


Increasing presence of xylazine in heroin and/or fentanyl deaths, Philadelphia, Pennsylvania, 2010–2019

Jewell Johnson , Lia Pizzicato, Caroline Johnson, Kendra Viner

Philadelphia Department of Public Health, Philadelphia, Pennsylvania, USA

Correspondence to

Jewell Johnson, Philadelphia Department of Public Health, Philadelphia, PA 19107, USA; jewell.johnson@phila.gov

Received 18 August 2020
Revised 2 November 2020
Accepted 13 November 2020
Published Online First
3 February 2021

ABSTRACT

Reports from active drug users state that xylazine, the veterinary tranquilliser, has been increasing in the illicit drug supply in Philadelphia. To describe trends and characteristics of unintentional deaths from heroin and/or fentanyl overdose with xylazine detections occurring in Philadelphia, Pennsylvania, the Philadelphia Department of Public Health analysed data on deaths from unintentional heroin and/or fentanyl overdose from the Philadelphia Medical Examiner's Office over a 10-year period (2010–2019). Xylazine went from being detected in less than 2% cases of fatal heroin and/or fentanyl overdose between 2010 and 2015 to 262 (31%) of the 858 fatal heroin and/or fentanyl overdose cases in 2019. Currently, information is limited on the presence of xylazine in continental United States. Xylazine's association with adverse outcomes in other locations indicates that potential health consequences should also be monitored in the USA. Whenever possible, jurisdictions should consistently test for xylazine.

INTRODUCTION

Xylazine is a non-opioid sedative, analgesic, and muscle relaxant used in veterinary medicine.¹ Human use of xylazine among people who take drugs has been well documented in Puerto Rico since the early 2000s, where it is known as 'anestesia de caballo' (horse anaesthetic).^{2–4} Increasingly, there have been reports of xylazine in the illicit drug supply in continental United States although motivations for its addition to the drug supply are unclear.^{5,6} In the USA, xylazine is not a scheduled medication, and although it is approved for use in veterinary medicine, the Food and Drug Administration has not approved it for human use. In humans, xylazine may cause hypotension, central nervous system depression, respiratory depression and bradycardia.¹ In addition, associations have been made between the use of xylazine and open skin ulcers among individuals who inject it.^{2,4} Research is limited on the effects of xylazine when used in combination with opioids and information on its presence in continental USA, especially in fentanyl dominated markets. In Philadelphia, the street name for xylazine is 'tranq', and heroin and fentanyl cut with xylazine is referred to as 'tranq dope'. This study examines trends in xylazine detections in postmortem toxicology tests among overdose decedents in Philadelphia, Pennsylvania, a city where fentanyl has largely replaced heroin in the illicit drug market since 2015.

METHODS

Using data from the Philadelphia Medical Examiner's Office (MEO), the Philadelphia Department of Public Health analysed unintentional overdose deaths with heroin and/or fentanyl detections that occurred between 2010 and 2019 in Philadelphia. Records were limited to deaths where drug intoxication was certified as the underlying or contributory cause of death, and full forensic toxicology testing was performed by the MEO. Full toxicology data of all drug detections at death were provided by the MEO for this analysis. For the duration of the study period, the Philadelphia MEO consistently tested for xylazine, fentanyl and heroin when conducting post mortem toxicology tests among overdose decedents. Overdose deaths among Philadelphia residents occurring outside of the city were excluded as full forensic toxicology was not available for these decedents. Non-residents who died in the city and were investigated by the Philadelphia MEO were included in the study sample. Given the increase in xylazine detections in 2019, we examined age, sex, race/ethnicity and additional toxicology detections among 2019 overdose decedents positive for heroin and/or fentanyl and stratified by the presence of xylazine. Chi-square tests were used to examine differences in categorical variables, and an alpha level of 0.05 was considered significant. We also analysed data on polydrug samples seized in Pennsylvania and tested by a Drug Enforcement Administration laboratory. Samples in which the primary drug (ie, the drug detected in the highest quantity) was heroin or fentanyl were examined for the presence of xylazine. Analyses were conducted using SAS (Studio; SAS Institute).

RESULTS

Between 2010 and 2015, xylazine was detected in 40 (2%) of the 1854 unintentional overdose deaths with heroin and/or fentanyl detections. This increased to 67 (11%) in 2016, 90 (10%) in 2017, 152 (18%) in 2018, and 262 (31%) in 2019 (figure 1).

In 2019, decedents with positive xylazine detections were predominately male (76%), between the ages of 35 and 54 years old (47%) and non-Hispanic, white (65%). Age, race/ethnicity and opioid detections were statistically different from those of heroin and/or fentanyl decedents without xylazine detected (table 1). Among 2019 decedents with positive detections for xylazine, 100% were positive for fentanyl, 10% were positive for heroin,



© Author(s) (or their employer(s)) 2021. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Johnson J, Pizzicato L, Johnson C, et al. *Inj Prev* 2021;**27**:395–398.

Brief report

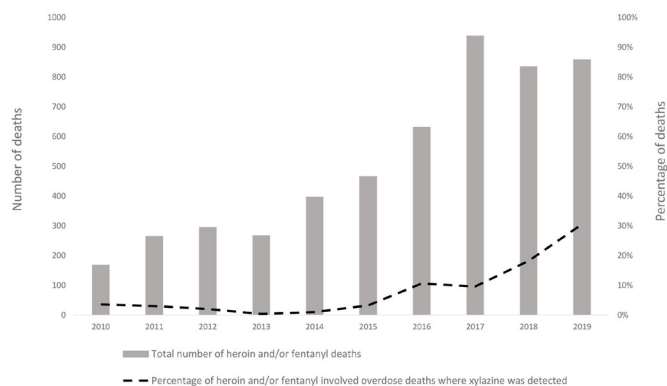


Figure 1 Number and percentage of heroin and/or fentanyl unintentional overdose deaths involving xylazine, Philadelphia, Pennsylvania, 2010–2019.

7% were positive for pharmaceutical opioids such as oxycodone, 6% were positive for methadone, 12% were positive for methamphetamine, 28% were positive for benzodiazepines and 53% were positive for cocaine (table 1). Evidence of injection was more prevalent among heroin and/or fentanyl decedents who were positive for xylazine than for those who were not ($p < 0.0001$) (table 1).

Drug seizure data tested in Drug Enforcement Administration laboratories indicates that xylazine is increasing in polydrug samples in which the primary drug detected is heroin or fentanyl.

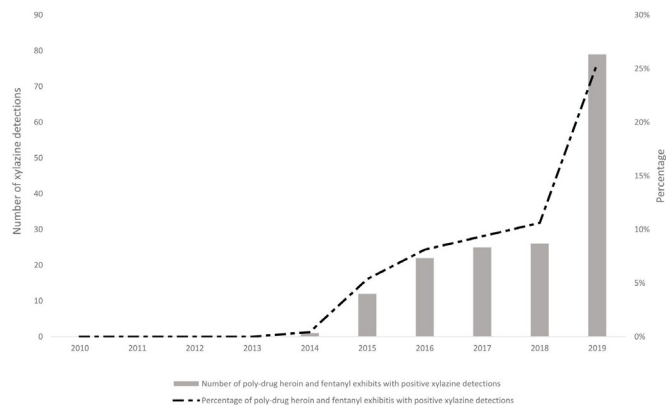


Figure 2 Number and percentage of xylazine detections in polydrug exhibits seized where the primary drug detected was fentanyl or heroin, Pennsylvania, 2010–2019.

While no polydrug seizures contained xylazine between 2010 and 2013, 5% contained xylazine in 2015, 9% in 2017 and 25% in 2019 (figure 2).

DISCUSSION

Harms of xylazine use in humans are not well documented, but evidence suggests that combined use of xylazine and an opioid such as fentanyl may increase the risk of overdose fatality.¹ Although naloxone, the opioid overdose reversal drug, is

Table 1 Demographic characteristics and toxicology detections of heroin and/ or fentanyl overdose decedents (n=858), Philadelphia, Pennsylvania, 2019

	Heroin and/or fentanyl without xylazine (n=596)		Heroin and/or fentanyl with xylazine (n=262)		Chi Square P value
	N	%	N	%	
Demographic characteristics					
Age (years)					0.0381
15–34	172	28.9	94	35.9	
35–54	285	47.8	124	47.3	
≥55	139	23.3	44	16.8	
Sex					0.9710
Male	452	75.8	199	76.0	
Female	144	24.2	63	24.0	
Race/ethnicity					<0.0001
Non-Hispanic, white	293	49.2	169	64.5	
Non-Hispanic, black	185	31.0	46	17.6	
Hispanic	111	18.6	42	16.0	
Other	7	1.2	5	1.9	
Toxicology					
Additional substance detected at death*					
Fentanyl	576	96.6	262	100.0	0.0027
Heroin†	172	28.9	27	10.3	<0.0001
Pharmaceutical opioids‡	73	12.2	18	6.9	0.0185
Methadone	21	3.5	15	5.7	0.1385
Methamphetamine	50	8.4	31	11.8	0.1122
Benzodiazepines	158	26.5	74	28.2	0.5984
Cocaine	313	52.5	140	53.4	0.8040
Evidence of injection					
No	458	76.8	159	60.7	<0.0001
Yes	138	23.2	103	39.3	

*Substances are not mutually exclusive as more than one additional substance may be detected at death.

†Heroin may include detections for morphine only.

‡Excludes detections for methadone and fentanyl.

not effective against xylazine alone, unintentional fatal overdoses with xylazine detections also had heroin and/or fentanyl detections in Philadelphia, indicating timely administration of naloxone is critical for preventing deaths. Additional treatment for xylazine poisoning may involve supportive care using intubation, ventilation and administration of intravenous fluid.¹

Of note, as fentanyl has largely replaced the heroin supply in Philadelphia, xylazine has been increasingly found in combination with fentanyl. Some evidence suggests that the combination of xylazine and fentanyl in humans may potentiate the desired effect of sedation and the adverse effects of respiratory depression, bradycardia and hypotension caused by fentanyl alone,¹ comparable to the synergistic effects of combining benzodiazepines with heroin and/or fentanyl.⁷ While benzodiazepines were detected in 97 (58%) of the 168 unintentional overdose deaths with heroin and/or fentanyl detections in Philadelphia in 2010, this decreased to 232 (28%) of the 858 unintentional overdose deaths with heroin and/or fentanyl detections in 2019. This decline may be the result of increasing demand for xylazine among people who use drugs in Philadelphia and/or changes in the illicit drug market as drug seizure data indicate that xylazine is increasing in polydrug samples. Indeed, focus groups with people who use drugs in Philadelphia have suggested that the addition of xylazine to fentanyl “makes you feel like you’re doing dope (heroin) in the old days (before it was replaced by fentanyl)” when the euphoric effects lasted longer. Users have suggested that xylazine gives them ‘the nod’ that heroin provided prior to the replacement of fentanyl in the drug supply. In Puerto Rico, xylazine use has been associated with use of ‘speedballs’, the combined use of heroin and cocaine.^{2,3} In semistructured interviews, Puerto Rican drug users indicated that the addition of cocaine to heroin and xylazine combinations was used to balance the ‘down’ of heroin and xylazine.⁴ Among 2019 decedents with positive detections for xylazine and an opioid in Philadelphia, 53% also had positive detections for cocaine, which may indicate speedball use locally (table 1).

Importantly, our results show that evidence of injection was more prevalent among decedents with xylazine and heroin and/or fentanyl detections. Despite limited literature on the health effects of chronic xylazine use, regular injection of xylazine has been associated with skin ulcers, abscesses and lesions in Puerto Rico.^{2,3} Semistructured interviews with people who use xylazine in Puerto Rico revealed that regular use of xylazine leads to skin ulcers.⁴ As skin ulcers are painful, people may continually inject at the site of the ulcer to alleviate the pain as xylazine is a potent α_2 -adrenergic agonist that mediates via central α_2 -receptors, which decreases perception of painful stimuli.¹ People may self-treat the wound by draining or lancing it, which can exacerbate negative outcomes.⁸ While Philadelphia has seen a rise in skin and soft tissue infections relating to injection drug use, it is not yet clear whether or not this is due to increased presence of xylazine in the drug supply.⁹

The results from this study have some limitations. This study examined the presence of particular substances detected in post mortem toxicology among overdose decedents, but we were unable to determine which drug, or particular combination of drugs, caused the overdose death. Furthermore, we were unable to determine why xylazine is increasing in the drug supply (eg, increased street value, enhanced effects) or whether the decedent intended to use xylazine either alone or in combination with other drugs. While focus groups conducted in Philadelphia indicate that some people who use drugs have developed a preference for opioids combined with xylazine, we were unable to determine intent using toxicology data alone. Polydrug samples

seized in Pennsylvania are enforcement driven and testing is done as required by courts. Thus, seizure data may not reflect the true prevalence of drugs at the street level. Findings from this study may not be generalisable outside of Philadelphia, and jurisdictions should independently assess whether xylazine is present in their illicit drug supply.

Results from this study suggests that the opioid epidemic throughout the USA continues to evolve. Although xylazine has been a drug of abuse in Puerto Rico since the early 2000s, fatal overdose toxicology data from Philadelphia and other jurisdictions suggest that its prevalence may be increasing in continental USA.^{5,6} Jurisdictions that do not currently test for xylazine should consider adding it to their routine toxicology testing. Further study is needed to understand the synergistic effects of fentanyl and xylazine use by humans and to better contextualise the reasons for its use in the USA.

What is already known on the subject

- ▶ Xylazine has been documented in Puerto Rico’s illicit opioid supply since the early 2000s.
- ▶ Xylazine has been associated with increased risk of skin ulceration and fatal overdose.

What this study adds

- ▶ Continental xylazine detections are evident in Philadelphia, Pennsylvania.
- ▶ While xylazine was detected in 2% of unintentional overdose deaths with heroin and/or fentanyl detections in Philadelphia during 2010–2015, detection increased to 31% by 2019.
- ▶ Prevalence of xylazine in overdose deaths may be under-reported in the rest of continental USA as xylazine may not be consistently reported if forensic toxicology was not completed at death.

Acknowledgements We thank the Drug Enforcement Administration Philadelphia Division for providing data on xylazine seizures in Pennsylvania as well as the Philadelphia Medical Examiner’s Office for providing data on unintentional overdose decedents.

Contributors JJ, LP, CJ and KV developed the study protocol. JJ and LP were responsible for the literature review. JJ performed the statistical analyses on data from the Philadelphia Medical Examiner’s Office and LP performed the statistical analyses on the data from the Drug Enforcement Administration Philadelphia Division. JJ drafted the first version of the manuscript. LP, CJ and KV contributed to the interpretation of the results and assisted with manuscript revisions. All authors approved the submission of this version of the manuscript.

Funding This study was supported by the Centers for Disease Control and Prevention CDC-RFA-CE19-1904 awarded to the Philadelphia Department of Public Health.

Disclaimer The funders had no role in the study design, analysis and interpretation of data, and preparation and review of the manuscript.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study was determined to be exempt by the institutional review board at the City of Philadelphia Department of Public Health.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Jewell Johnson <http://orcid.org/0000-0002-0478-1145>

REFERENCES

- 1 Ruiz-Colón K, Chavez-Arias C, Díaz-Alcalá JE, *et al*. Xylazine intoxication in humans and its importance as an emerging adulterant in abused drugs: a comprehensive review of the literature. *Forensic Sci Int* 2014;240:1–8.
- 2 Rodríguez N, Vargas Vidot J, Panelli J, *et al*. GC-MS confirmation of xylazine (Rompun), a veterinary sedative, in exchanged needles. *Drug Alcohol Depend* 2008;96:290–3.
- 3 Reyes JC, Negrón JL, Colón HM, *et al*. The emerging of xylazine as a new drug of abuse and its health consequences among drug users in Puerto Rico. *J Urban Health* 2012;89:519–26.
- 4 Torruella RA. Xylazine (veterinary sedative) use in Puerto Rico. *Subst Abuse Treat Prev Policy* 2011;6:7.
- 5 Maryland Poison Control Center. ToxTidbits: Xylazine [Internet]. Baltimore, MD. University of Maryland School of Pharmacy, 2019. Available: <https://www.mdpoison.com/media/SOP/mdpoisoncom/ToxTidbits/2019/Jan%202019%20ToxTidbits.pdf> [Accessed 10 Jun 2020].
- 6 Ohio Department of Health. Health advisory: xylazine, an adulterant for illicit opioids, has been detected in three decedents who died from a drug overdose [Internet]. Columbus, OH. Ohio State Government, 2019. Available: <http://rosscountyema.com/wp-content/uploads/2019/05/Health-Advisory-Xylazine.pdf> [Accessed 15 Jun 2020].
- 7 McClure FL, Niles JK, Kaufman HW, *et al*. Concurrent use of opioids and benzodiazepines: evaluation of prescription drug monitoring by a United States laboratory. *J Addict Med* 2017;11:420–6.
- 8 Harris RE, Richardson J, Frasso R, *et al*. Experiences with skin and soft tissue infections among people who inject drugs in Philadelphia: a qualitative study. *Drug Alcohol Depend* 2018;187:8–12.
- 9 Philadelphia Department of Public Health. Hospitalizations for infections related to injection drug use, 2013–2018 [Internet], 2020. Available: <https://www.phila.gov/media/20200206154343/CHART-v5e1.pdf> [Accessed 16 Jun 2020].

Xylazine-Induced Skin Ulcers in a Person Who Injects Drugs in Philadelphia, Pennsylvania, USA

Srikrishna V. Malayala¹, Bhavani Nagendra Papudesi², Raymond Bobb¹, Aliya Wimbush¹

1. Addiction Medicine, Merakey, Philadelphia, USA 2. Internal Medicine, Suburban Hospital, Philadelphia, USA

Corresponding author: Srikrishna V. Malayala, varun_msk@yahoo.com

Review began 08/14/2022

Review ended 08/16/2022

Published 08/19/2022

© Copyright 2022

Malayala et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Xylazine, an alpha-2 adrenergic receptor agonist typically used as a sedative and analgesic in veterinary medicine, is being illicitly supplied to persons who inject drugs (PWID), especially in Puerto Rico and Philadelphia, Pennsylvania in the USA. There is a high prevalence (up to 78%) of xylazine in fentanyl in these areas and also a steep increase in fatalities from its overdose.

In this case report, we discuss a case of xylazine-induced skin ulcers in a PWID in the city of Philadelphia. The patient is a 37-year-old female who was injecting about eight to ten "bags" of "dope" (fentanyl, which is typically mixed with xylazine in Philadelphia) every day. She typically injected into her veins on the hands and sometimes into the legs. She presented with ulcers on her lower extremities extending from the knees to ankles, associated with copious purulent drainage and a foul smell. There was extensive necrosis of the subcutaneous tissues, abscesses, and tibial osteomyelitis. This led to multiple hospitalizations with bacteremia from *Strep pyogenes*, methicillin-resistant *Staphylococcus aureus*, methicillin-sensitive *S. aureus*, *Enterococcus faecalis*, *Escherichia coli*, and *Proteus* requiring intravenous antibiotics. She required debridement of the wounds and topical care to treat them.

In the areas with a high prevalence of the use of xylazine mixed with fentanyl or heroin, abscesses, and painful skin ulcers are very often reported. The mechanism is thought to be due to its direct vasoconstricting effect on local blood vessels and the resultant decreased skin perfusion. Prolonged use can lead to decreased perfusion and impaired wound healing, leading to higher chances of infection of these ulcers. In addition to the topical effect of vasoconstriction, xylazine also leads to hypotension, bradycardia, and respiratory depression.

A skin ulcer in a PWID, similar to the ones reported in our case, should raise clinical suspicion for the presence of xylazine in opiates and other substances.

Categories: Dermatology, Internal Medicine, Public Health

Keywords: substance use disorder (sud), intravenous drug user, foot ulcer, chronic ulcer, drug withdrawal, heroine withdrawal, opiate use, opioid withdrawal, drug addiction, xylazine

Introduction

Xylazine is an alpha-2 adrenergic receptor agonist, similar to clonidine, and is a non-narcotic sedative used for analgesia and muscle relaxation exclusively in veterinary medicine [1]. Illicit use of xylazine among persons who inject drugs (PWID) has been reported in Puerto Rico since the early 2000s [2] and more recently in Philadelphia, Pennsylvania [3]. As of now, there is no precise categorization or confirmatory evidence regarding the trends, geographical distribution, and health risks.

In veterinary medicine, xylazine has been termed as 'anesthesia de caballo' (horse anesthetic) [4]. In Philadelphia, xylazine has been more popularly termed as 'tranq', and the more commonly used illicit drugs, heroin and fentanyl cut with xylazine, have been referred to as 'tranq dope' [3]. In the United States, Xylazine is not a scheduled medication. Although it is approved for veterinary medicine, the Food and Drug Administration has not approved it for human use.

From 2000 to 2006, cocaine was the leading drug associated with overdose deaths, which was replaced successively by prescription opioids (2007-2013), heroin (2014-2015), and illicitly-manufactured fentanyl (2016-present) [5]. In more recent years, a sharp increase in fatalities has been linked to systemic polysubstance use and potent synthetic compounds in numerous drug classes, including synthetic opioids such as fentanyl [6], sedatives like benzodiazepines, and stimulants such as methamphetamine [7], and novel benzodiazepines [8]. Recent news articles report a high prevalence (up to 78%) of xylazine in fentanyl screen-positive urine samples in Puerto Rico and Philadelphia and also a steep increase in fatalities from xylazine overdose [9]. In a recent report from Philadelphia, xylazine increased from being detected in less than 2% of cases of fatal heroin or fentanyl overdose between 2010 and 2015 to 31% of fatal heroin or fentanyl overdose cases in 2019 [10].

How to cite this article

Malayala S V, Papudesi B, Bobb R, et al. (August 19, 2022) Xylazine-Induced Skin Ulcers in a Person Who Injects Drugs in Philadelphia, Pennsylvania, USA. Cureus 14(8): e28160. DOI 10.7759/cureus.28160

With this extent of the use of xylazine and its malicious effects, there is an urgent necessity to focus on the manifestations of xylazine on PWID, the dynamics of its usage, and fatality trends to understand its role in shifting the current US overdose dynamics. In this case report, we present a case of skin ulcers that were noticed in a PWID in the city of Philadelphia. We also hypothesize the presumed mechanism of skin injury and illustrate the latest trends in xylazine usage, its morbidity, and mortality trends all across the USA. We intend to increase suspicion of novel health risks of xylazine, specifically skin ulcers and abscesses.

Case Presentation

The patient in this case report is a 37-year-old Caucasian female with a known history of opiate use disorder. She had a very long history of polysubstance abuse and injection drug use. She was homeless at that time, living off the streets. She is a resident of Philadelphia City. She was on a methadone maintenance program (MMT), taking 80 mg of methadone daily but on an irregular basis. Apart from drug use, she also had a history of multiple infectious complications from drug use, including left clavicle osteomyelitis, left sternoclavicular septic arthritis, and multiple bacteremias. Most of her treatments were incomplete in the past as she had a tendency to leave the hospital against medical advice (AMA) in the middle of her hospitalizations. She also had a prolonged QT interval at the baseline, measuring approximately 480 ms, likely due to the concurrent use of methadone and illicit opiates.

She presented to the addiction medicine office for a follow-up visit. During that time, she was using about 10 bags of intravenous fentanyl/heroin every day and around five alprazolam "bars" every day. She was also smoking a pack of cigarettes every day. At this clinic visit, she reported ulcers on her lower extremities (Figures 1-2) that started a few weeks ago and gradually got worse. She had a low-grade fever of 99.8 °F, a blood pressure of 100/48 mm Hg, and a heart rate of 92/minute. The ulcers were foul-smelling, had copious purulent drainage, and were present on both the anterior aspects of her legs, extending from just below the knee to above the ankle. They were extending into the bone at some places.



FIGURE 1: Xylazine-induced leg skin ulcers, cellulitis and osteomyelitis in a person who injects drugs in Philadelphia



FIGURE 2: Xylazine-induced right leg cellulitis, wound infection and osteomyelitis in a person who injects drugs

She reported that the ulcers started spontaneously a few weeks ago and gradually got worse. She denied any injury or insect bites that might have led to the wounds. She usually injects into her hands, but sometimes into her legs as well. Whenever she missed a vein, she noticed that the areas were ulcerated. She reported that these wounds were progressively getting worse, unlike any of her prior wounds.

After addressing the dose of methadone, she was advised to go to the emergency room for the management of the ulcers. In the emergency room, she had a CT scan of her lower extremities that showed acute and active osteomyelitis in the proximal third of the right anterior and anterolateral tibia. There was also a soft tissue abscess in the right anterior compartment musculature of the proximal third of the leg and one more abscess in the right anteromedial soft tissues of the proximal and mid-leg region. On the left leg, there was no cortical irregularity to suggest osteomyelitis of the left lower extremity, but the findings were consistent

with a soft tissue abscess and cellulitis. She was admitted to the hospital with broad-spectrum antibiotics including intravenous Vancomycin and Piperacillin/Tazobactam. Subsequently, when the patient refused to get any blood draws to monitor their therapeutic vancomycin level, the antibiotic was changed to intravenous daptomycin. The lower extremity wounds were debrided at the bedside. Topical wound care was offered and continued. Pain management and opiate withdrawal management were continued without any interruptions. The methadone dose was titrated while she was admitted. However, she left against medical advice from the hospital, and her ongoing injection opiate use continued. The blood cultures in this hospitalization grew *Streptococcus pyogenes*.

She presented to the emergency room and was admitted five times over the next eight weeks with very similar presentations, and at each visit, she was admitted with the resumption of intravenous antibiotics and topical wound care. She had bacteremia from methicillin-resistant *Staphylococcus aureus*, *Proteus mirabilis*, methicillin-sensitive *S. aureus*, and *Enterobacter* species. She was also evaluated by a plastic surgeon who recommended definitive reconstruction of the wounds once the infection resolves. In the last hospitalization, the patient stayed in the hospital for a few weeks and completed the recommended treatment. She was discharged to a recovery house with oral antibiotics (levofloxacin and doxycycline) for eight more weeks. She was advised to apply Silvadene ointment to the wounds, wash them with an antiseptic solution, and redress them with Xeroform, ABD pads, and Kerlix.

Discussion

Addiction is one of the most significant hardships and one of the most challenging clinical conditions to deal with, especially without external support or interventions. The consequences are much worse when they cause new medical conditions or worsening of comorbid conditions and pre-existing diseases in a patient who is already apprehensive about seeking healthcare due to multiple factors like the fear of being judged, social stigma, poor economic status, poor health care awareness and limited access to healthcare. These patients typically tend to seek help or present to the hospital only at late stages, which makes our case report very pertinent.

Xylazine was discovered in 1962 in Leverkusen, Germany, and was used as an anti-hypertensive agent [11]. It is a partial alpha-2 adrenergic agonist. Peripherally, alpha-2 agonist causes arterial constriction, but centrally, it acts as a sympathetic antagonist, decreasing heart rate and contractility [11].

Xylazine can be swallowed, inhaled, smoked, snorted, or injected into the muscle or vein. There are no data on vaping. Intoxication mimics clonidine and tizanidine as they all share the same mechanism of action. The most common side effects in humans include transient hypertension secondary to vagus nerve stimulation, bradycardia, respiratory depression, hypotension, acidemia, coma, and a decrease in cardiac output [5]. Other rare but very concerning side effects that can occur are areflexia, asthenia, ataxia, blurred vision, disorientation, dizziness, drowsiness, dysarthria, dysmetria, fainting, hyporeflexia, slurred speech, somnolence, staggering, coma, apnea, shallow breathing, sleepiness, premature ventricular contraction, tachycardia, miosis, dry mouth, hyperglycemia, and diabetes [12]. It is also reported to cause hypotonia, dry mouth, urinary incontinence, and nonspecific electrocardiographic ST-segment changes [5]. Xylazine has a rapid onset within minutes and can last for eight hours or longer depending upon the dose, route of administration, and whether it was mixed with opioids or other drugs. But the duration of symptoms after an overdose can vary widely, all the way from 8 to 72 hours [5]. Due to all these side effects, it was not approved by the FDA for use in humans. It is to be noted that the traditional drug screen does not detect the presence of xylazine in urine or blood samples.

A high prevalence of abscesses and painful skin ulcers [13] developed over various body parts irrespective of the IV injection site was reported. The mechanism is thought to be mediated by its direct vasoconstricting effect on local blood vessels and resultant decreased skin perfusion [6]. In addition to vasoconstriction, it causes hypotension, bradycardia, and respiratory depression, leading to lower tissue oxygenation in the skin [14]. Thus, chronic use of xylazine can progress the vasoconstriction and skin oxygenation deficit, leading to severe soft tissue infections, including abscesses, cellulitis, and skin ulceration. Decreased perfusion also leads to impaired healing of wounds and a higher chance of infection of these ulcers [15].

In a recent study mentioning data from ten jurisdictions representing all four U.S. Census regions, xylazine was increasingly present in overdose deaths. The highest xylazine prevalence data was observed in Philadelphia (25.8% of deaths), followed by Maryland (19.3%) and Connecticut (10.2%). Illicitly manufactured fentanyl was present in 98.4% of xylazine present-overdose-deaths, suggesting a solid ecological link between fentanyl and xylazine compared to fentanyl's association with other illicit substances such as cocaine (45.4%), benzodiazepines (28.4%), heroin (23.3%), and alcohol (19.7%). PWIDs in Philadelphia described Xylazine as a "sought after" adulterant that lengthens the short duration of fentanyl injection's effects [7]. It is also used as a cutting agent for other opioid drugs. Some of the PWID who took xylazine without knowing may not report that they had it but ask the patient a few questions like "do you sometimes do not experience the usual dope like the high feeling after taking dope but feel excessively tired and dry mouth after having "dope"? This may lead the patient to enter a vicious cycle of using more illicit substances. One more important thing to consider from these studies on rodents is that the incidence and severity of corneal lesions are prevented or reduced with the administration of Yohimbine (an α -2 adrenergic

antagonist) [15]. This could shed some light and lead to some clues in research on the treatment of cases of acute or chronic side effects of xylazine in PWID.

Conclusions

There has been a rapid increase in the adulteration of illicit IV drugs with highly harmful substances, particularly those that are not even approved for human use. These substances are used for a multitude of reasons, like prolonging the duration of effect, using them as a cutting agent, and increasing the ease of availability of the base drug. The use of xylazine is rapidly becoming more frequent, and there is a potential risk that in the near future, this may be used alone or combined with a variety of illicit drugs that can lead to devastating acute and chronic clinical consequences in PWIDs and excess utilization of healthcare resources that could otherwise be prevented. Physicians should possess a high clinical suspicion for accurately diagnosing acute xylazine-induced naloxone-resistant overdoses and identifying chronic effects caused by xylazine, like ulcers and abscesses. More research is needed to study the trends of xylazine use across the US, its clinical effects, and the focus on therapy exclusively directed towards treating acute and chronic effects of xylazine. Extreme measures should be exercised by the local and federal government bodies to halt the increasing availability and use of Xylazine, along with other illicit drugs.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

- Nunez J, DeJoseph ME, Gill JR: Xylazine, a veterinary tranquilizer, detected in 42 accidental fentanyl intoxication deaths. *Am J Forensic Med Pathol.* 2021, 42:9-11. [10.1097/PAF.0000000000000622](https://doi.org/10.1097/PAF.0000000000000622)
- Rodríguez N, Vargas Vidot J, Panelli J, Colón H, Ritchie B, Yamamura Y: GC-MS confirmation of xylazine (Rompun), a veterinary sedative, in exchanged needles. *Drug Alcohol Depend.* 2008, 96:290-3. [10.1016/j.drugalcdep.2008.03.005](https://doi.org/10.1016/j.drugalcdep.2008.03.005)
- Johnson J, Pizzicato L, Johnson C, Viner K: Increasing presence of xylazine in heroin and/or fentanyl deaths, Philadelphia, Pennsylvania, 2010-2019. *Inj Prev.* 2021, 27:395-8. [10.1136/injuryprev-2020-043968](https://doi.org/10.1136/injuryprev-2020-043968)
- Reyes JC, Negrón JL, Colón HM, Padilla AM, Millán MY, Matos TD, Robles RR: The emerging of xylazine as a new drug of abuse and its health consequences among drug users in Puerto Rico. *J Urban Health.* 2012, 89:519-26. [10.1007/s11524-011-9662-6](https://doi.org/10.1007/s11524-011-9662-6)
- Ruiz-Colón K, Chavez-Arias C, Díaz-Alcalá JE, Martínez MA: Xylazine intoxication in humans and its importance as an emerging adulterant in abused drugs: A comprehensive review of the literature. *Forensic Sci Int.* 2014, 240:1-8. [10.1016/j.forsciint.2014.03.015](https://doi.org/10.1016/j.forsciint.2014.03.015)
- A case of skin necrosis caused by intravenous xylazine abuse . (2021). Accessed: May 13, 2022: <https://shabstracts.org/abstract/a-case-of-skin-necrosis-caused-by-intravenous-xylazine-abuse/>.
- Friedman J, Montero F, Bourgeois P, Wahbi R, Dye D, Goodman-Meza D, Shover C: Xylazine spreads across the US: a growing component of the increasingly synthetic and polysubstance overdose crisis. *Drug Alcohol Depend.* 2022, 233:109380. [10.1016/j.drugalcdep.2022.109380](https://doi.org/10.1016/j.drugalcdep.2022.109380)
- Ciccarone D: Fentanyl in the US heroin supply: a rapidly changing risk environment . *Int J Drug Policy.* 2017, 46:107-11. [10.1016/j.drugpo.2017.06.010](https://doi.org/10.1016/j.drugpo.2017.06.010)
- Han B, Cotto J, Etz K, Einstein EB, Compton WM, Volkow ND: Methamphetamine overdose deaths in the US by sex and race and ethnicity. *JAMA Psychiatry.* 2021, 78:564-7. [10.1001/jamapsychiatry.2020.4321](https://doi.org/10.1001/jamapsychiatry.2020.4321)
- Laing MK, Ti L, Marmel A, et al.: An outbreak of novel psychoactive substance benzodiazepines in the unregulated drug supply: Preliminary results from a community drug checking program using point-of-care and confirmatory methods. *Int J Drug Policy.* 2021, 95:103169. [10.1016/j.drugpo.2021.103169](https://doi.org/10.1016/j.drugpo.2021.103169)
- Korn WR, Stone MD, Haviland KL, Toohey JM, Stickle DF: High prevalence of xylazine among fentanyl screen-positive urines from hospitalized patients, Philadelphia, 2021. *Clin Chim Acta.* 2021, 521:151-4. [10.1016/j.cca.2021.07.010](https://doi.org/10.1016/j.cca.2021.07.010)
- Torruella RA: Xylazine (veterinary sedative) use in Puerto Rico . *Subst Abuse Treat Prev Policy.* 2011, 6:7. [10.1186/1747-597X-6-7](https://doi.org/10.1186/1747-597X-6-7)
- Greene SA, Thurmon JC: Xylazine--a review of its pharmacology and use in veterinary medicine . *J Vet Pharmacol Ther.* 1988, 11:295-313. [10.1111/j.1365-2885.1988.tb00189.x](https://doi.org/10.1111/j.1365-2885.1988.tb00189.x)
- Zwick LS, Patrick DJ, Knupp LC, Ramos MF: Ketamine/xylazine anesthesia-related corneal lesions in rats with surgically implanted venous catheters utilized in nonclinical intravenous studies. *Toxicol Pathol.* 2021, 49:598-601. [10.1177/0192623320960705](https://doi.org/10.1177/0192623320960705)
- Liu CM, Chiu MJ, Fang CC, Chen WJ: Xylazine abuse: a rare cause of syncope . *Clin Toxicol (Phila).* 2007, 45:309-11. [10.1080/15563650601073520](https://doi.org/10.1080/15563650601073520)