	Nov 2014, Feb 2022	7.0, 3 df, < 0.001	0.02	−0.06
Stranger	0.95%	7.9%	*None found*	.	.	.	.
Response Behaviors & Services							
Percent of reversals reported							
Rescue Breathing	52.1%	34.3%	Jan 2014	Oct 2009, Apr 2018	4.0, 3 df, p < 0.001	0.013	−0.24
CPR Performed (percent of reversals)	35.8%	9.0%	Aug 2017	Feb 2016, Feb 2019	15.6, 3 df, p < 0.001	0.31	−0.25
911 Called (percent of reversals)	6.9%	5.4%	Dec 2017	Apr 2016, Aug 2019	9.6, 3 df, p < 0.001	0.06	−0.16
Hospital Transport*	0%	7.7%	*None found*				
Doses Per ORE	1.30 doses	1.78 doses	*None found*		0.28, 3 df, p = 0.60		
Adverse Reactions							
"Felt sick"	3.9%	1.5%	Aug 2019	Apr 2019, Jan 2020	43, 3 df, p < 0.001	0.006	−0.007
Angry	3.1%	11.9%	May 2020	Sep 2019, Dec 2020	35, 3 df, p < 0.001	0.004	−0.003
Shaking*	2.2%	0%	Dec 2018	Sep 2016, Mar 2021	5.7, 3 df, p = 0.0013	−0.0006	−0.0003
Confused*	0.10%	0.64%	*None found*		0.18, 3 df, p = 0.18		
Emesis*	0.05%	22.5%	*None found*				
Diarrhea*	0.09%	0.28%	*None found*				

* Low sample size values may result in lack of model precision. See supplemental material for plots.

https://doi.org/10.1371/journal.pone.0315026.t002

with greater representation by individuals identifying as Black, and fewer of Latine origin [61]. Unlike age and sex, the impact of the state legislation on race was less immediately evident and more nuanced. Segmented regression identified an inflection point in January 2015, showing an increase in non-White new participants (Table 2, Fig S4 in S1 File). However, segmented regression revealed that the increase in Black new participants did not actually start until a year later, after the end of December 2015 (Table 2, Fig 4).

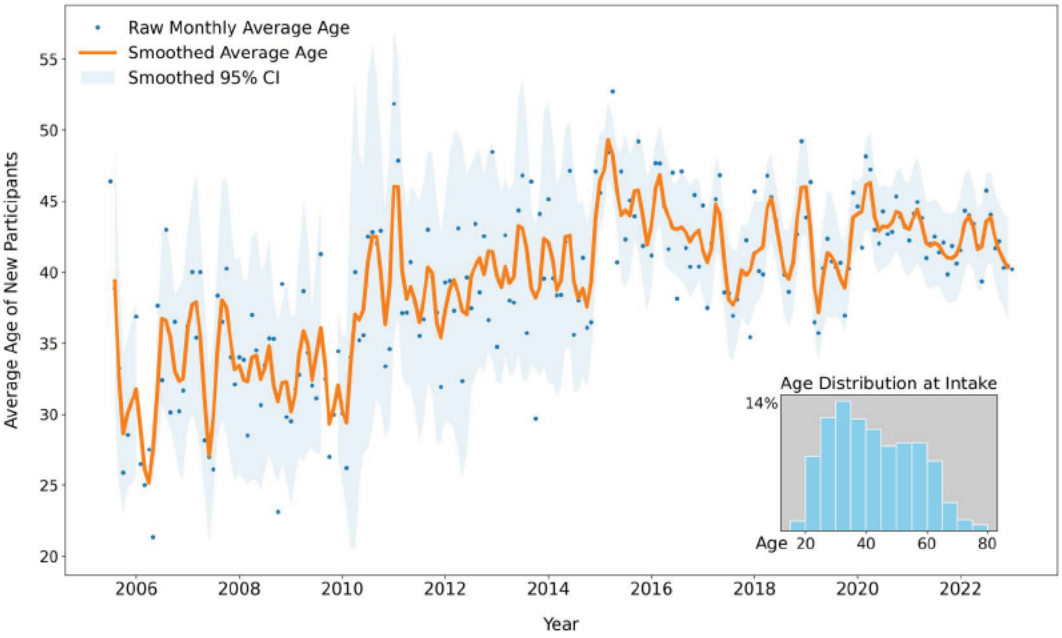

Fig 3. Average age of new participants receiving overdose reversal training and naloxone. Dots represent average age of new participants, by month. Time series of monthly average age for new participants receiving initial overdose prevention training and naloxone dispensing. Time series line (orange) and shaded 95% confidence interval of the mean (light blue) have been smoothed, and raw average age per month is depicted as dots. Inset plot is a histogram of average age of new participants, by 5-year bin increment, during the entire observation period: July 2005 to January 2023.

https://doi.org/10.1371/journal.pone.0315026.g003

Programmatic context. Prevention Point Pittsburgh staff noted that the increase in Black participants after 2015 was not surprising and was planned. A retrospective analysis of the first ten years of service delivery was conducted by staff in 2016 [16], which starkly quantified what up until then had been a casual observation, namely that the predominant race of participants was White, and that different strategies would be needed to engage people of color.

The statistical breakpoint in January 2016 conforms with a significant service change: In February 2016, Prevention Point Pittsburgh intentionally increased outreach to a predominantly Black neighborhood via mobile-based services and hiring community health advocates from the community to do naloxone distribution. A second predominantly Black neighborhood was served starting in late September 2019. While the law itself did not lead to a passive increase in Black participants, Prevention Point Pittsburgh staff did credit the law in allowing them to distribute naloxone in more places. For example, a barber shop in a predominantly Black neighborhood served as an early expansion site for naloxone distribution, a partnership that was brokered with the support of a local community leader identified by program staff. Staff further noted this active outreach was different than inbound solicitations from community groups for naloxone trainings; people who sought out Prevention Point Pittsburgh for group trainings tended to be serving White communities.

Iterative modeling and further contextualization

Based on explanations by Program staff, time trend analysis was refined. Spline models with knots at the dates of law enactment and the two outreach expansion dates demonstrated good fit for these inflection points; however, the period from September 2019 to January 2023 displayed non-linear temporal distribution (Fig S5 in S1 File). Visual inspection was corroborated empirically by the predicted output from the mixed effects model, which showed that the percent of Black new participants increased considerably after September 2019 ($\hat{y}_{\text{September}} = 27.0\%$ to $\hat{y}_{\text{October}} = 39.2\%$).

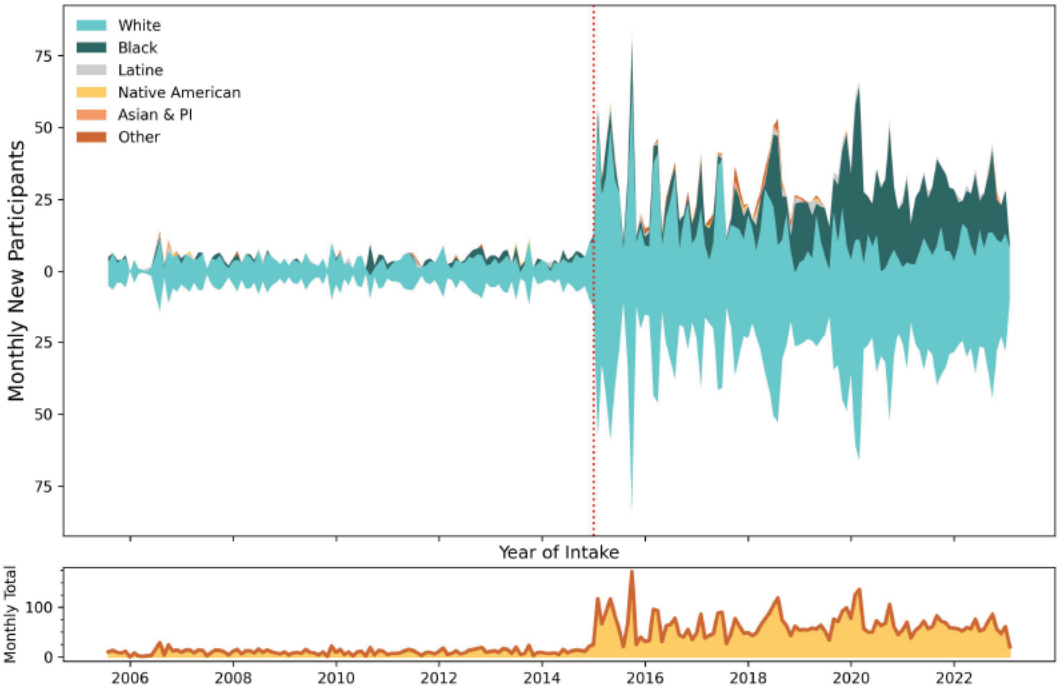

Fig 4. Racial identity of new participants dispensed naloxone. Top frame depicts timeline in new participant volume to naloxone training and dispensing, by self-reported racial identity. The vertical red dashed line at December 2014 represents the change in state legislation. Bottom frame is a smoothed sparkline of total volume of all new monthly participants. Study dates: July 2005 to January 2023.

https://doi.org/10.1371/journal.pone.0315026.g004

However, time-restricted segmented regression (Fig S4 in S1 File) identified a potential change point of December 2020 after which a decline in the percent of Black participants accelerated through the end of observation in January 2023, a result of expanded mobile services in another Pittsburgh neighborhood with a younger, predominantly White population. This particular mobile site was characterized by physicians who could start low-threshold buprenorphine inductions (i.e., a flexible treatment approach with same-day initiation, relaxed adherence requirements, and availability in non-traditional settings) [62] in the field. Low-threshold buprenorphine provision also drew participants to the harm reduction service side of the program, where take-home naloxone was also provided. Therefore, the increase in younger, White participants was the combined function of local demographics and the spillover effect stemming from providing medications for opioid use disorder.

In summary, enactment of a law in Pennsylvania led to an immediate increase in naloxone dispensed to concerned family and friends of people who use drugs. The law enabled Prevention Point Pittsburgh to expand to underserved neighborhoods, but inclusion of more racialized minorities also required service delivery innovation.

Naloxone distribution

Quantitative results. During the 17.5-year period, half of all naloxone doses dispensed by Prevention Point Pittsburgh were in 1 mL (0.4 mg/mL) vials (n = 35,715; 50.8%), followed by 10 mL (0.4 mg/mL) vials (n = 18,420; 26.2%), and 4 mg nasal spray (n = 16,063; 22.9%). Only 36 doses of the autoinjector were dispensed during a one-month period in 2016 with donated product. During the first decade of operation (Fig 5), Prevention Point Pittsburgh distributed the 10 mL vial exclusively.

Programmatic context. Program staff provided context for the two points where lines crossed. Initially the 10 mL vial was the only formulation available, but the 10 mL vial was replaced by 1 mL vials starting in October 2012 due to a new

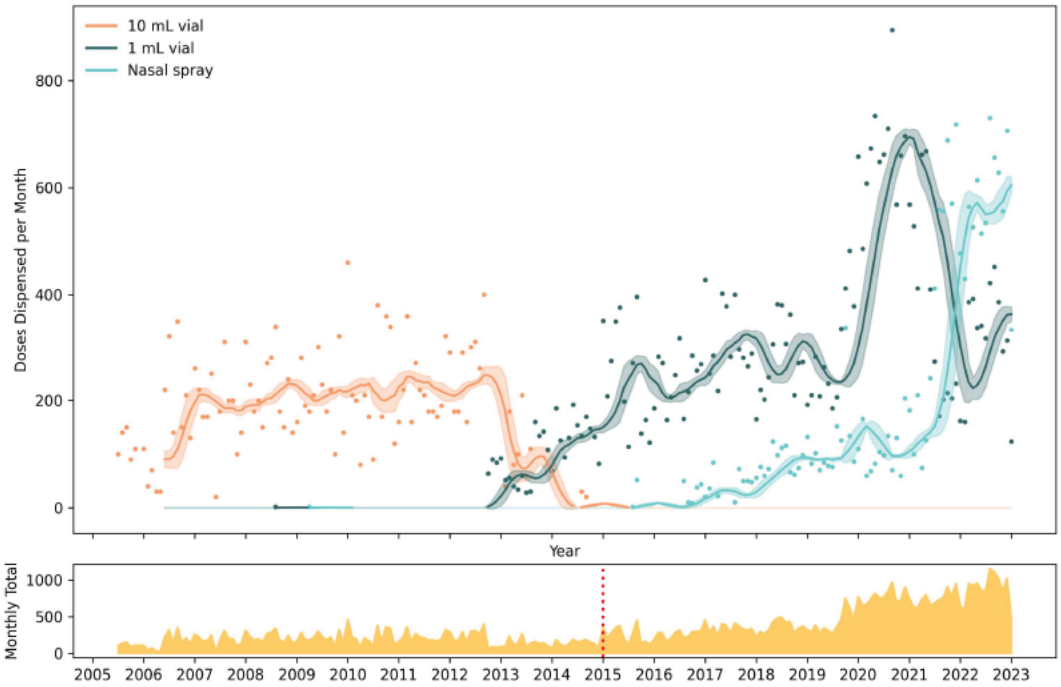

Fig 5. Major forms of naloxone distributed, July 2005 to January 2023. In the top panel, smoothed time series are displayed along with 95% confidence intervals of doses dispensed per month, by formulation. Colored dots represent raw counts of doses by month. The bottom panel is a sparkline showing total number of doses per month of naloxone distributed across all formulations. Initially only 10 mL vials were available for distribution. The vertical red dashed line at December 2014 represents the change in state legislation. The only other form of naloxone distributed by Prevention Point Pittsburgh was 36 units of an auto-injector in June 2016, which are not depicted. Study dates: July 2005 to January 2023.

https://doi.org/10.1371/journal.pone.0315026.g005

contract with the manufacturer. With this transition, by August 2013 all IM distribution was of 1 mL vials, packaged by the program as kits containing two 1 mL vials. The other line crossing occurred in Spring 2021 when a manufacturing problem disrupted 1 mL vial production. From May 2021 to September 2022, a manufacturing shortage of affordable naloxone led to a shortage of the 1 mL vials. The State of Pennsylvania was able to increase bulk nasal naloxone to Prevention Point, but the organization had to hire a part-time staff person to help other community-based programs with accessing the state ordering portal. After the shortage was resolved, 1 mL vial purchases resumed in late 2022.

Reasons for refill

Quantitative results. Over the 17.5 years, there were 16,904 participant-encounters by Prevention Point Pittsburgh staff, of which 44.8% (n = 7,567) were initial trainings (Table 1). The remainder of dispensing events occurred when refill requests participants who had previously been trained returned for a refill.

A total of 70,234 doses of naloxone were dispensed: 27,279 during initial training encounters (38.8%) and 42,955 (61.2%) during refills. The average number of doses dispensed per participant was 4.15, cumulatively.

"Used it" was the most common reason for refill in 57.5% of refill requests (Table 1, Fig 6). Segmented regression revealed that prior to August 2017, about 70% of refill requests were after naloxone had been used (Table 2, Fig S8 in S1 File). After this date, participants increasingly asked for refills for other reasons.

Obtaining a refill for naloxone because of expiration date was relatively rare, at 3.9% of refill requests overall. Segmented regression found an initial decrease in expired naloxone after April 2010 (Table 2), but inspection of trendlines

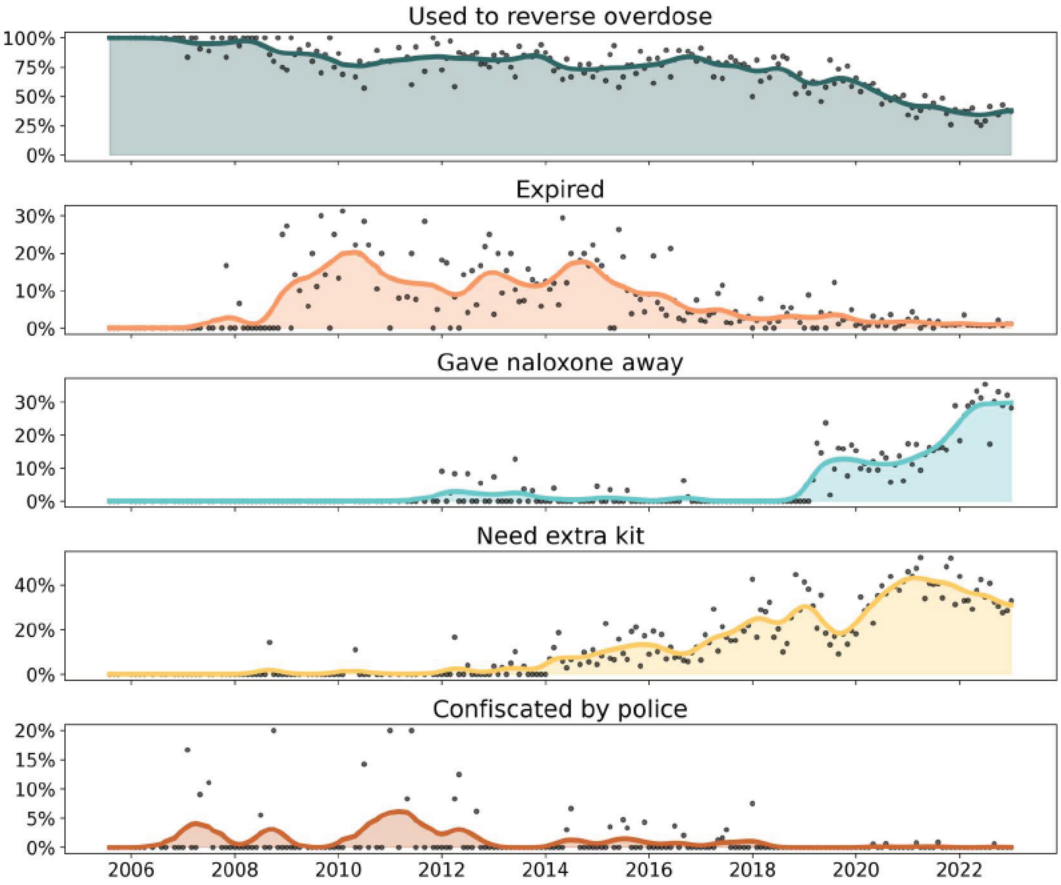

Fig 6. Reasons for requesting naloxone refills. Smoothed sparklines depicting monthly proportion of refill requests by reason for refill. Grey dots represent raw counts by month, while the colored lines are smoothed monthly average. Study dates: July 2005 to January 2023.

https://doi.org/10.1371/journal.pone.0315026.g006

(Fig 6) reveal further peaks over time, finally stabilizing in a lower proportion of refills from 2017 or 2018 onwards. Comparing these findings to Fig 5, the likelihood of expired naloxone refill does not correspond to the switch from 10 mL vials to 1 mL vials in calendar years 2012–2013. The further decline in proportion of expired naloxone in later years (2017 onwards) is somewhat contemporaneous with availability of the nasal spray, but samples are too small to draw further conclusions.

"Need an extra kit" was used by program staff to record when individuals who already had a kit and wanted a second one. This comprised 24.0% of refill requests overall, and segmented regression identified January 2012 as a change point (Table 2, Fig S7 in S1 File). Cumulatively, about 30% of refill requests were for this reason. This does not include people who used a kit and were looking for a refill.

"Gave away" increased substantially starting around July 2018 (Table 2, Fig S6 in S1 File), as suggested by segmented regression. While this reason was only 10.5% cumulatively, nearly a quarter of all refill requests were because of secondary distribution ("gave away"). Secondary distribution is a well-documented phenomenon where participants directly accessing harm reduction services obtain additional supplies for distribution among their peer networks informally [63,64].

Law enforcement confiscation of naloxone occurred mostly before the enactment of the statewide standing order in December 2014, in 37 instances. Other reasons for refill were very rarely reported (less than 1% combined), including only one or two reports of breakage of glass vials.

Programmatic context. Program staff clarified that, following the law change, increased participant reports of sharing naloxone with others ("gave away") may not represent a true change in behavior, but rather a gradual increase in participants' level of comfort reporting giving away naloxone as a form of secondary distribution, a phenomenon documented elsewhere after law changes [65]. Prior to the law change and the official sanction of naloxone distribution, coded language was often used by participants to emphasize the *personal* need for the naloxone because third-party prescribing was not legally sanctioned. Program staff attributed the legacy of prescription status and the requirement to have a documented clinical encounter as having conditioned participants to only talk about needing naloxone for themselves. As third-party prescribing of naloxone became less legally risky over time, participants became more willing to candidly discuss that they were giving their naloxone kits away to others. Prevention Point Pittsburgh staff noted a de-stigmatizing of naloxone after the passage of the law, an advance that was critical to enabling more honest dialogue with participants about their experiences.

Program staff provided more context for "need an extra kit" responses. This category often refers to individuals wanting to have naloxone available in multiple locations, such as both at home and in cars, or one for home and one to carry in a handbag.

Naloxone administration

Naloxone administration reports were limited to those instances where naloxone had been used (n = 5,521), instead of refill requests for other reasons. Naloxone was generally *administered* by the person to whom it had been prescribed and trained in 79.2% (n = 4,374) of OREs, leaving 19.5% on average administered by "someone else" at the scene (Table 1). However, this was different (Wald $\chi^2 = 218$, df 5, $p < 0.001$) by formulation: 33.2% of OREs with nasal sprays were done by someone else, whereas intramuscular formulations ranged from 10.1% to 16.4%. This suggested the necessity to examine to whom the naloxone was administered.

Naloxone used on whom

Quantitative results. The largest category represents 81.2% of ORE that were performed on friends and acquaintances, which decreased slightly over time (Fig 7, Table 1). Segmented regression yielded June 2013 as a change point after which other categories of people slightly increased in being administered naloxone instead of friends and acquaintances (Fig S10 in S1 File).

Naloxone was used on the person reporting the ORE ("you") in only 8.9% of cases. In these cases, the person who had been prescribed naloxone was also the person who had experienced the overdose and was self-reporting the ORE. Self-reported OREs were 7.6% in the first two years of program operations and had continued to decline until May 2018 after which they approximately doubled (Table 2, Fig S9 in S1 File). In the last 6 months of the observation period, the person reporting the ORE was also the person who experienced the overdose in 16.3% of reports. Interestingly, the percent of OREs on the reporter themselves was twice as high for nasal sprays (16.9%) than for injectable (8.5% 10 mL vial, 5.9% 1 mL vial) formulations.

Naloxone was administered on family and strangers rarely. OREs on family members were 4.8% overall (Table 1, Fig S11 in S1 File). In segmented regression, family OREs climbed gradually, but July 2018 emerged as a possible change point after which OREs of family members declined. Use on family members did not differ by formulation type (range across formulations: 4.4% to 5.3%), suggesting that both intramuscular and nasal formulations were equally likely to be used on family.

During the first two years of operations, naloxone administration to strangers was less than 1% but increased to 7.9% of ORE reports in the last 6 months of observation. Cumulatively, there were 239 (4.4%) total OREs on strangers. No change point was detected in segmented regression models. The nasal spray was slightly more likely to be used on strangers (5.7%, n = 78) than the 1 mL vial (4.2%, n = 128), and ahead of the 10 mL vial (2.7%, n = 23) distributed in early years.

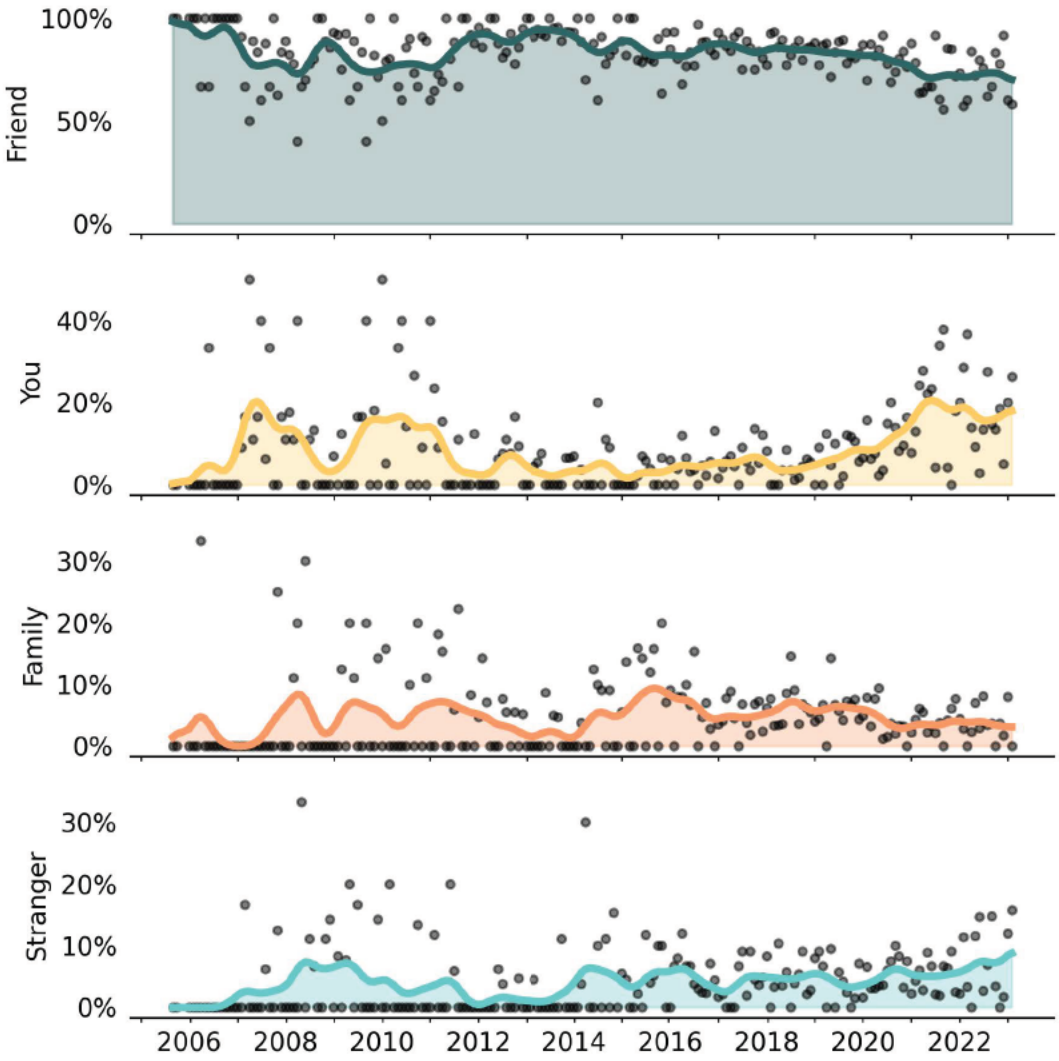

Fig 7. Person to whom naloxone was administered, monthly proportion of ORE reports. Dots represent monthly proportions for each exclusive category. Percents are based on total ORE reports as the denominator. The majority of naloxone administrations were performed on friends or acquaintances of the person reporting the overdose response event. "You" refers to the overdose having been experienced by the person who was reporting the overdose. Study dates: August 2005 to January 2023.

https://doi.org/10.1371/journal.pone.0315026.g007

Self-administration of naloxone was reported in 0.8% of ORE (n = 44 out of 5,521). Of these events, injectable formulations were self-administered in 77.3% (n = 34) of instances. Half of all self-administrations (n = 22) were a single dose, and 36.4% (n = 16) were two doses, comprising 86.4% of self-administration OREs. Self-administration happened when participants could immediately feel the strength of the opioid agonist, had naloxone on hand, and consciously felt that they had ingested a higher quantity than expected, all before the onset of serious overdose symptoms. Supporting this chain of events, self-administration was about 3 times more likely to occur during the years (2005–2016) of heroin and prescription opioid overdoses (14.4 per 1,000 ORE), compared with years (2016–2023) of unregulated fentanyl availability (5.5 per 1,000 ORE), likely due to the quicker onset of action with the latter.

Programmatic context. Prevention Point Pittsburgh staff offered a plausible explanation for the increase in "you" as the person who had been revived from overdose with naloxone. In the latter two years of the observation period, a

community outreach worker had been specifically engaging with "trap houses" where people congregated to use drugs [66,67]. Naloxone distribution in trap houses followed a different pattern than other types of community distribution, in what amounted to active case finding of people who had already experienced an overdose. The outreach worker would bring naloxone for distribution to the trap house, ask if anyone had recently had an overdose reversed with naloxone, and record these reversals. This practice was important for targeting naloxone distribution to a population who had already experienced an overdose and remained at elevated risk for subsequent overdoses. The corresponding data implication was that trap house delivery resulted in more "you" reports because naloxone was being provided to people *after* experiencing an overdose that had been reversed with naloxone by a peer. This stands in contrast to other community outreach settings where naloxone was provided to people *before* they had experienced an overdose.

Program staff did not have specific contextual or programmatic explanation for the increase in administration on strangers, pointing to the small numbers and cautioning against drawing conclusions. Staff emphasized that people use whichever formulation they have on hand, and that differences in rates usage by formulation are not purely a function of device usability. At Prevention Point Pittsburgh, where both intramuscular and nasal naloxone are equally available and participants are given the choice of which naloxone to take with them, many participants select intramuscular formulations if they believe *themselves* to be at risk of an overdose, and conversely, choose the nasal formulation if they expect to administer it *on acquaintances*. Therefore, when a stranger is encountered in an unresponsive state, participants administer whichever formulation of naloxone they are carrying at the time. Staff emphasized the parity between injectable and nasal formulations, in terms of usability and preference, as reported by the participants; each has its place in community-based overdose response and there was no strong preference for the nasal spray just based on its form factor.

Naloxone doses administered

Quantitative results. The cumulative number of naloxone doses administered was 8,756 during 5,521 ORE reports, Table 3. With the 1 mL vial, there were n = 4,551.25 doses administered during 3,082 OREs; n = 2,216 doses administered during 1,373 OREs used 4 mg nasal spray; 1,555.25 individual doses (1 mL) were administered from 10 mL vials during 880 OREs. Multiple forms of naloxone were administered in 151 ORE reports (n = 408.5 doses). Injectable forms of naloxone constituted 72.0% of all naloxone doses administered during OREs.

Cumulative utilization rates are a quantification of the number of dispensed doses used in OREs. Dose-standardized utilization rates were similar for the 1 mL vial (8.6 per 100 doses) and nasal spray (8.5 per 100 doses), and 4.8 per 100 doses for the 10 mL vial (Table 3).

The cumulative arithmetic average number of naloxone doses per overdose response event was 1.63 (95% CI: 1.60, 1.65), and the geometric mean was 1.44 (95% CI: 1.42, 1.46). Time trends presented in Fig 8 show two distinct patterns. The 1 mL vial and 4 mg nasal spray were used mostly as one or two doses (roughly bimodal), whereas the 10 mL vial and multiple forms represent more continuous distributions, including titrated fractional doses and administration of less than one full labeled dose to achieve reversal. When multiple forms of naloxone were administered, the number of total doses was greater (median of two versus median of one) than single formulation administrations.

The average doses per overdose response event was lowest for 1 mL vial with 1.51 doses (95% CI: 1.48, 1.54), Table 3. Using 1 mL vials as a reference group, the average number of doses per ORE was 7.5% higher (95% CI: 3.7%, 11.5% higher, $\chi^2 = 3.9$, Wald $p < 0.001$) for the nasal spray with 1.63 doses per ORE (95% CI: 1.58, 1.68). For the 10 mL vial, doses were 22.1% (95% CI: 15.6%, 28.9% higher doses, $\chi^2 = 7.1$, $p < 0.001$) higher than the 1 mL vial with 1.85 doses per ORE (95% CI: 1.75, 1.94). When multiple forms were used, the average doses were 2.76 doses per ORE (95% CI: 2.58, 2.94).

The overall rate of naloxone doses per overdose response event in Pittsburgh remained stable over a 17.5-year period (Fig 9). Segmented regression did not yield any statistically verifiable change points ($\chi^2 = 0.28$, 3 df, $p = 0.60$; Table 2) during the 17.5-year observation period of the number of doses per overdose response event (Fig S13 in S1 File).

Table 3. Distribution, overdose responses, and dosing by naloxone formulation.

NALOXONE DISTRIBUTION						
Naloxone Formulation	Dispensed by Prevention Point					
	Units	Doses				
1 mL vial	35,715 vials	35,715				
Nasal spray (4 mg)	8,032 two-packs	16,063				
10 mL vial	1,842 vials	18,420				
Autoinjector	18 two-packs	36				
Nasal adaptor		0				
Multiple forms		.				
Missing		0				
Totals		70,234				
OVERDOSE RESPONSE EVENTS						
			Utilization: ORE per 100 Units or Doses			
	Reversals	%	By Units	By Dose		
1 mL vial	3,082	56	8.63	8.63		
Nasal spray (4 mg)	1,373	25	17.1	8.55		
10 mL vial	880	16	47.8	4.78		
Autoinjector	14	0	77.8	38.9		
Nasal adaptor	1	0				
Multiple forms	151	3				
Missing	20	0				
Totals	5,521	100				
DOSES ADMINISTERED						
	Doses per ORE					
	Doses	Mean	95% CI	Relative Dose	95% CI	Wald Test
1 mL vial	4,551.25	1.51	1.48, 1.54	ref		
Nasal spray (4 mg)	2,216	1.63	1.58, 1.68	+7.5%	3.7%, 11.5%	x2 = 3.9; p < 0.001
10 mL vial	1,555.25	1.85	1.75, 1.94	+22.1%	15.6%, 28.9%	x2 = 7.1; p < 0.001
Autoinjector	23	1.64	1.20, 2.08	+8.6%	−16.2%, 40.7%	x2 = 0.6; p = 0.53
Nasal adaptor	2	2.00		+32.2%	29.7%, 34.7%	x2 = 28.8; p < 0.001
Multiple forms	408.5	2.76	2.58, 2.94	+82.4%	70.3%, 95.4%	x2 = 17.1; p < 0.001
Missing	153					
Totals	8,756					

Poisson regression, with x2-scaled residuals, and robust variance estimator, using complete case data (n = 5,375). 1 mL vials used as referent group. Model-based Wald x2 test, with 4 degrees of freedom.

* Estimated under the assumption that doses administered were dispensed by Prevention Point Pittsburgh. As the presence of the nasal adaptor report suggests, some participants may have obtained naloxone from other sources, such as pharmacy or other harm reduction programs, and would not be accounted for in the denominator.

https://doi.org/10.1371/journal.pone.0315026.t003

We summarized the continuous data by looking at the number of doses administered per ORE across the 3 waves of the opioid overdose epidemic. During the first wave (2005–2011), prescription opioid analgesics and heroin were the primary substances of concern, and naloxone doses per ORE was 1.92 (95%CI: 1.79, 2.05); as previously mentioned, this coincided with then the formulation type dispensed by Prevention point was exclusively 10 mL vials. From 2012 to 2015, as street availability of prescription opioids decreased and heroin was resurgent, average naloxone doses per ORE was 1.57 (95% CI: 1.50, 1.64). During the third wave (2016–2023), dominated by unregulated fentanyl the average naloxone doses per ORE was 1.60 (95% CI: 1.57, 1.63).

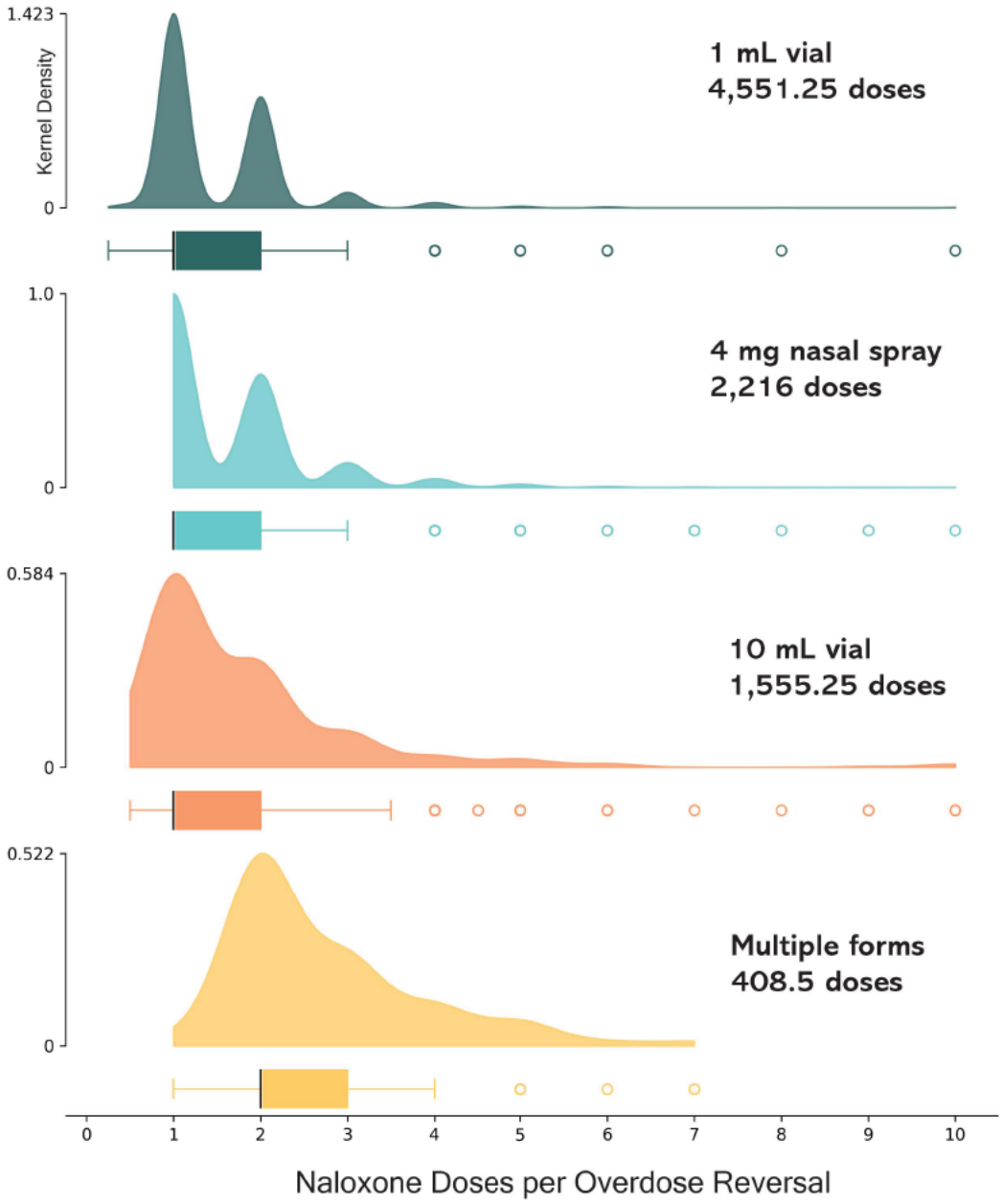

Fig 8. Number of naloxone doses administered per overdose response event. Average number of naloxone doses administered per overdose response event are presented with the vertical axis, smoothed using Gaussian kernel density estimators. For 1 mL and 10 mL vials, fractional dosing was observed, with less than a single full dose (1 mL of 0.4 mg/mL) being administered; this was not possible for the nasal spray, resulting in the visible left-truncation of the kernel density plot. Box plots below each graph show median and interquartile range are presented horizontally; circles represent outlier observations. Study dates: August 2005 to January 2023.

https://doi.org/10.1371/journal.pone.0315026.g008

Programmatic context

Program staff described that with the 10 mL vial it was easy for people to administer additional doses, and that unit dosing with the 1 mL vial and nasal spray reduced this behavior. Regarding re-dosing, training materials and curricula have always emphasized that participants should wait at least three minutes before giving an additional dose. In instances

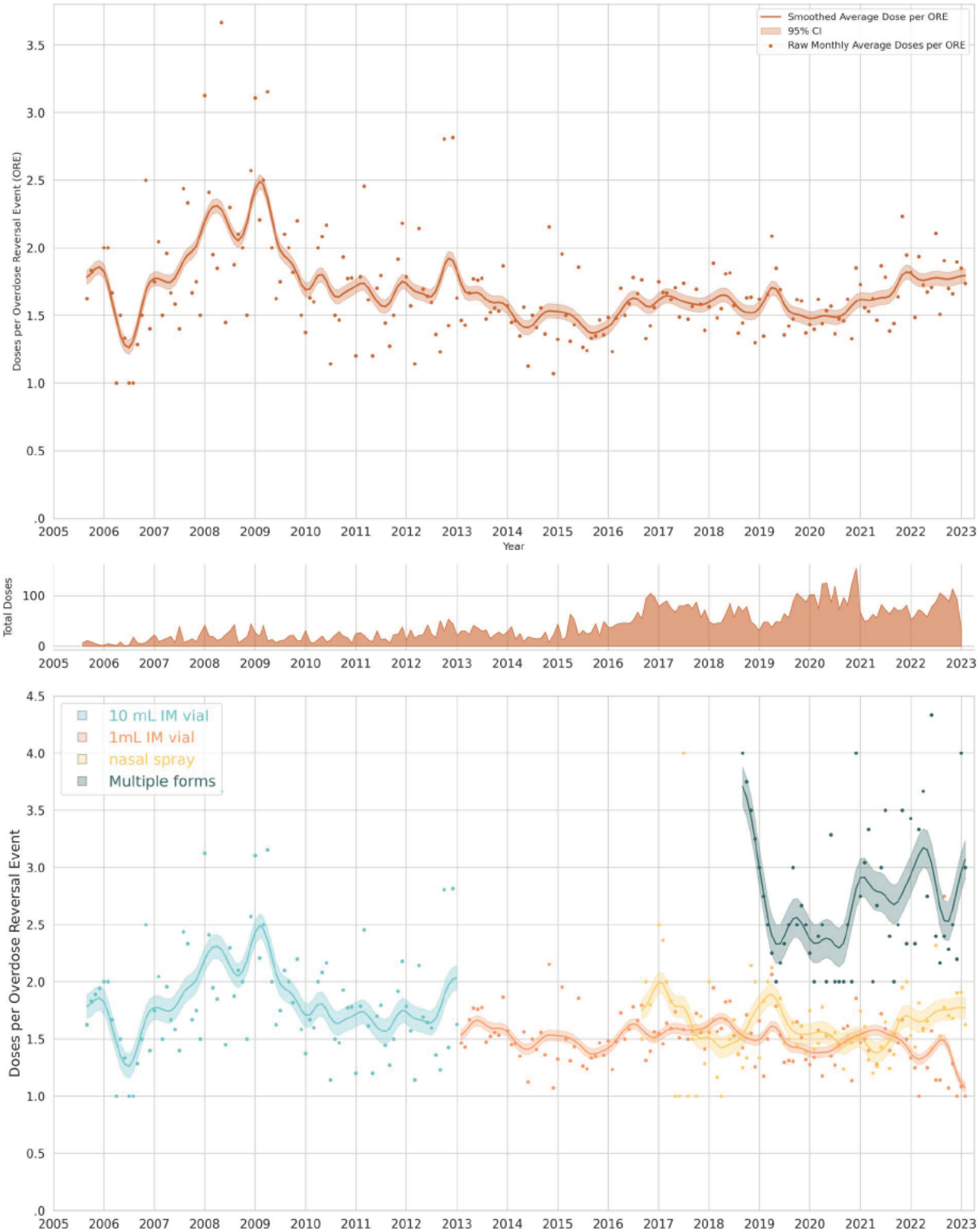

Fig 9. Time trends in naloxone doses per overdose response event, cumulatively and by formulation. Average number of naloxone doses administered per overdose response event for all formulations are presented in the top frame. In the bottom frame the same data are broken out by the three dominant formulations. The vertical axis corresponds to average monthly dose per overdose response event, with dots representing the raw monthly

average, and the trend lines depicting the Gaussian-smoothed rolling three-month rolling average. Shaded fill areas represent the 95% confidence interval of the smoothed mean doses per overdose response event per month. Study dates: July 2005 to January 2023.

https://doi.org/10.1371/journal.pone.0315026.g009

where many doses and/or multiple forms had been administered, program staff described that it was common for people to receive additional doses of naloxone after police or paramedics arrived, even if the person was already revived and was breathing. Therefore, extreme numbers of reported doses administered may reflect circumstances beyond the reporter's control, and doses not dispensed by Prevention Point Pittsburgh. Dose titration was also identified by program staff and the rest of the study team as an important phenomenon for exploration, and one that had not been previously characterized in scientific publications. Program staff believed that titration would be associated with fewer or less severe withdrawal-related adverse events, and this hypothesis was the basis for subsequent investigation.

Response behavior: Rescue breathing

Quantitative results. The percent of overdose response events in which rescue breathing was reported was 43.8% (n = 2,419 out of 5,521), Table 1. Segmented regression identified January 2014 (Fig 10) as a possible changepoint after which the percent of ORE with rescue breathing declined (Fig S14 in S1 File). In the last 6 months of observation, 34% of overdose response events mentioned rescue breathing, down from 52% in the first 2 years of the observation period (Fig 10). The COVID-19 pandemic did not appreciably accelerate the long-term temporal trend of declining rescue breathing during overdose response events. Segmented regression with an imposed breakpoint in March 2020 did not produce a meaningful statistical association, meaning that rescue breathing continued to decline at a linear decay trajectory consistent with the immediately preceding time period (Fig S14 in S1 File), independent of the pandemic.

Programmatic context

During the study period, Prevention Point Pittsburgh trainings recommended rescue breathing during an overdose response event. However, this recommendation was not made strongly during the height of the COVID-19 pandemic, but was re-emphasized in trainings starting in 2023, after xylazine started appearing in the local unregulated opioid supply in 2022 [68].

Program staff also noted that while rescue breathing was taught at the initial trainings, it was not reinforced during refill encounters, with one exception: If participants reported needing to use more than 2 doses of naloxone, they were counselled to use rescue breathing and count respiration in future reversals. Therefore, the slight uptick in rescue breathing in 2022 may have been influenced by this directive. In the same year, xylazine started to appear alongside fentanyl in the local unregulated drug supply, complicating reversals because the person who had overdosed may not become responsive to stimuli upon naloxone administration, even if respiration was adequately restored. It was not until March 2023, beyond the end of observation, that Prevention Point Pittsburgh formalized the recommendation to reemphasize counting breaths after naloxone administration (and provide rescue breathing if needed) to participants via handouts and flyers in the context of xylazine; the intent was to dissuade unnecessarily high doses of naloxone being administered if the participant was breathing adequately but did not become immediately reanimated. This was also contemporaneous with the start of disposable xylazine test strip distribution. While this programmatic evolution was not formalized until after the end of the observation period, Prevention Point Pittsburgh noted that the same advice had been delivered to participants in less systematic ways in the months prior. Staff also pointed out that the current over-the-counter label [49] for naloxone nasal sprays does not include instructions for rescue breathing but that they provide the instructions themselves.

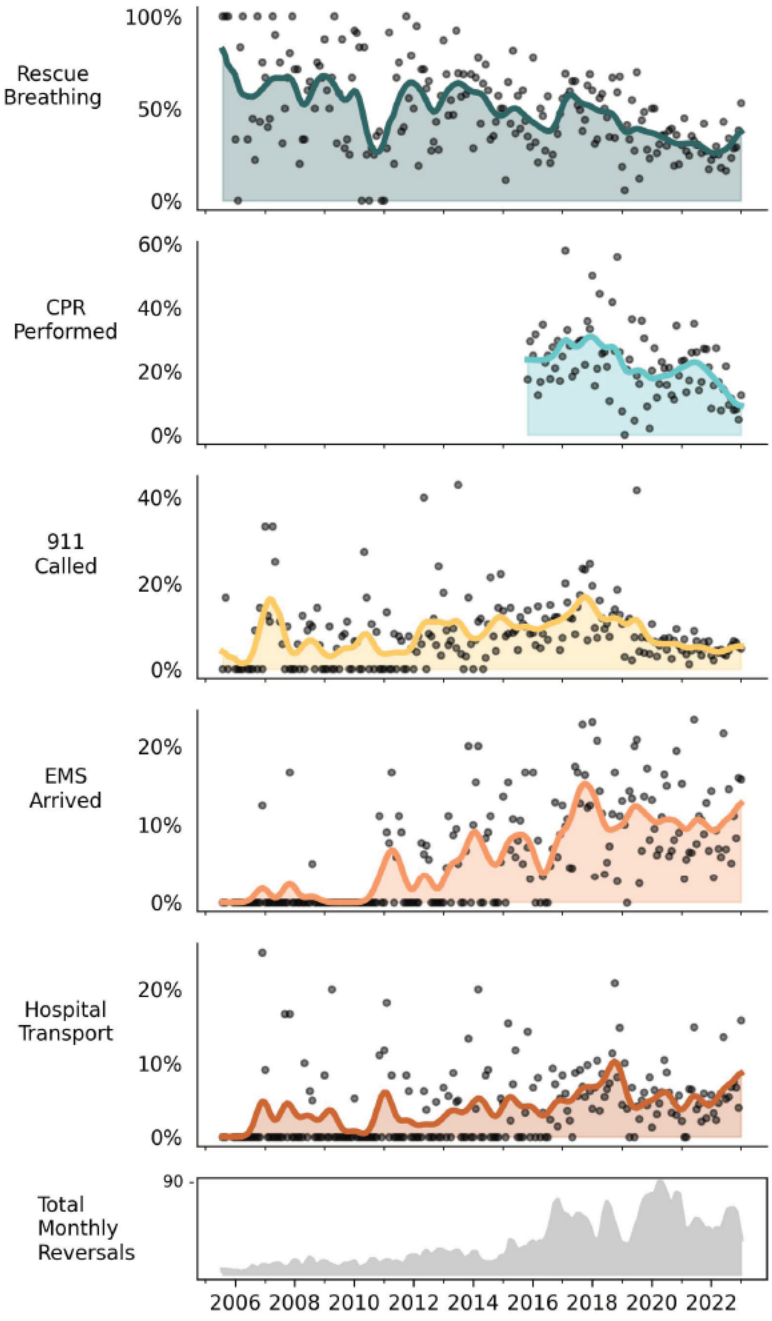

Fig 10. Proportion of naloxone administration reports in which response behaviors were reported. Smoothed time series depicting the percent of overdose response events in which response behaviors were reported. Time series for EMS arrived is conditional on participant having called 911 (*n*=903); an additional 36 events are not represented when EMS arrived and the participant had not called 911.The bottom panel shows monthly volume of total overdose response events (ORE). Study dates: August 2005 to January 2023.

https://doi.org/10.1371/journal.pone.0315026.g010

Response behavior: Chest compressions

Quantitative results. Data on chest compressions (commonly called "CPR" for cardio-pulmonary resuscitation) were recorded from 2016 to 2023. Chest compressions were reported to have been conducted in only 23.7% of OREs (n=711

out of 3,004 reports). Segmented regression identified February 2017 as a changepoint after which chest compressions declined (Table 2, Fig 10).

Programmatic context. Prevention Point Pittsburgh staff pointed out that in 2016, the New York State Health Department convened a working group of physicians and scientists to establish the necessity of recommending CPR for opioid overdose reversal. At the time, CPR was recommended widely in Canada but not by the World Health Organization, and within the US instructions were inconsistent. The onset of data collection at Prevention Point was intended to inform this debate. The medical consensus of the New York State working group was that chest compressions were not required [69]. As a result, Prevention Point Pittsburgh modified recommendations to participants de-emphasizing chest compressions, which had been part of the original training. They attribute the decline in CPR in 2017 to be related to this programmatic shift.

Response behavior: Calling 911

Quantitative results. Overall, 911 was called in 16.4% (n = 903 out of 5,521) of ORE reports (Table 1, Fig 10). When 911 was called, EMS arrived half the time, or 49.2% of reports (n = 444 out of 903, with 0.3% missing). Segmented regression identified December 2017 as a changepoint after which calls to 911 decreased considerably; during the last 6 months of the observation period, 911 was called in only 5.4% of OREs.

Programmatic context. Calling emergency medical services (EMS, i.e., 911) was universally recommended in trainings by Prevention Point Pittsburgh. However, fear of criminal prosecution is expected to have dampened the likelihood of this behavior. The Pennsylvania "Good Samaritan" Act 139 was enacted in December 2014, offering limited criminal immunity for minor drug possession charges when calling EMS during an overdose [70]. In spline regression, comparing before and after the law change (Fig S17 in S1 File), there appears to have been a transitory increase in calls to 911, which was not sustained over time. Program staff also stated that people who do not use drugs are more likely to call 911, and increases in dispensing naloxone outside of networks of people who use drugs in the years after state legislation enactment could have contributed to the transitory increase in 911 calls.

Program staff offered explanations to account for the surprisingly low rate of EMS arrival, based on conversations during the ORE report intake that were not quantified on forms. The common theme was wanting to avoid encountering first responders (which could include police) unless absolutely necessary, especially in the context of drug-induced homicide laws as documented elsewhere [71]. Successful reversals may have resulted in a follow-up call to 911 stating that EMS were no longer required. The reporter may have called EMS, administered naloxone, and then left the scene, and therefore may not know for certain if EMS arrived. For these reasons, program staff cautioned in the interpretation of the seemingly low rate of EMS arrival in these data.

Response behavior: Hospital transport

Quantitative results. Among the 5,521 ORE reports, hospital transport was reported in 5.0% (n = 274) of OREs. No temporal changepoint was detected in segmented regression, Table 2. Visual inspection of the time trend revealed heavy concentration of zeros (e.g., no hospital transport) in the first 11 years of the observation period (Fig 10). The last six months of the observation period suggested an uptick, with 7.7% (95% CI: 3.3%, 12.0%) of OREs having had hospital transport.

Programmatic context. Empirical data show that hospital transport had a sudden peak in 2017 [72]; program staff pointed out that this was the year with peak overdose deaths in Allegheny County, as well being contemporaneous with the brief emergence of carfentanil in the unregulated drug supply. Additionally, based on interviews during ORE reports, program staff suggested that emergence of xylazine in 2022 may have led to more hospital transport due to lack of reanimation.

Adverse events

Granular information on specific adverse events (AEs) was recorded systematically starting in August 2016 and are thus available for 4,606 ORE reports, which constitutes the denominator for rate calculations. Any adverse event was noted in 31.4% (n = 1,446/4,606) of OREs. Overall, emesis (vomiting), anger, and "feeling sick" were the most commonly reported adverse events. Annualized time trends in AE counts and rates per OREs are displayed in Fig 11 for the 6 calendar years (2017−22) with complete reporting. The two most common AEs (Table 4) described in free text notes were confusion (n = 11) and diarrhea (n = 4), which only were reported with the 1 mL vial. There was no indication in free text fields for wooden chest syndrome, muscle rigidity, laryngospasm, or pulmonary edema, which are other adverse events of concern with illicitly manufactured synthetic opioids.

OREs in which adverse events were reported had slightly higher average naloxone doses 1.66 (95% CI: 1.62, 1.71) compared with all OREs 1.59 (95% CI: 1.56, 1.61). More than one dose of naloxone was associated with higher incidence of any reported adverse event, 47.3% of OREs (n = 685/1,446), compared to 40.7% (n = 1,287/3,160) of OREs when one or fewer doses were administered (Wald $\chi^2 = 17.8$, 1 df, $p < 0.001$), a rate difference of 6.6 per 100 OREs (95% CI: 3.5, 9.7).

Adverse events: Emesis

Quantitative results. Emesis (vomiting or "puking") was reported in 13.2% (n = 607) of OREs, but differed (Wald x^2 108, 2 df, $p < 0.001$) considerably by formulation. OREs using the 4 mg nasal spray were twice as likely to result in emesis compared to the 1 mL vial (20.8% versus 9.6%), Table 4. After adjusting for doses administered, there were 106 (95% CI: 82, 130) more emesis events per 1,000 OREs with the 4 mg nasal spray than the 1 mL vial at 0.4 mg/mL.

In both absolute and relative (to OREs) rates, Fig 11, emesis increased as a reported adverse event from 2017 to 2022. In the era when only 1 mL vials were distributed, about 16% of ORE involved emesis, going up to about 23% when naloxone distribution included vials and 4 mg nasal spray both, contemporaneous also with the advent of illicitly manufactured fentanyl.

Programmatic context. Prevention Point Pittsburgh staff noted that emesis was the most objectively observable adverse event, and that it would be more likely to be reported than other more subjective adverse events, impacting interpretation of relative prevalence between AEs. But they did not identify a reason why reporting of emesis would be different between formulations, providing credence to inter-formulation comparisons.

Adverse events: Anger

Quantitative results. Anger was reported in 11.9% of OREs (n = 546/4606) and differed by formulation (Wald χ^2 108, 2 df, $p < 0.001$). The 1 mL vial was associated with fewer angry AE reports, at 10.2%, compared to 15.1% of OREs with the 4 mg nasal spray, Table 4. After adjusting for doses administered, per 1000 OREs there were 48.5 (95% CI: 47.8, 49.2) additional cases of anger after administration of the nasal spray.

In both absolute and relative measures, anger after naloxone administration was most reported in 2020, during the phases of COVID-19 pandemic isolation. However, even though 4 mg nasal spray supplanted 1 mL vials during a sudden injectable naloxone supply shortfall in 2021−22 (Fig 5), reports of anger after naloxone administration returned to pre-pandemic levels despite the formulation change. This shortfall was the result of manufacturing difficulties at the single manufacturer that supplied the Naloxone Buyers Club, resulting in nationwide lack of availability for harm reduction programs [73].

Programmatic context. Prevention Point Pittsburgh staff cautioned that if someone was vomiting, they may not be able to simultaneously express anger, and therefore the reported numbers are likely an undercount of experience. Perceptions of what constitutes anger could also be subjective, and in very rare cases extreme, with confrontational action against the person reversing the overdose. But they did not identify reasons why reporting would be different by formulation.

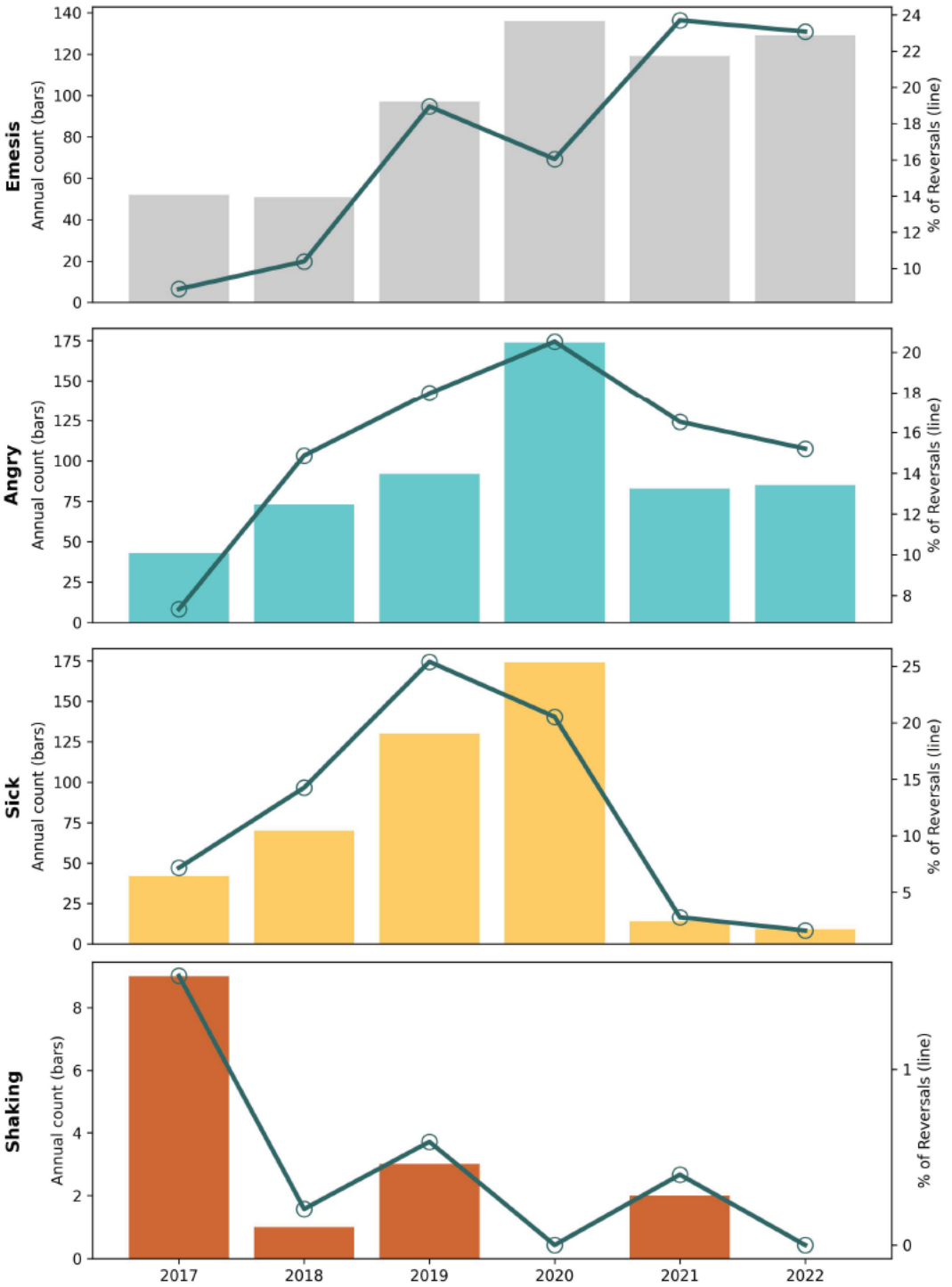

Fig 11. Annual counts and percents of adverse events following naloxone administration. Vertical bars are counts of adverse event reports by year. Green lines are percents of overdose response events annually (N = 4,606 total), enumerated on the right vertical axis.

https://doi.org/10.1371/journal.pone.0315026.g011

Table 4. Adverse events reported after naloxone administration, by formulation and dose, August 2016 to January 2023.

			Naloxone Formulation				Doses Administered		
		Total	1 mL vial	Nasal 4 mg	Multiple Forms	Wald Test*	Average Doses (95% CI)	Cases >1 Dose	Percent of Cases > 1 Dose
	All Reversals	4,606	3,082	1,373	151		1.59 (1.56, 1.61)	1,972	43.6%
	Reversals with any AE recorded below	1,446	820	557	69		1.66 (1.62, 1.71)	685	47.8%
Emesis	Cases	607	296	284	31	x2 108, p < 0.001	1.73 (1.65, 1.81)	308	50.7%
	(Percent) or Rate per 1,000 Reversals	(13.2%)	96.2	207.6	205.3				
	Rate Difference per 1,000 reversals relative to 1 mL vial, adjusted for dose		ref	+106	+90.3				
	Rate difference 95% CI			+82.0, +130	+22.6, +158				
Angry	Cases	546	314	206	31	x2 31, p < 0.001	1.61 (1.53, 1.68)	237	43.4%
	(Percent) or Rate per 1,000 Reversals	(11.9%)	102.1	150.6	205.3				
	Rate Difference per 1,000 reversals relative to 1 mL vial, adjusted for dose		ref	+48.5	+103				
	Rate difference 95% CI			+47.8, +49.2	+101, +105				
Felt Sick	Cases	440	291	136	18	x2 1.1, p = 0.56	1.58 (1.50, 1.67)	186	42.3%
	(Percent) or Rate per 1,000 Reversals	(9.6%)	94.6	99.4	119.2				
	Rate Difference per 1,000 reversals relative to 1 mL vial, adjusted for dose		ref	+4.8	+24.6				
	Rate difference 95% CI			+4.2, +5.4	+22.8, +26.4				
Death	Cases	47	24	20	3	x2 5.6, exact p = 0.043	1.94 (1.63, 2.24)	29	61.7%
	(Percent) or Rate per 1,000 Reversals	(1.02%)	7.8	14.6	2.0				
	Rate Difference per 1,000 reversals relative to 1 mL vial, adjusted for dose		ref	+4.5	+8.4				
	Rate difference 95% CI			−2.6, +11.6	−14.9, +31.6				
Shaking	Cases	33	27	5	1	x2 10.5, exact p = 0.005	1.97 (1.50, 2.43)	21	63.4%
	(Percent) or Rate per 1,000 Reversals	(0.7%)	8.8	3.7	6.6				
	Rate Difference per 1,000 reversals relative to 1 mL vial		ref	−5.1	−2.1				
	Rate difference 95% CI			−5.0, −5.3	−1.7, −2.6				
Confusion**	Cases	11	11	0	0		2.36 (1.40, 3.32)	8	72.7%
	Rate per 1,000 Reversals		3.6						
Diarrhea**	Cases	4	4	0	0		1.25 (0.45, 2.0)	1	25.0%
	Rate per 1,000 Reversals		1.3						

* Model-based Wald chi-square test with 2 df. Fisher's Exact test was used if any cell count was less than 10.

** Interpret with caution.Derived from free text notes, not recorded on structured form.

https://doi.org/10.1371/journal.pone.0315026.t004

Adverse events: "Felt Sick"

Quantitative results. "Felt sick" was understood by participants to mean "dopesick" from precipitated opioid withdrawal. Cumulatively, 440 cases of "feeling sick" were reported, in 9.6% of OREs (Table 4). The incidence rate difference between formulations was negligible.

Adverse events where the recipient "felt sick" were highest in 2019, in nearly 25% of OREs, but highest in terms of absolute number (about 175 per year) in 2020, Fig 11. There was a drop in reports of "feeling sick" in 2021−2.

Programmatic context. Prevention Point Pittsburgh staff did not have a specific attribution to explain temporal variation in feeling sick. However, they pointed out that feeling dopesick was a subjective experience that may not be entirely or objectively observable by the person who administered naloxone and was providing the ORE report.

Study co-author and Prevention Point Staff member MV provided insight into how withdrawal severity can influence immediate or repeated re-dosing with opioid agonists, thereby putting someone at risk for another overdose. In testimony provided at a scientific conference, MV described visiting a city where he found himself among strangers. Unfamiliar with the strength of the local drug supply, he overdosed on heroin, and bystanders administered 3 doses of naloxone and called 911. Soon thereafter, he received multiple additional doses from uniformed first responders, even though not required. The aftermath, both immediate and later, revealed two distinct concepts of adverse events. He felt very anxious and was vomiting so frequently he had trouble breathing: "I tried to re-dose with heroin every 15 minutes to feel anything other than this horrible feeling. For months after that bad overdose, I was super hesitant to use around others. I mostly wanted to use alone to avoid something like that from happening again which put me at great risk." [74] The data collected by Prevention Point Pittsburgh did not record opioid redosing behavior post-overdose, and participants likely interpreted "felt sick" as it related to the day of the overdose event, but program staff felt that in the context of interpreting quantitative results, that the experiential context provided by MV was insightful.

Adverse events: Shaking

Quantitative results. Shaking was systematically collected, and was reported in n = 33 OREs, and differentially by formulation: n = 27 cases using the 1 mL vial, n = 5 with nasal alone, and n = 1 with multiple forms (Fisher's Exact 10.8, 2 df, $p < 0.005$). The incidence rate difference of −5.1 cases (95% CI: −5.0, −5.3) per 1,000 OREs slightly favored the nasal spray over the 1 mL vial. Shaking was mostly reported in 2017, Fig 11, with 9 cases, and three or fewer in subsequent years.

Programmatic context. Shaking was interpreted by Prevention Point Staff to be a sign of opioid withdrawal, as opposed to seizures. No plausible explanation for this phenomenon was offered by Prevention Point Pittsburgh staff.

Adverse events: "Was Okay" versus death

Quantitative results. Participants presenting for refills had been asked if the person on whom naloxone was administered "was okay" after the ORE, to the best of their knowledge, since the start of study observation. This category is conceptually understood to encompass survivorship, even if hospital transport or adverse events occurred, and serves as a contextual adjunct to deaths. Cumulatively, in 5,449 out of 5,521 reports (98.7%) from 2005 to 2023, the participant felt confident enough to respond. The person on whom naloxone had been used was judged to be "okay" 98.0% of the time (n = 5,340/5,449 among the three dominant naloxone formulations). Differences by formulation were observed (Pearson χ^2 32.7, 3 df, $p < 0.001$), but were small: 98.5% okay with 1 mL vial, 99.2% with 10 mL vial, 96.4% with 4 mg nasal spray, and 95.4% with multiple forms.

Death as an adverse event was collected from 2016 onwards. There were 47 out of 4,606 reports (1.0%) of death following naloxone administration.

Programmatic context. Program staff had strong cautions about interpretation of deaths following naloxone administration. The death case review provides additional context below. In addition, program staff felt that as the volume

of naloxone distributed has increased within networks of people using drugs together, there should be increased likelihood of someone at the scene carrying naloxone. Therefore, they interpreted deaths following naloxone administration as an indirect indicator of people who had been using drugs alone. Forced isolation during the first year of the COVID pandemic provided an opportunity to test this hypothesis, as described below.

Death case review

Quantitative results. From 2020 through 2022, encounter notes with contextual information were available for 22 out of 23 deaths. In 18 cases the person was found "too late" after death for naloxone to be effective, for example the morning after an overdose that had likely occurred the previous evening. In three cases, paramedics told the reporter that there was an alternative cause of death other than overdose. In one instance, a reporter said that police had not allowed her to administer the naloxone that she was carrying, and the person died.

Quantitative AE data allowed empiric corroboration that deaths increased during the height of pandemic isolation. Most years, 5 or fewer deaths were reported, Fig 12. However, in 2020, the annual reports tripled in both absolute and relative terms. This single-year increase paralleled the time-trend with AEs for anger, but with much lower sample size.

Programmatic context. Program staff posited that, under the assumption that using drugs alone was more common during forced social isolation and quarantine periods of the first year of the COVID-19 pandemic, people who had overdosed may have been less likely to have been found for timely action. Alternatively, additional respiratory compromise stemming from viral infection could be a plausible contributory cause. Overwhelmed EMS during the early pandemic could also in part explain the single year increase in reported deaths. Program staff emphasized that they did not experience a drop in service provision during COVID and increased how much supplies were distributed per visit to reduce the need for return visits, as well as providing additional services (food, clothing, etc.) to meet community needs.

Adverse events and dose titration

During the period where AE information was being systematically recorded (2016 onwards), the 1 mL vial offers a unique opportunity to conceptually explore dose-response between naloxone dose and adverse events. The expectation was that naloxone dose titration would result in fewer adverse events. Titration was defined as reporting fractional dosing (n = 117 OREs), and non-titration was defined as integer doses of naloxone administered (n = 2,953 OREs). This imperfect exploratory measure deserves reiteration of the caveat for misclassification: Two half doses administered separately would be reported as 1.0 dose, but in this simple metric would be misclassified integer dosing. This is expected to bias towards the null.

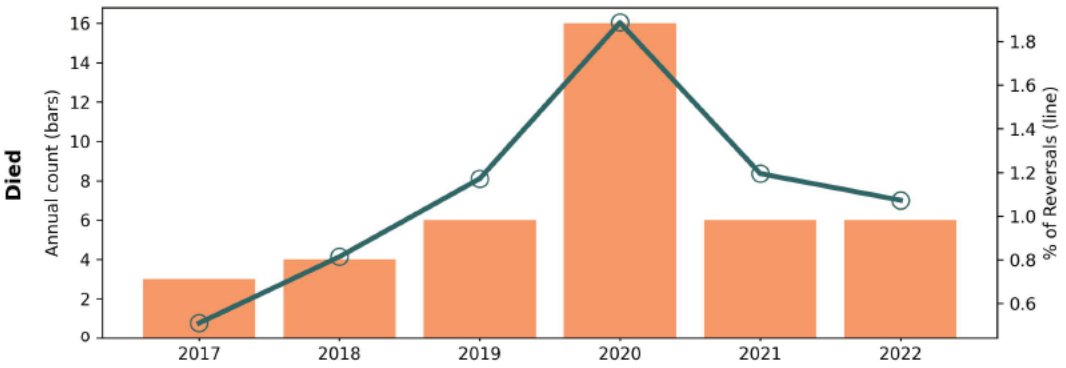

Fig 12. Annual counts and percents of deaths reported. Vertical bars are counts of adverse event reports by year. Green lines are percents of overdose response events annually (N = 4,606 total), enumerated on the right vertical axis.

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Titration of naloxone was recorded in only 4.0% of OREs, but titration of naloxone showed favorable incidence rate ratios (IRR) for the three most common adverse events (Table S3 in S1 File). Titration was associated with less emesis IRR = 0.26 (95% CI: 0.084, 0.80; Wald χ^2 2.36, $p = 0.018$), less anger IRR = 0.081 (95% CI: 0.011, 0.57; Wald χ^2 2.5, p = 0.012), and less "feeling sick" IRR = 0.44 (95% CI: 0.186, 1.051; Wald X^2 3.8, $p = 0.051$). Death and shaking also showed favorable tabular distributions for titration, but model-based IRRs could not be computed due to zero cell counts.

Programmatic context. Program staff and public health advocate co-authors noted that ability to titrate dose is often the first or second most cited characteristic among people who use drugs who prefer injectable over nasal naloxone; in currently marketed and labeled formulations, injectable is titratable, while 4 mg nasal is not. They also noted that dose titration is a practice that emerged organically from the very onset of community naloxone distribution in the 1990s. They further cited the Practice-based Performative Work of Science tenant of EMI: While it would have been preferable to have more precise measurement of titration and AEs, community-setting titration has been largely ignored in the scientific literature. The consensus among co-authors is that this analysis is important for hypothesis-generation and future studies with more exact measurement are welcomed.

Discussion

Community naloxone distribution at Prevention Point Pittsburgh resulted in more than five thousand reported overdose response events, over 17.5 years. However, previous studies of community naloxone distribution are of short duration, providing limited insight into program implementation and evolution. In addition, the preponderance of real-world data on overdose reversal with naloxone has originated from emergency medical settings and hospitals, leaving a gap in the increasingly common practice of community overdose response. Therefore, this comprehensive report includes key findings from both implementation and biomedical perspectives.

In this sample of individuals returning to a harm reduction program for naloxone refills, the majority of reported OREs indicated success (i.e., the person survived), even in recent years with fentanyl, xylazine, and methamphetamine prevalent in the local drug supply. A minority, but not a trivial proportion, had adverse events suggesting precipitated withdrawal.

Research questions 1 & 2: Naloxone utilization after law change

State law changes at the end of 2014 were intended to remove barriers to naloxone distribution for harm reduction programs, thereby enabling the intervention to reach broader populations. The key programmatic finding was that enabling state legislation alone was insufficient to expand services to populations at greatest risk for overdose [51]. Before the law change, which expanded legal protections and relaxed prescribing policies, Prevention Point Pittsburgh served a predominantly White network of people who used heroin, a cohort that remained steady and aged over time. While enabling legislation in 2015 led to greater naloxone dispensing volume (10.4 doses per month to 65.9 per month in the year that followed), ORE report volume did not keep apace: ORE per new participant fell from 1.46 to 0.47 in the year before versus after the law change. Demographic characteristics offer explanations. In the year after the law was enacted, new participants were more likely to be older (average age increasing from 37 to 46 years-old), more female (increasing from 35% to 58%), and family or friends of people who use drugs, a marked shift. Compared to a previous evaluation of Prevention Point data, our observations are consistent: After enabling legislation, the earlier analysis found that these demographically different new participants were only 0.04 times as likely to reverse an overdose compared to people who use drugs [16]. Instead, refocusing distribution directly to networks of people who use drugs required programmatic effort and intentionality including hiring people from target communities, providing safer smoking supplies, and starting mobile buprenorphine initiation services.

During the first decade of naloxone distribution and before the 2015 enabling legislation, the most common response to whom naloxone was administered was "friend or acquaintance." This could reflect social desirability bias due to the

stigmatized nature of the intervention at the time, and fear of revealing that the participant had transferred the naloxone to someone to whom it had not been prescribed. Naloxone reversals were concentrated within social networks: 81% of OREs were performed on friends and acquaintances, not the person to whom it had been prescribed. Less than 5% was used on family members or the individual who reported the ORE. Interestingly, the percent of reversals on the reporter themselves (i.e., the person prescribed the naloxone) was twice as high for nasal sprays (16.9%) than for injectable (8.5% 10mL vial, 5.9% 1mL vial) formulations.

Monthly ORE rates (per 100 doses dispensed, or number of new participants, Fig 2) offer new possibilities for tracking the impact of policy or programmatic changes in naloxone distribution. ORE per new participants closely reflects the observations of program staff during corresponding time periods; although the metric is useful for retrospective analysis, it confirms what the program already knew from their direct care provision experience. In addition, time series of OREs per 100 doses dispensed also showed obvious peaks when there were fluctuations in the drug supply, namely the emergence of illicitly manufactured fentanyl and carfentanil. We suggest that these metrics may be useful in future epidemiologic studies and serve as a useful tool for programs to monitor. However, drawing from the research team's national experience providing technical assistance, we also acknowledge that reversal record keeping requirements from funders can be a considerable impediment to actual service delivery. Therefore, we feel that data utility should be secondary to naloxone distribution, and the former should not impede the latter.

Research question 3: Racial identity of new participants

Addressing our third research question, as overdose death rates in underserved racialized minority communities began to increase, the program intentionally fostered new mobile outreach sites in January 2016, and started distributing safer smoking supplies that met the needs of that community. Black racial identity of new participants increased from 27% to 39%. These innovations led to significantly more naloxone distribution *and* ORE reports. However, time-series evaluation identified an inflection point in December 2020 after which the share of White participants increased. Programmatic context revealed that this was due to expansion of mobile services to additional neighborhoods to provide on-demand buprenorphine treatment for opioid use disorders, where take-home naloxone was also provided. Racial disparities in the uptake of buprenorphine services have been well-documented [75,76], and are known to have been exacerbated during the COVID pandemic [77]. These national trends and the experience at Prevention Point Pittsburgh are consistent. The findings suggest that new targeted programmatic strategies will be needed to expand medications for opioid use disorder treatment to communities of color.

Research questions 4 & 5: Doses per overdose response event

Per our fourth and fifth research questions, we found that the average doses of naloxone needed to reverse an overdose has not changed over time (segmented regression change point $p = 0.60$); however, formulation effects were also observed. In the first decade of operation when overdoses were predominantly due to heroin, distribution of 10 mL naloxone vials resulted in an average of 1.85 doses per ORE. When naloxone distribution shifted to single-unit packaging, coincident with the appearance of illicitly manufactured fentanyl in the local drug supply [52], average doses were lower: 1.51 doses per ORE with the 1 mL vials, and 1.63 doses with the 4 mg nasal spray. Utilization implications for single- versus multi-dose packaging for liquid pharmaceuticals has been explored in the context of image contrast media [78] and vaccines [79], but has not been previously described for naloxone. However, studies on formulation preference between injectable and nasal forms of take-home naloxone have revealed mixed desires among the target population [80], and the current programmatic recommendation is to offer both. Programmatic context in our study revealed that preferences are not static within an individual and are related to how naloxone might be used: injectable for home and to be used on themselves, versus nasal spray for carrying in a purse to be used on others. Higher dose naloxone products were not evaluated in this study but have been described elsewhere [81,82].

We also found that doses per ORE did not change with the emergence of unregulated fentanyl: naloxone dose was 1.57 during the period (2012–2015) when heroin dominated the local drug supply, compared to 1.60 during years (2016–2023) of unregulated fentanyl. Further investigation into the relationship between the drug supply and ORE behaviors is warranted, especially with the infiltration of non-opioid sedatives in the street drug supply.

There was also an uptick in doses per ORE administered in 2022, as xylazine entered the local drug supply [83]. Average dose of naloxone in 2021 was 1.67 (95% CI: 1.58, 1.75) increasing to 1.75 (95% CI: 1.67, 1.84) in 2022. Additional doses may have been administered because lack of reanimation even if respiration was restored. Program staff adapted to this circumstance by emphasizing counting breaths before administering more naloxone, and specifically counselling respondents who reported using more than two doses. The influence of xylazine on community-based naloxone administration practice needs further research.

Research question 6: Calling 911

We found that 911 was only called in 16% of ORE reports across the 17.5 year observation period. There was a transient increase in calls to 911 after enactment of the Good Samaritan law in January 2015, but by December 2017 the proportion dropped considerably, so much so that in the last 6 months of observation, less than 6% of OREs involved calling 911. There is ample evidence that people who use drugs remain fearful of arrests [84–87] when calling 911, despite the Good Samaritan law. Other possible factors that could be considered include the perception that there is no need for further treatment, fear of getting additional naloxone from uniformed first responders, stigma, cost, and wanting to use again because of withdrawal symptoms. The observed reluctance to call 911 also has implications when considering data derived from EMS and other medical encounters, given that these represent an unknown fraction of actual overdose reversals and are therefore a selected sample that may not be representative of all reversal events, in terms of formulations, doses, AEs, and outcomes.

Research question 7: Deaths

Research question 7, which addressed circumstances surrounding deaths, was examined using empirical findings and narrative review of reports of deaths. Most deaths (18 out of 23) occurred when the person was found “too late” to intervene. We were able to observe that deaths peaked in 2020 during the isolation phase of the COVID pandemic. Program staff emphasized that in all their years working in this program, they are not aware of any participants stating that they had administered naloxone but the person still died because they did not have enough naloxone. There were 4.5 per 1,000 OREs more deaths reported with the nasal spray than 1 mL vial; however, strong cautions are warranted about drawing conclusions because using alone and being discovered “too late” could confound the empirical observation.

Research question 8: Adverse events and titration

Per research question 8, concerning the relationship between formulation or dose titration and adverse events, we found significant differences by formulation for the most common AEs, emesis and anger. Per 1,000 OREs, there were 106 additional reports of emesis with the 4 mg nasal spray compared to 1 mL vials; for anger, there were 48 additional reports per 1,000 OREs. Events of wooden chest syndrome and stiffness, related to synthetic opioid exposure, were not reported in this study.

Limitations

This study has several limitations that should be considered. It represents the experience of a single harm reduction program and, per the EMI framework, study results are not generalizable to other community settings or cities. Self-reported interview data are subject to recall bias, with respondents potentially more likely to remember extreme or negative events. Participant reports were from laypersons without medical training, and reporting of adverse events may have varying

accuracy. Naloxone obtained from other sources in Pittsburgh are not captured in dispensing data. While it is possible that the same overdose event may be reported by the person who administered naloxone as well as the person to whom it was administered, this is unlikely because *refills* were recorded. It was not possible to link to hospital or vital statistics in this anonymized dataset. There was no way to observe the counterfactual, namely what would have happened if the antidote had not been administered; some overdoses may have been self-resolving without naloxone administration. Despite these limitations, the detailed quantitative and programmatic context documented provide a broad historical perspective on naloxone distribution and use.

Finally, we acknowledge that record keeping of OREs has been contentious among harm reduction programs because it can place substantial administrative burden on staff that detracts from their ability to distribute naloxone and provide other direct services. By adopting the collaborative EMI process, we present an alternative model whereby important programmatic considerations and quantitative insights are given equal credence, and where the research questions are mutually agreed upon.

Policy implications

Our findings suggest five policy implications. First, enabling legislation to expand naloxone access is necessary but insufficient alone to reach those at highest risk for overdose. Laws and policies intended to expand community-based naloxone distribution should consider what additional practical support is required to reach the underserved. In this example from Prevention Point Pittsburgh, outreach to underserved communities and high-risk populations represent deliberate strategies that were enabled by the legislation. Diversification of harm reduction services beyond naloxone and provision of sterile injecting equipment can also increase naloxone dispensing, such as occurred in this setting with the inclusion of safer smoking supplies and mobile buprenorphine services. These program adaptations are consistent with national trends; the Centers for Disease Control & Prevention recently reported that smoking has supplanted injection as the route of administration most often implicated in overdose death [88].

Second, enabling legislation in Pennsylvania led to a decrease in naloxone being confiscated by law enforcement, but one death was reported following an incident in which someone carrying naloxone was prohibited by police from administering it. In addition, reports of excessive additional doses administered by EMS and police after successful revival by peers should be investigated. EMS policy and protocols should be re-evaluated in the context of bystander administration to ensure naloxone dosing conforms to evolving medical best practice.

Third, the Good Samaritan law appeared to have an observable but time-limited effect on increasing calls to 911. These state laws may need to be revised if they are to be more effective. The very low rate of calling 911 in recent years bears further investigation [89], such as to clarify when support services are most medically necessary, and identify social and legal barriers including the impact of drug-induced homicide laws [90]. These investigations will be crucial in the context of over-the-counter naloxone, which has explicit instructions to call 911.

Fourth, consistent with previous analyses [16,19,91], we found that 1 mL vials injected intramuscularly were effectively used in thousands of reversals. Certain adverse events were lower than with the 4 mg nasal spray, but participants expressed a desire for both injectable and nasal formulations. Given historical fluctuations in funding for and availability of naloxone, program participants would be best served knowing how to use both types of naloxone, and policies, standing orders, and laws should allow parity in access between different formulations. Differences in adverse event profiles between naloxone formulations [81,82] may be of relevance to policymakers. The behavior of titrating doses of naloxone to prevent adverse events also suggests that there may be underrecognized demand for formulations that deliver smaller or fractional doses, and reinforces the policy importance of ensuring that multiple forms of naloxone are available. Education on dose titration within harm reduction programs may also be an opportunity to prevent or reduce adverse events.

Fifth, sharing of naloxone between participants is a natural phenomenon, especially when provided at no cost to the participant. While secondary distribution of sterile syringes has been extensively studied in many countries [92–96],

corresponding studies for naloxone distribution have not been published. Primary encounters with harm reduction staff provide opportunity for additional services to be offered (not just drug-related), a benefit that is attenuated through secondary distribution. Furthering this trend, over-the-counter versions of naloxone nasal sprays were approved by FDA in 2023, naloxone-dispensing vending machines are rapidly expanding [97], and mail order naloxone distribution has been established on a national scale [98], eschewing the direct human connection necessary for the comprehensive harm reduction services like Prevention Point Pittsburgh have traditionally provided. Concerted policy, technology, telehealth, and communication innovations could supplement these innovative distribution channels to re-establish more comprehensive care possibilities in an era where naloxone distribution is becoming more indirect. As demonstrated by the rich programmatic context in this paper, traditional harm reduction programs possess a depth of untapped applied experience that can inform broader policy and regulatory decisions.

Future research needs

Severe precipitated withdrawal should not be dismissed as an "unavoidable" adverse event expected to occur in some OREs using antagonists, but rather needs to be studied independently, especially as it could lead to short- and long-term changes in behavior that increase risk for subsequent overdose; further research is needed to determine how withdrawal-related AEs can be reduced. Recent findings from a qualitative study [99] provide details on how severe naloxone-precipitated withdrawal can make it difficult for overdose survivors to accept information about treatment options in the immediate aftermath.

To empirically establish post-overdose behavioral consequences, validated and easy-to-use outcome measures for overdose severity and response could be developed. Randomized field studies, such as comparing formulations of opioid antagonists, could also provide empirical evidence to inform policy and local purchasing decisions. Further research may also be warranted into other factors at the pharmaceutical formulation level, in terms of pharmacokinetics or packaging. And finally, training on timing and titration of dose administration and rescue breathing all bear scientific scrutiny. Qualitative studies involving those with lived experience should be considered to bring light to dimensions of community-based naloxone distribution and bystander naloxone administration that are not observable quantitatively [100,101]. Regardless of the method, there is pressing need for this type of work to more fully understand unmet needs in a changing environment.

Conclusion

This comprehensive analysis of a harm reduction program reveals that while enabling state legislation can create the environment for expanded naloxone distribution, when naloxone is distributed to people not at risk of overdose or their immediate social networks, increases in dispensing volume can become negatively decoupled from actual administration and overdose reversal. Expanding services to underserved communities requires additional innovation. We also found that the long-term consistency of less than 2 doses per ORE, high survival rate, and robust utilization all lend confidence in prioritizing naloxone distribution directly to people who use drugs. Finally, we found lower rates of adverse events with lower doses of naloxone, titration, and with injectable intramuscular formulations. Collectively, these findings can help re-prioritize community-based naloxone distribution to those most likely to use the antidote to reverse an opioid overdose.

Supporting information

S1 File. Supplemental Information.
(DOCX)

S2 File. STROBE Checklist.
(DOCX)

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Emergence of Medetomidine in the Illicit Drug Supply: Implications for Emergency Care and Withdrawal Management

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The US illicit drug supply continues to evolve with increasingly dangerous adulterants, with medetomidine a new agent seen in acute care and other practice settings. We reviewed available literature on illicit drug adulterants, medetomidine intoxication, and sequelae. Although little is known about withdrawal and the clinical manifestations are stark, we reviewed the best available literature on dexmedetomidine withdrawal and suggest approaches for treatment. [Ann Emerg Med. 2025;■:1-8.]

Keywords: Medetomidine, Adulterants, Illicit fentanyl, Withdrawal management, Alpha-2 agonists.

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INTRODUCTION

Medetomidine, a potent veterinary alpha-2 adrenergic agonist, recently emerged within illicit fentanyl products, first identified in Maryland in 2022 and subsequently linked to overdose and withdrawal cases in Philadelphia, Pittsburgh, and Chicago by 2024. Medetomidine produces prolonged sedation, bradycardia, and biphasic blood pressure effects. Its toxicity persists after naloxone administration, complicating emergency care. Unlike opioid withdrawal, medetomidine withdrawal is rapidly progressive, severe, and often resistant to traditional therapies. In contrast to many other sedative withdrawal syndromes, medetomidine withdrawal symptoms can begin within 4 to 6 hours of last use and include anxiety, tremor, vomiting, hypertension, tachycardia, and delirium. Laboratory findings may include lactic acidosis, hypokalemia, and QTc prolongation. Many patients receive intensive care, and standard treatments such as benzodiazepines and opioids offer little relief.

Effective management centers on early and aggressive antiemetic therapy with dopamine antagonists and administration of alpha-2 agonists such as clonidine, guanfacine, and, in severe cases, intravenous dexmedetomidine. A combined approach using oral, transdermal, and parenteral therapies provides symptom relief and facilitates tapering. We share a treatment protocol and encourage continued evaluation of interventions.

Diagnosis remains clinical due to limited testing availability, and recognition is key to initiating treatment. The emergence of medetomidine parallels prior trends seen with xylazine and reflects ongoing shifts in the illicit drug market. Rapid dissemination of clinical observations and management strategies is critical. Multidisciplinary coordination between emergency medicine, medical toxicology, public health, and harm reduction networks is vital to mitigate the growing effect of this novel adulterant.

BACKGROUND OF ADULTERANTS IN THE US DRUG SUPPLY

Substance use and associated harms including acute toxicity or "overdose," death, withdrawal, and health complications increased over the past 2 decades in the United States. When viewed from the perspective of unintentional overdose deaths, one framework noted 4 sequential overlapping waves beginning with a rise in overdose deaths associated with heroin, prescription opioids, fentanyl, and most recently with fentanyl and stimulants.[1] Although the nature and causes of primary drug-associated unintentional deaths changed, parallel growth and evolution of secondary added adulterants also occurred.

Adulterants are substances deliberately mixed into illicit drugs. They may enhance the drug effects, imitate its action to reduce the amount of the main ingredient needed, or help offset harmful side effects caused by the primary agent.[2] The term adulterant and "contaminant"

are often used interchangeably but in error. Contaminants typically refer to substances or products inadvertently included in a drug sample either as a byproduct of manufacturing, cross-contamination with another product, or microbial corruption.[3] Examples of contamination include botulism in "black tar" heroin, brodifacoum in synthetic cannabinoids, or *Salmonella* spp. present in some "kratom" products.[4-6]

Adulterants of the illicit opioid supply changed over the last 2 decades. Diphenhydramine, local anesthetics, and quinine have historically been found in heroin samples.[2] Emerging adulterants include the alpha-2 agonists, which potentiate the sedating effect of opioid analgesics including fentanyl.[7] Xylazine, a non-imidazoline alpha-2 receptor agonist approved only as a veterinary tranquilizer, was initially reported among people who use drugs in Puerto Rico and Philadelphia in the early 2000s.[8] In the late 2010s through early 2020s, the prevalence and range of xylazine grew throughout the United States.[9,10] Commonly referred to as "tranq" or "tranq dope," acute toxicity and deaths associated with xylazine began to rise more sharply in Philadelphia in 2017. By 2023, xylazine was present in 99% of Philadelphia's illicit fentanyl supply.[11] Xylazine adulteration triggers many acute effects when used as an opioid adulterant including prolonged sedation, sinus bradycardia, and hypotension.[12] Repeated use has been associated with a reported withdrawal syndrome of anxiety, tremor, and autonomic activation unresponsive to opioid withdrawal management, usually peaking 24 to 72 hours after the most recent dose.[13] Chronic exposure to xylazine is linked with necrotic skin wounds resulting in infectious complications and amputations.[11,13]

Medetomidine, another veterinary tranquilizer, is an imidazoline alpha-2 receptor agonist first identified in illicit samples from Maryland in 2022, now detected in samples from multiple states.[14,15] In May 2024, reports of medetomidine complicating overdose and withdrawal manifestations of people presenting to emergency departments (ED) arose in Philadelphia, Chicago, and Pittsburgh.[16-18] We review the existing knowledge and clinical observations surrounding this new adulterant and offer early management suggestions.[19]

MEDETOMIDINE PHARMACOLOGY

Medetomidine is a racemic mixture of levomedetomidine and more active dexmedetomidine enantiomers. The mixture is approved for intravenous use as a veterinary short-term sedative (akin to xylazine), whereas intravenous isomeric dexmedetomidine is approved for human use as a short-term surgical and critical care sedative.[20] Medetomidine has a greater affinity for alpha-2 versus alpha-1 receptors, with a selectivity of 1,620:1, compared with clonidine (220:1) and xylazine (160:1).[21]

Medetomidine is readily available after intravenous injection and can be absorbed through the nasal and buccal mucosa; bioavailability following oral ingestion is limited by extensive first-pass effects.[22] Human illicit use is usually through injection or nasal exposure ("snorting"). Initial plasma distribution activates alpha-2 receptors in vascular smooth muscle resulting in vasoconstriction, increased systemic vascular resistance, hypertension, and baroreceptor-mediated sinus bradycardia.[23] Subsequent sympatholytic activity in presynaptic alpha-2 receptors reduces circulating catecholamines causing hypotension and bradycardia.[24] Sedation is due to activation of sleep pathways in the locus coeruleus with relatively minimal effect on respiratory drive in the absence of other sedative or analgesic agents.[25] When used in combination with fentanyl, dexmedetomidine acts synergistically to reduce the fentanyl dose necessary to achieve analgesia but may result in greater risk of respiratory depression than with dexmedetomidine or fentanyl alone.[26]

The elimination half-life of dexmedetomidine following hepatic metabolism is 2 to 3 hours in healthy volunteers and 2 to 4 hours in ICU patients.[20] Prolonged elimination may occur in those with impaired hepatic function.[27]

MEDETOMIDINE TOXICITY

Acute medetomidine toxicity follows its pharmacology. In most cases, medetomidine is identified in conjunction with fentanyl (plus or minus added xylazine) and is commonly referred to as "tranq," "rhino tranq," "mede," or "dex."[15] Following naloxone administration for opioid toxicity, respiratory drive may be restored but the medetomidine sedation persists, often deep. People may also exhibit initial hypertension and bradycardia, followed by hypotension and bradycardia, and often have miosis.[16,28]

Naloxone has no substantive reversal effects on clinically diagnosed medetomidine toxicity.[16] The goal of naloxone administration in the setting of acute opioid toxicity is to reverse respiratory depression from any opioid, not to achieve full arousal. Consequently, dosing recommendations for naloxone administration remain unchanged when either pure opioid or opioid/adulterant exposure is suspected—give naloxone until restoration of adequate ventilatory effort and effect.

The management of medetomidine toxicity is supportive. Given the risk of aspiration, elevate the head of the bed if possible. Some may benefit from endotracheal intubation and mechanical ventilation for airway protection.[16] Sinus bradycardia with rates as low as 30 to 40/min is common and may have associated hypotension; perfusion is commonly sustained with intravenous isotonic fluid therapy alone absent any dromotropic therapy. In rare cases, vasopressors are used to restore or maintain adequate blood pressure and tissue perfusion.[19]

Postacute observation periods vary but typically require at least 3 to 6 hours for resolution of acute intoxication. To date, it seems ongoing medetomidine exposure does not have the same association with necrotic wound development as xylazine though conclusions are limited by the overlapping presence of both substances in the illicit drug supply.[29]

Drug testing for medetomidine is limited in most clinical settings. There is no FDA-approved immunoassay. Advanced comprehensive drug testing can identify medetomidine and its metabolites.[17,18] Diagnosis of acute toxicity and/or withdrawal is therefore clinical rather than laboratory based.

There is no medetomidine reversal agent approved for humans. Atipamezole, an imidazoline alpha-2 receptor antagonist, is approved as a veterinary reversal agent.[30] Beyond lack of availability, use of an alpha-2 reversal agent in humans seems attractive but likely would result in greater harm than benefit.[28] Precipitated withdrawal can manifest acute, life-threatening illness, whereas toxicity from alpha-2 agonists is typically transient and can be managed effectively with supportive care.

MEDETOMIDINE WITHDRAWAL

Medetomidine withdrawal is a potentially severe clinical syndrome seen in many presenting to an ED and other care locations where those with substance use seek help.[17,18] One parallel exists—the approved enantiomer, dexmedetomidine, can trigger withdrawal after as little as 24 hours of use. The withdrawal pattern seen after dexmedetomidine, usually in a critical care setting, is of anxiety, agitation, diaphoresis, tachycardia, hypertension, and delirium.[31] Withdrawal severity is influenced by higher daily cumulative or peak dose and duration of treatment.[31,32] Clonidine and guanfacine may reduce the risk of withdrawal and facilitate weaning of iatrogenic dexmedetomidine based on clinical observations and case series, not better evidence.[33,34]

Starting in 2024, cases of severe medetomidine withdrawal in the ED were reported in Philadelphia and Pittsburgh, PA. The pattern was someone with a history of illicit opioid use, with or without initial sedation dominance, who then had rapid progression (a few hours) of anxiety, tremor, diaphoresis, nausea, vomiting, agitation, sympathetic hyperactivity, and delirium.[17,18] Initially, the abrupt transition from sedative like intoxication to profound hyperactivity inside a few hours did not have a clear known cause. Many postulated about a co-occurring stimulant toxicity or withdrawal from substances present in the Pennsylvania illicit drug supply such as nonpharmaceutical benzodiazepines, bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate, xylazine, and medetomidine.[35] Xylazine had a large presence in the drug supply for years, but without evidence of this severe syndrome. Early treatment efforts included high doses of benzodiazepines and phenobarbital with minimal effect on the syndrome, making benzodiazepine withdrawal less likely. Medetomidine and its metabolites were verified in those who had presented with the combination of symptoms now attributed to medetomidine withdrawal.[17,18]

Medetomidine withdrawal progresses rapidly in most cases. Given the short half-life, patients who present with acute toxicity and monitored for resolution can progress to withdrawal during the same ED encounter. Early symptoms include anxiety, tremor, flushing, and diaphoresis within 4 to 6 hours of last illicit drug use—a much quicker timeline than seen in most common or historical experiences. Nausea and vomiting follow and are frequently resistant to treatment. As the withdrawal progresses, patients develop sinus tachycardia and hypertension which can be severe. Clinical reports note heart rates exceeding 170/min with elevated systolic blood pressures over 240 mmHg and diastolic blood pressures over 120 mmHg.[36] Some patients may become delirious, agitated, and hyperthermic.[17,18,36]

Multiple laboratory and other abnormal clinical findings can exist in patients with medetomidine withdrawal including hypokalemia, metabolic acidosis with high lactic acid levels, QTc prolongation, troponin elevation, acute cardiomyopathy with reduced ejection fraction, and posterior resolving encephalopathy syndrome.[19] Seizure activity reports exist, but typically in patients experiencing concomitant gamma-aminobutyric acid (GABA) agonist withdrawal.[36] The latter means it is unclear whether medetomidine withdrawal causes seizures.

The progression of withdrawal from relatively mild to severe effects accompanied by profound vital sign derangements and potential encephalopathy typically occurs over 6 to 12 hours, but sometimes this interval is longer. Clinicians experienced in the management of the

withdrawal syndrome believe it can develop up to 24 hours after the last use of medetomidine-adulterated opioids, even if early vital signs seem normal.

A common experience among providers caring for patients with this syndrome is a sense of treating something very different than they have previously encountered. Another concern is common medications and doses used may do little to slow the progression of illness. Patients may demonstrate little response to GABA and opioid agonists. Nausea and vomiting typically do not respond to ondansetron. Although the description of medetomidine withdrawal overlaps with that of opioid and GABA agonist withdrawal, the rapid and marked severity coupled with the ineffectiveness of medications used to treat those conditions differentiates it and aids diagnosis. Consultation with a medical toxicologist or poison center can assist both diagnosis and management.

MEDETOMIDINE WITHDRAWAL MANAGEMENT

The treatment of medetomidine withdrawal is evolving based on local experiences. As more experience accrues, refined treatment guidelines will emerge.[19]

Most importantly, early and aggressive administration of alpha-2 agonist medications is recommended to address the underlying pathophysiology. We share a proposed framework and algorithm to treat those with medetomidine withdrawal based on available evidence and experience (Figure).

Nausea and vomiting are managed with intravenous dopamine antagonists such as prochlorperazine, droperidol, or olanzapine. Control of nausea may require repeated and high antiemetic doses to allow administration of oral alpha-2 agonist medications. Topical scopolamine and intramuscular trimethobenzamide are occasionally employed. Dopamine antagonists all carry a risk of QTc prolongation from potassium channel blocking activity; given the features of this syndrome, we suggest ECG monitoring. To date, no reports of polymorphic ventricular tachycardia exist, perhaps because sinus tachycardia limits the risk of triggering early after depolarizations.

We also recommend a combination approach of alpha-2 and imidazoline receptor agonists. We start with oral therapy, though many will require parenteral management. Both clonidine and guanfacine can reduce withdrawal features from dexmedetomidine in critical care environments.[33,34] Longer-acting scheduled formulations of alpha-2 agonists are coupled with shorter-acting doses as needed. On recognition of developing medetomidine withdrawal, we recommend simultaneous initiation of 3 parallel management pathways.

First, give oral clonidine and repeat up to 2 additional times within the first hour as a loading dose. Clonidine follow-up dosing is based on symptom progression: more frequent doses than commonly given in other settings may be needed. Currently, there is no validated medetomidine withdrawal scale, so we apply the Clinical Opioid Withdrawal Scale (COWS) given its familiarity.[37] Peak plasma levels of clonidine are achieved at 1 to 3 hours with elimination half-life of 12 to 16 hours which can be prolonged in the setting of renal failure.[38]

Simultaneously, we start immediate release oral guanfacine at the outset as a standing dose. The immediate release formulation achieves a higher maximum concentration than extended-release formulations offering potential benefit in symptom control.[39] Peak guanfacine plasma levels develop between 1 and 4 hours with a mean elimination half-life of 17 hours.[40]

Finally, as a look toward later de-escalation, we add transdermal clonidine after above but still early in care. The time to therapeutic effect of transdermal clonidine is 2 to 3 days, and plasma concentrations of transdermal clonidine remain stable for approximately 8 hours after removal with an elimination half-life of 21 hours.[41]

The combination of alpha-2 agonists by different delivery routes and with different pharmacokinetic properties may allow tapering and smoother transition to eventual discontinuation. When oral clonidine doses are no longer needed as determined by COWS for 24 hours, typically 3 to 5 days after initiation, taper guanfacine and remove any clonidine patch.

Sublingual dexmedetomidine, currently only approved for agitation associated with schizophrenia and bipolar disorder, could limit the use of titrated intravenous dexmedetomidine (see later) that requires ICU admission.[42]

Tizanidine is another imidazoline alpha-2 adrenergic agonist used for the management of both xylazine and medetomidine withdrawal.[13,19] Tizanidine acts primarily on spinal alpha-2 receptors, whereas clonidine and guanfacine have more significant cardiovascular effects and activity at the locus coeruleus where the hyperactivity from medetomidine withdrawal is thought to originate.[43-45] Nevertheless, given the severity of the withdrawal syndrome and novelty of treatment approaches, the addition of tizanidine is another option.

Despite attempts to administer multimodal alpha-2 agonist and antiemetic therapies, many patients have refractory vomiting or progression of severe tachycardia, hypertension, agitation, and delirium. In these cases, we

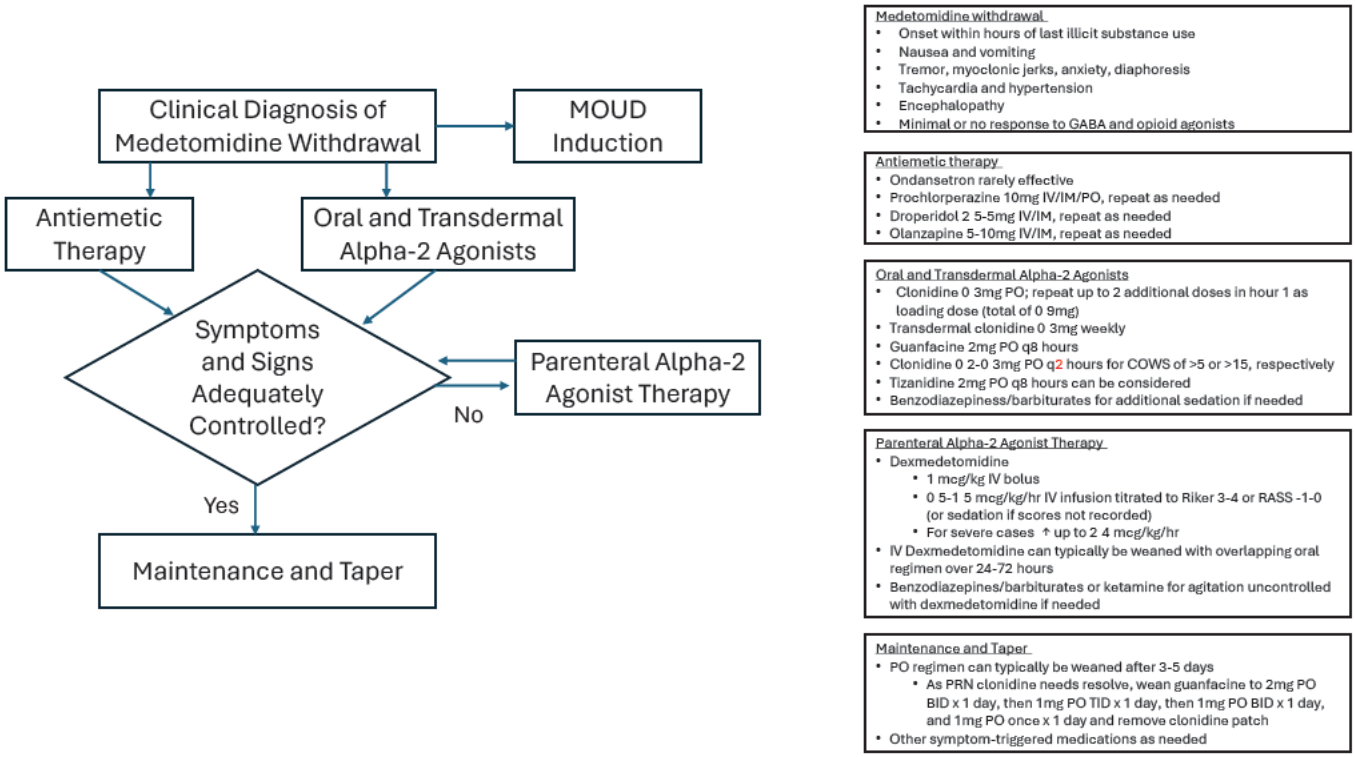

Figure. UPMC medetomidine withdrawal treatment approach. *MOUD*, medications for opioid use disorder.

use intravenous dexmedetomidine, effectively replacing the removed agent. Typical dosing of dexmedetomidine is a bolus followed by infusion titrated to adequate control of agitation and hyperadrenergic vital signs. The typical maximum infusion rate for dexmedetomidine is 1.5 μg/kg per hour due to potential for adverse effects including hypotension, bradycardia, and excessive sedation at higher doses.[46] Phase II studies of dexmedetomidine for sedation included infusion rates up to 2.5 μg/kg per hour.[47] We titrate dexmedetomidine infusions as high as 2.4 μg/kg per hour targeted to light sedation by Richmond Agitation Sedation Scale or Riker Scale.[48] Some patients have developed sinus bradycardia on high doses of dexmedetomidine but there have not been other significant adverse effects reported with this maintenance rate.

Once initiated, patients typically require 24 to 72 hours of dexmedetomidine infusion and rarely require mechanical ventilation. When patients can tolerate oral medications, add oral clonidine and guanfacine plus transdermal clonidine to allow tapering of dexmedetomidine infusion and transfer to a noncritical care unit.

Despite efforts to avoid ICU admission on dexmedetomidine through early oral and transdermal therapies, many patients have progressive symptoms including intractable vomiting, potentially life-threatening vital sign abnormalities, and agitated encephalopathy requiring ICU care. In early case series 77% to 90% of patients diagnosed with this syndrome were admitted to the ICU though limitations in testing prevent accurate awareness of a denominator from which to describe a definitive rate of ICU admission.[17,18,36]

Escalating doses of benzodiazepines, phenobarbital, and ketamine have a limited effect, but may augment alpha-2 agonist therapies.[17,18,36] Patients experiencing co-occurring GABA agonist withdrawal benefit from titrated doses of long-acting GABA agonists.

In addition to managing medetomidine withdrawal, it is important to address underlying opioid withdrawal and use disorder. A variety of hospital-based induction pathways for both methadone and buprenorphine exist.[49] One pitfall is early opioid use disorder treatment with buprenorphine based on COWS score. Symptoms of medetomidine and opioid withdrawal overlap, but medetomidine withdrawal begins much sooner. Patients who appear to have moderate to severe opioid withdrawal within hours of their last use are likely exhibiting alpha-2 agonist withdrawal. Treatment with buprenorphine may, therefore, precipitate opioid withdrawal. In general, management with short-acting full opioid agonists in conjunction with a microdose buprenorphine induction protocol with transdermal, intravenous, or buccal formulations is best. Alternatively, induction on

methadone can occur immediately with titration of dosing to withdrawal symptoms and craving. When initiating and titrating methadone, ECG should be monitored, specifically the QTc interval. In most patients, early QTc prolongation improves with resuscitation, control of withdrawal, and correction of metabolic derangements.

OBSERVATION TIME AND DISPOSITION

Opioid use disorder and withdrawal are often managed in the ED with referral to outpatient follow-up care. Direct transfer to residential treatment facilities is an option for some patients depending on their level of care needs and concurrent medical conditions. Hospital-based management of opioid withdrawal has rarely been necessary unless a corresponding medical (eg, infectious or other) complication or co-occurring GABA agonist withdrawal state is present. In general, the progression of opioid withdrawal symptoms is predictable, and effective treatments can be deployed without need for prolonged ED stay or observation periods. The presence of medetomidine complicates prognosis and safe disposition.

Medetomidine withdrawal symptoms usually begin earlier than other syndromes, often within 4 to 6 hours of last illicit opioid use though some patients have milder symptoms initially then progress up to 24 hours later. The variability in progression and limited experience with medetomidine withdrawal make defining an ideal observation time challenging. The most predictive characteristic of potentially severe medetomidine withdrawal is a previous episode requiring hospitalization. Point-of-care testing is not widely available, and objective criteria to predict an individual course are lacking.

Clinical suspicion for medetomidine toxicity may aid in anticipating progression to withdrawal. Patients with prolonged sedation, sinus bradycardia, and/or hypotension after reported overdose are candidates for ongoing and close monitoring. Overall, patients who exhibit no signs of persistent alpha-2 agonist toxicity or withdrawal in a 6 to 12-hour observation period are less likely to progress to severe withdrawal. Nevertheless, careful anticipatory guidance to return for intractable vomiting, diaphoresis, tremor, agitation, or identified vital sign abnormalities should be provided at ED discharge to patients and their caregivers.

HEALTH CARE SYSTEM EFFECT AND FUTURE CONSIDERATIONS

The emergence of medetomidine resulted in changes in management and disposition of many with an illicit opioid use disorder. The recognition of this new threat—and any other that might come—underscores the need for ongoing surveillance, multidisciplinary collaboration, and continual reassessment of evolving drug threats, toxicity profiles, and withdrawal syndromes. Proactive coordination among hospitals, health care organizations, and public health agencies to share observations, data, and expertise is key. We offer early, practical suggestions informed by experience but supported with limited evidence. We hope that either the threat will dissipate or more robust evidence-based practices will evolve.

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Short communication

Thematic analysis of medical examiner narratives to understand the socio-spatial context, recency of drug use, and likely mechanism of stimulant toxicity deaths

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ABSTRACT

Background: Drug toxicity as a cause of death is challenging to establish and may be based on limited evidence, especially in deaths attributed to stimulants. We developed a method for characterizing stimulant deaths, focusing on potential mechanisms and opportunities for intervention.

Methods: We used medical examiner case narratives and medical records from a mixed methods study of fatal acute stimulant toxicity in San Francisco. We coded case narratives for circumstances surrounding death events, including physical location, bystander presence, decedent disposition, and evidence of recent street drug use; medical records provided data on potential mechanism of death when not present in case narratives.

Results: Of 101 deaths (70 stimulants-no-opioids, 31 stimulants-fentanyl), 85 were unwitnessed, including 69 unwitnessed deaths in spaces inaccessible to bystanders. Drug use was observed before collapse in 1 of 14 witnessed stimulant-no-opioid and 1 of 2 witnessed stimulant-fentanyl deaths. Among unwitnessed events, scene evidence of drug use was found in 36 of 56 stimulant-no-opioid and 25 of 29 stimulant-fentanyl deaths. Twelve of 14 witnessed stimulant-no-opioid deaths and none of two witnessed stimulant-fentanyl deaths included an apparent cardiovascular or cerebrovascular event.

Conclusions: Deaths occurred in physically and socially isolated contexts, limiting opportunities for bystander intervention. Compared to stimulant-fentanyl deaths, stimulant-no-opioid deaths may be more likely to be witnessed and involve a cardiovascular event, and less likely to involve recent drug use. Applying a thematic analysis of medical examiner records to a larger sample, including other opioid deaths, could guide prevention strategies.

1. Introduction

Age-adjusted mortality attributed to acute methamphetamine or cocaine toxicity rose 14-fold in the U.S. from 2011 to 2021 (Spencer et al., 2023). While deaths involving stimulants without opioids increased (Spencer et al., 2023), most of the increase also involved opioids (Jones et al., 2020; Ciccarone, 2021; Hoopsick et al., 2023), including 61 % of stimulant "overdoses" in 2021 (Hoopsick et al., 2023).

While the mechanism of opioid overdose death is well described, including rapid onset of respiratory depression after opioid use, death from acute stimulant toxicity is not clearly defined. Taking too large a dose of a stimulant is often called "overamping"; in contrast to opioid overdoses, these events vary in presentation and severity but are rarely fatal (Harding et al., 2022; Mansoor et al., 2022). Compared to fatal opioid overdoses (Stockings et al., 2019; Riley et al., 2022), deaths attributed to stimulants tend to occur in older people with more comorbidities and often have cardiovascular or cerebrovascular events listed as contributing causes (Turner et al., 2018; Stockings et al., 2019; Riley et al., 2022), suggesting many of these deaths may be sequelae of chronic diseases (Turner et al., 2018; Riley et al., 2022) and terms such as "overdose" or even "acute toxicity" may be misleading.

Cause of death determination is completed for legal purposes and the process can vary between jurisdictions (Slavova et al., 2015; Hochstatter et al., 2022). Drug toxicity as a cause of death is primarily based on

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toxicology results and scene examination with varying and often limited contribution from autopsy and medical records (Cina et al., 2011). Distinguishing drug toxicity from other causes of death may be impossible in some cases, particularly when decedents have multiple comorbidities (Merlin et al., 2022), and overdose is often a "diagnosis of exclusion" (Merlin et al., 2022). Moreover, these data provide limited insight into the dose or context of drug use.

As health professionals seek to reduce mortality from stimulant use, labeling these deaths "overdoses" may distract from the role of chronic disease and poverty and lead away from effective interventions. We developed a new method for characterizing deaths attributed to acute stimulant toxicity through review of medical examiner case narratives and medical records, with a focus on the socio-spatial context of the deaths, evidence of recent street drug use, and likely mechanism of death. We applied our method to 101 stimulant-associated deaths from a mixed methods study of stimulant deaths (Antolin Muniz et al., 2025) and used the results to generate hypotheses for further investigation.

2. Methods

2.1. Sample and data collection

We used data from a parent study of unintentional deaths attributed to acute cocaine or methamphetamine toxicity, which combined informant interviews with review of medical examiner case narratives and medical records to explore factors associated with deaths attributed to acute stimulant toxicity. The parent study included a non-random sample of decedents identified through record review of the California Electronic Death Registry System (CA-EDRS) and the San Francisco Office of the Chief Medical Examiner (OCME) (Antolin Muniz et al., 2025). The sample intentionally included 70 deaths involving stimulants without opioids ("stimulant-no-opioid") and 31 deaths involving stimulants and fentanyl ("stimulant-fentanyl") that occurred from June 2022 through December 2023. The parent study sought an even split between deaths attributed to cocaine and to methamphetamine: stimulant-no-opioid cases included 35 deaths attributed to cocaine, 32 to methamphetamine, and three to both; stimulant-fentanyl cases included 12 deaths attributed to cocaine, 15 to methamphetamine, and four to both.

The study was approved by the University of California San Francisco, Human Research Protection Program (#21–35305) and the State of California Health and Human Services Agency Committee for the Protection of Human Subjects (#2022–091).

2.2. Socio-spatial characteristics

Using the framework of reflexive thematic analysis (Braun and Clarke, 2006), case narratives were reviewed and coded for themes related to the social and physical contexts of death. Coding was performed by the study RN and physician (authors FB and POC), both of whom have training in qualitative analysis, with both blinded to which drugs the deaths were attributed. Coding was carried out iteratively until a set of stable thematic codes emerged, with coders meeting to discuss codes until consensus was reached. These codes were used to create five measures (Table 1) which were reviewed and discussed with co-authors, refined, and arranged in a nested categorization system (Fig. 1).

2.3. Recent use of street drugs

Evidence of recent street drug use was analyzed separately for witnessed and unwitnessed deaths. For unwitnessed deaths, evidence was coded as present if the case narrative indicated possible street drugs (e.g. white powder, crystal substance) or associated equipment (e.g. glass pipes, syringes) found at the scene of death, excluding alcohol, tobacco, and cannabis products. For witnessed deaths, evidence was coded as present if the case narrative indicated that the decedent was seen using opioids, stimulants, or unspecified drugs in the period immediately prior to the medical emergency resulting in death (approximately one hour).

Table 1
Socio-spatial death characterization codes.

Variable	Levels
Presence of witnesses	Witnessed: event (e.g., collapse, loss of consciousness, physical distress) was observed in real time by other people Unwitnessed: event was not seen in real time (e.g., no evidence of potential witnesses present, or potential witnesses did not observe event)
Location of death	Public: visible and accessible to passersby (e.g., street, lobby, parked car) Private: not visible and not accessible to passersby (e.g., residence, hotel room)
Time since decedent was seen prior to event[a]	$\leq$ 12 hours $>$ 12 hours
Person who discovered decedent	Family/friend: person with a personal relationship with the decedent (e.g. roommate, partner, family member) Staff: person acting in a professional role (e.g. healthcare worker, housing staff) Bystander: person with no relationship to the decedent
Disposition of decedent when found	Found dead: decedent was clearly beyond resuscitative efforts when found Declared at scene: resuscitation was attempted but ceased and death was declared at scene Transported: transportation was initiated before death was declared (e.g., declared in ambulance, emergency department, or hospital inpatient unit)

[a] 12 hours was chosen for cutoff as decedents seen within 12 hours were generally using drugs within a social context while decedents who had not been seen for greater than 12 hours generally had not been seen for multiple days.

2.4. Mechanism of death

Although all deaths in the sample had acute stimulant toxicity listed as a cause of death, we sought to determine the likely physiological mechanism of the event resulting in death. We could only assess this if there was information about the nature of the event, limiting analysis to witnessed deaths. Case narratives and medical records were reviewed by the study team physician (POC) to determine the likely mechanism of death, coded as cardiovascular, cerebrovascular, respiratory, or uncertain/other. If a clear mechanism was not described in the case narrative and medical records, we coded the event as follows: cardiac if the decedent experienced a sudden collapse after vigorous activity or signs of cardiovascular distress (e.g. clutching chest); respiratory if the decedent was described as having ceased breathing after using drugs without signs of cardiovascular distress; and uncertain in all other cases.

2.5. Analysis

We calculated frequencies and proportions of sociodemographic and socio-spatial characteristics of death, evidence of substance use, and mechanism of death. For age, which was continuous and skewed, we calculated a median and interquartile range (IQR). We presented results overall and separately for stimulant-no-opioid and stimulant-fentanyl deaths.

3. Results

3.1. Demographics

The median age of decedents was 58 (IQR: 47–61); 44 % were White and 36 % Black; 69 % were unhoused or marginally housed (Table 2). Most decedents (75 %) were classified as male.

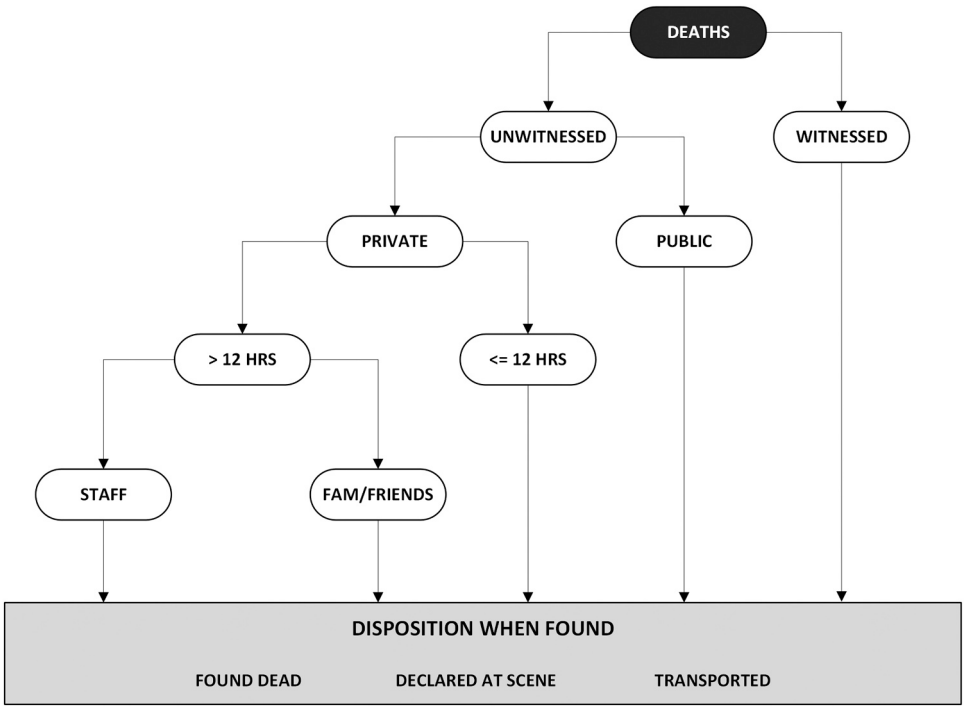

Fig. 1. Nested death categorization system All deaths were characterized by disposition of decedent when found; unwitnessed deaths were additionally categorized by public vs. private location of death. Deaths occurring in private were coded by time elapsed since decedent was last seen alive; decedents not seen within 12 hours were also coded by who found the body.

3.2. Sociospatial characteristics of deaths

Of 101 deaths, 85 were unwitnessed, including 80 % (56) of stimulant-no-opioid and 94 % (29) of stimulant-fentanyl deaths; 68 % of all deaths occurred unwitnessed in private spaces (Fig. 2) and none of these decedents were resuscitated on scene or found by bystanders (Fig. 3). In over half (52 %) of all deaths, the decedent was found dead beyond resuscitative efforts in a private space after not being seen for more than 12 hours.

Table 2
Sociodemographic Characteristics of Decedents from Acute Cocaine or Stimulant Toxicity in San Francisco, June 2022-December 2023 (N = 101) % (n).

	All deaths (n 101)	Stimulant-no-opioid (n 70)	Stimulant-Fentanyl (n 31)
Age	58 (median), IQR 47–61	58 (median), IQR 52–61	50 (median), IQR 43–59
Sex[a]			
Female	25 (25 %)	16 (23 %)	9 (29 %)
Male	76 (75 %)	54 (77 %)	22 (71 %)
Race/ethnicity			
Black	36 (36 %)	29 (41 %)	7 (23 %)
White	44 (44 %)	28 (40 %)	16 (52 %)
Hispanic/Latine	14 (14 %)	7 (10 %)	7 (23 %)
Asian/Pacific Islander	4 (4 %)	4 (6 %)	0 (0 %)
Multiracial	3 (3 %)	2 (3 %)	1 (3 %)
Housing status[b]			
Unhoused	20 (20 %)	12 (17 %)	8 (26 %)
Marginally housed	49 (49 %)	37 (53 %)	12 (39 %)
Stably housed	32 (32 %)	21 (30 %)	11 (35 %)

[a] Sex was determined post-mortem and may represent sex assigned at birth or gender at time of death.

[b] Unhoused includes living on streets or in a vehicle. Marginally housed includes temporary housing (e.g. hotel, halfway house). Stably housed implies owning or renting one's own place, living in an adult residential facility, or staying with family.

3.3. Evidence of drug use prior to death

Information on scene evidence of drug use was available for 83 of the 85 unwitnessed deaths. Of these cases, evidence was found for 36 (65 %) of 55 stimulant-no-opioid deaths and 25 (89 %) of 28 stimulant-fentanyl deaths.

Of the two witnessed stimulant-fentanyl deaths, one occurred immediately after the decedent injected a brown substance and stopped breathing. The other had minimal information about the scene of the event; the patient was transported to the hospital and died after a three-month intensive care unit stay. Among the 14 witnessed stimulant-no-opioid deaths, 13 (93 %) did not involve drug use leading up to the event (e.g., decedent collapsed while grocery shopping or during an argument); in one case the decedent smoked from a glass pipe immediately before collapsing.

3.4. Mechanism of death

For the 16 witnessed deaths, 10 of the collapses (all stimulant-no-opioid) were likely cardiac, two (both stimulant-no-opioid) were cerebrovascular accidents, one (stimulant-fentanyl) was likely respiratory, and three (two stimulant-no-opioid, one stimulant-fentanyl) lacked sufficient detail for determination.

4. Discussion

Through iterative analysis of medical examiner case narratives and medical records, we developed a system for characterizing deaths attributed to acute stimulant toxicity, applied this to a small sample of deaths, and developed three hypotheses for further investigation. First, most deaths attributed to acute stimulant toxicity occur in physically and socially isolated contexts where bystander response (e.g. with CPR or hypothetical reversal agents) would not be available, likely limiting the utility of such interventions. Second, there was limited evidence of recent street drug use among stimulant-no-opioid deaths, suggesting

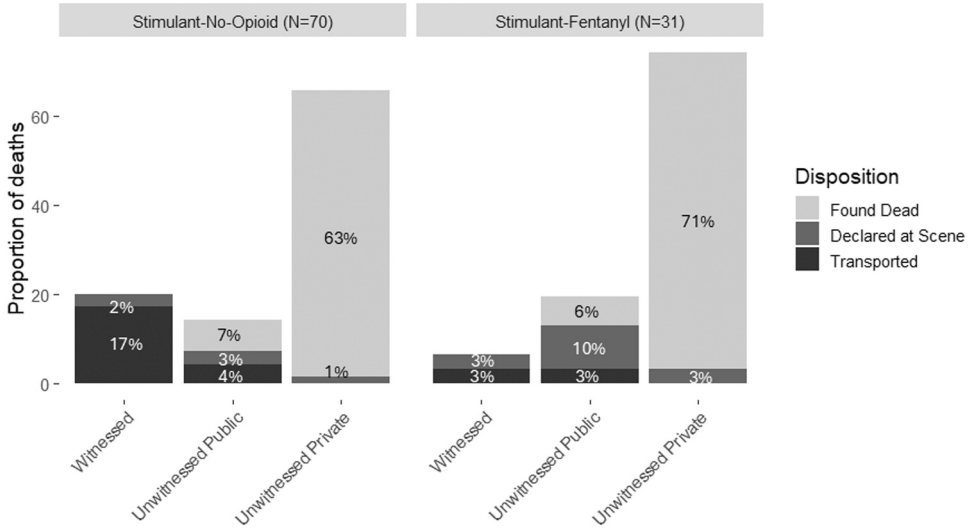

Fig. 2. Spatial contexts of deaths attributed to stimulants among decedents in a psychological autopsy study by fentanyl involvement (N = 101). Witnessed deaths include events that occurred in public and private spaces; unwitnessed deaths are shown broken down by public vs. private.

that many of these may not be driven by acute toxicity, but instead be the result of chronic disease contributed to by substance use. Third, stimulant-fentanyl deaths were generally unwitnessed and had more evidence suggesting recent drug use, and thus may be primarily attributable to fentanyl.

The deaths in our sample were characterized by marked social and physical isolation: 69 of 101 deaths occurred in private spaces without witnesses. In 53 of 101 deaths, over 12 hours had elapsed since the decedent was last seen; 33 of these decedents were found by professionals such as building staff or case managers rather than by family or friends. A typical case report for these deaths would be a body found decomposing in a public housing unit during a wellness check after the person had not been seen for several days. Even if the mechanism of death could be addressed by bystanders, the majority of these deaths had no opportunity for bystander intervention.

Two of 31 (6 %) stimulant-fentanyl deaths were witnessed, compared to 14 of 71 (20 %) stimulant-no-opioid deaths. Given that witnessed opioid overdoses should have a mortality rate under 1 % (McDonald and Strang, 2016), and possibly lower in a city with ready access to overdose prevention services, the low rate of stimulant-fentanyl deaths being witnessed is not surprising if those events resulted from opioid-induced respiratory depression. In contrast, out-of-hospital cardiac arrest, a likely etiology for stimulant-no-opioid deaths (Turner et al., 2018; Riley et al., 2022), has a mortality rate approaching 90 % (Tsao et al., 2022). The presence of witnesses would thus be less protective against death and could account for the finding of more witnessed stimulant-no-opioid deaths. These findings suggest that stimulant-fentanyl deaths should be considered as different from stimulant-no-opioid deaths.

If the deaths we studied were due to a common understanding of the term “overdose”, we would expect to find evidence of drug use shortly prior to the event resulting in death. While the one witnessed stimulant-fentanyl death with details about the event had such evidence, only 1 out of 14 witnessed stimulant-no-opioid deaths involved a report of witnessed drug use shortly preceding collapse. For the 83 unwitnessed deaths where information on scene drug evidence was available, evidence was more often present for stimulant-fentanyl (89 %) than stimulant-no-opioid deaths (65 %), suggesting that some stimulant-no-opioid deaths may not have been immediately preceded by drug use. Toxicology results imply some recency of use but remain positive for hours for cocaine and days for methamphetamine. If deaths attributed to acute stimulant toxicity were not immediately preceded by stimulant

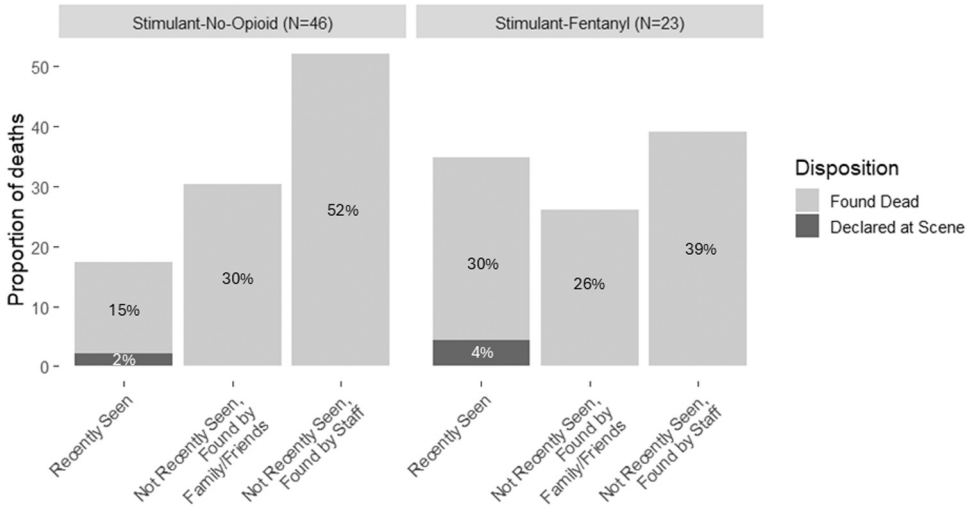

Fig. 3. Social contexts of deaths attributed to stimulants among decedents in a psychological autopsy study by fentanyl involvement (N = 69). Recently seen decedents were seen within 12 hours of death; decedents not recently seen are shown broken down by who found the body.

use, hypothetical stimulant reversal agents (analogous to naloxone) would have no role in prevention. Instead, preventing stimulant-no-opioid deaths would demand attention to prevention and management of chronic cardiovascular and related diseases (Riley et al., 2022).

This study has several limitations. First, our work was exploratory with a small sample size and should be considered hypothesis-generating. Second, our sample was drawn from a parent study in which each decedent had at least one informant who was successfully interviewed, implying that the marked social isolation we observed may be an underestimate. Finally, our coding of recency of street drug use relied upon witness reports and scene evidence. Witness reports were likely specific for recent use, but may have been insensitive as decedents may have used drugs out of view; scene evidence may have been sensitive for recent street drug use, but less specific as the presence of a drug or associated supplies would not necessarily imply recent use. Nonetheless, these data were readily available from case narratives, and the consistent finding in both sets of data suggests that these proxies were informative.

5. Conclusion

We developed an approach to analyzing medical examiner case narratives that provides insight into the nature of deaths attributed to acute stimulant toxicity and the viability of interventions. In our pilot sample, such deaths often occurred alone in isolated settings, often without evidence of recent drug use, and in many cases may more appropriately be considered sequelae of chronic disease. In contrast to deaths involving opioids, which may be prevented by bystander overdose response strategies, preventing stimulant-no-opioid deaths may require upstream interventions to address chronic disease, poverty, and social isolation. Application of this approach to a larger dataset, including other opioid deaths, would be valuable to inform public health interventions targeting acute drug toxicity.

CRediT authorship contribution statement

McMahan Vanessa M: Writing – review & editing, Visualization, Validation, Software, Investigation, Formal analysis, Data curation. **Chang Yi-Shin G:** Writing – review & editing, Investigation, Data curation. **Rodda Luke:** Writing – review & editing, Resources, Investigation, Data curation. **Coffin Phillip O:** Writing – original draft, Visualization, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Black Finn:** Writing – original draft, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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