

Xylazine Usage and Awareness Among People Who Use Drugs in Denver, Colorado

Marina Yamada BS¹, Brittany Quinn BA¹, Sophie Zachary BS¹, Megan Schrage BS¹, Andreas Edrich MD MBA FASAM MRO², Mark Payton PhD³, Jean Bouquet DO¹, Rachel M.A. Linger PhD³

1. Rocky Vista University, College of Osteopathic Medicine, Englewood, CO
2. Heritage Hills Family Medicine, Addiction Medicine and Mental Health P.C. Centennial, CO
3. Rocky Vista University, Biomedical Sciences Department, Englewood, CO

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Statements and Declarations

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Abstract

Background: Xylazine, also known as “tranq,” is an alpha-2 agonist with various effects including central nervous system depression, analgesia, and vasoconstriction. Since xylazine is a non-opioid, its effects are not reversible with naloxone, complicating overdose treatment. Xylazine is becoming increasingly prevalent in the illicit drug supply, especially on the east coast of the United States. This study aims to understand xylazine usage and awareness among people who use drugs (PWUD) in Denver, Colorado. *Methods:* This project was conducted with the Harm Reduction Action Center (HRAC), a public health agency working with PWUD. An anonymous 16-question survey was conducted among its participants (n=148), evaluating their usage and awareness of xylazine from July to August 2023. *Results:* Fifty-three percent of participants had heard of xylazine and 16.3% of participants reported that they had used xylazine. No participants selected xylazine as their primary drug of choice. Those who selected fentanyl or heroin as their primary drug of choice were significantly more likely to have used xylazine (p=0.0001 and p=0.0027, respectively) compared to participants whose primary drug of choice was methamphetamines or THC. Out of the participants who said that they had used or were unsure if they had used xylazine (n= 37), 75.7% said it was unintentional use. *Conclusion:* These data suggest that awareness of xylazine is still limited among PWUD in Denver despite its presence in the community. Future research is warranted to determine whether raising awareness about xylazine helps PWUD make informed medical choices in addition to reducing the rates of overdose in the community.

Introduction

Xylazine (*N*- (2,6-dimethylphenyl)-5,6 dihydro-4H-1,3-thiazin-2-amine), also known as “tranq,” is an alpha-2 (α_2) adrenergic receptor agonist that was originally developed in 1962 as an antihypertensive agent, but resulted in severe central nervous system depression and was subsequently not approved for human use.¹ In addition to central nervous system depression, other effects of xylazine include muscle relaxation, analgesia, respiratory depression, sedation, and peripheral vasoconstriction.^{2,3} Vasoconstriction at the site of xylazine injection can increase infection risk and cause skin necrosis and ulcers, and severe cases can result in limb amputation.⁴ Wounds associated with xylazine have also been reported to be barriers to care, including substance use treatment.⁵

Xylazine has become increasingly prevalent in the unregulated drug supply in the United States, most notably in Philadelphia and other cities on the east coast.^{6,7} Evidence from the Philadelphia Medical Examiner’s office⁸ revealed xylazine was found in less than 2% of heroin/fentanyl overdoses in 2010, 14% in 2018, and 26% in 2020. A 2021-2022 study of the Maryland drug supply found xylazine and fentanyl were most frequently combined; 80% of drug samples that tested positive for fentanyl also tested positive for xylazine.⁷ Additionally, another study analyzed xylazine-positive urine samples from patients in 25 states and found fentanyl to be the most frequently detected copositive substance, which suggests an association between fentanyl and xylazine use.⁹ In 2019, the Centers for Disease Control and Prevention (CDC) reported that xylazine was involved in overdose deaths in 25 out of 38 states evaluated.¹⁰ In 2021, the drug was detected in 36 states,² and xylazine-involved overdose deaths rose 1238% from 2018 according to data from the CDC.¹¹ A 2022 study found that among PWUD, xylazine users, compared to non-users, were more likely to have a history of recent overdose.¹² As of March 2023, xylazine has been reported in 48 states.^{7,11}

Xylazine is less fatal than fentanyl, and its emergence is thought to be related to the displacement of heroin from the opioid supply. Xylazine is being used to make opioids cheaper and longer lasting,³ and those that mix it with fentanyl claim that fentanyl provides the “rush” while xylazine prolongs the normally short high.³ A 2022 study of the Philadelphia drug supply found that the average drug sample contained 30-40% xylazine and 2-10% fentanyl. In contrast, out of 187 drug samples, only 6 contained a significant amount of heroin.³ Due to this increasing prevalence of xylazine in the illicit drug supply, many PWUD are using xylazine when purchasing fentanyl or heroin. A study in Maryland surveying syringe services program participants from 2021-2022 found that xylazine was detected in 90.9% of samples when participants intended to buy “fentanyl” and in 84.3% of samples when participants intended to buy “fentanyl and/or heroin.”⁷ However, despite its increasing presence, xylazine use appears to be mostly unintentional. A study in Texas found that among all xylazine exposures reported to poison centers from 2000-2014, 64% of them were unintentional.¹³ Similarly, a 2022 study surveying PWUD on Reddit found that 74% did not seek out xylazine¹⁴. Even among those who use xylazine knowingly, 61.2% preferred not to use xylazine.¹²

The exact prevalence of xylazine in the drug supply may be significantly underreported since illicit drugs are frequently contaminated with other substances and testing practices for xylazine are inconsistent.² Additionally, because xylazine has recently become more prevalent in the United States, many healthcare providers are unaware of its potential contributions to patients’

symptoms, and health care facilities often lack the proper equipment to test for its presence.¹¹ Xylazine can only be detected on specialized drug panels that are performed by commercial or forensic laboratories.¹⁵

Since xylazine is not an opioid, its effects cannot be reversed with naloxone.¹¹ Animal studies have shown use of atipamezole hydrochloride, an alpha-2 (α 2) adrenergic receptor antagonist, to reverse the sedative and cardiopulmonary effects of xylazine¹⁶; however, there are currently no xylazine-reversal agents approved for human use.¹¹ Although there is limited information regarding xylazine's pharmacokinetics, it is thought to be rapidly distributed, which can lead to an onset of toxic effects quickly.^{17,18} Concurrent use of xylazine with other illicit substances can complicate treatment for substance use disorders since it could produce a variety of withdrawal symptoms.¹¹ Research on withdrawal symptoms of xylazine is limited and inconsistent, most likely due to xylazine's frequent concurrent usage with other substances.¹⁷ Xylazine withdrawal symptoms have been reported in some case studies and include dysphoria and agitation as well as possible hypertensive emergency, as seen typically in clonidine withdrawal.^{11,17,19}

A study surveying PWUD in Connecticut and Philadelphia found that three-quarters of participants were aware of xylazine²⁰; however, there are currently no published studies surveying PWUD's awareness or usage of xylazine in Colorado. The objective of this study is to understand xylazine awareness and usage among PWUD in Denver, Colorado. We hypothesized that awareness of xylazine was limited, that xylazine usage was unintentional, and that usage of xylazine would be associated with fentanyl use.

Methods

This project was conducted with the Harm Reduction Action Center (HRAC) in Denver, Colorado, a public health agency that works with PWUD. An IRB-exempt anonymous 16-question survey was distributed among HRAC participants (n=148) from July to August 2023. Respondents were required to be a registered participant at HRAC to complete the survey, and each participant was limited to one response. Informed consent was obtained from each participant before administering the survey. The survey was administered on paper and took 5-10 minutes to complete. The survey was completed in private, but participants were provided reading assistance if needed. Survey questions included: drug of choice; awareness of xylazine; usage of xylazine; whether usage was intentional; and usage of xylazine testing strips. Survey questions used for analysis are depicted in Table 1. Individual question responses were excluded from analysis if more than one answer choice was selected (For example: "What is your drug of choice? Please select only one answer.") Responses to questions beginning with "If you answered yes to the above question" were excluded if the response to the previous question was "no."

Table 1. Survey Questions with Answer Options.

What is your drug of choice? Please select only one answer.	<input type="radio"/> Heroin <input type="radio"/> THC <input type="radio"/> Psilocybin (magic mushrooms) <input type="radio"/> Xylazine <input type="radio"/> Alcohol	<input type="radio"/> Meth <input type="radio"/> Cocaine <input type="radio"/> Benzodiazepine (Benzos) <input type="radio"/> MDMA/Ecstasy <input type="radio"/> LSD (Acid)	<input type="radio"/> Fentanyl <input type="radio"/> Crack <input type="radio"/> Other opioids (not heroin or fentanyl) <input type="radio"/> Ketamine <input type="radio"/> Other
Have you ever heard of xylazine, a veterinary sedative, that commonly goes by “Tranq”?	<input type="radio"/> Yes	<input type="radio"/> No	<input type="radio"/> Unsure
Have you ever used xylazine?	<input type="radio"/> Yes	<input type="radio"/> No	<input type="radio"/> Unsure
If you answered yes to the above, was it intentional use?	<input type="radio"/> Yes	<input type="radio"/> No	<input type="radio"/> Unsure
Have you ever used xylazine testing strips?	<input type="radio"/> Yes	<input type="radio"/> No	<input type="radio"/> Unsure
If you answered yes to the above question, have the testing strips ever been positive?	<input type="radio"/> Yes	<input type="radio"/> No	<input type="radio"/> Unsure

Statistical analyses were conducted with SAS Version 9.4 (SAS Institute, Cary, NC). To determine associations of drug of choice and xylazine usage, 2x3 contingency tables were created and gamma statistics were calculated for each of the four most selected drugs of choice (fentanyl, heroin, methamphetamine, and THC). The xylazine usage responses had three levels, “yes,” “no,” and “unsure.” Since these levels can be thought of as ordinal (yes>unsure>no), an ordinal-by-ordinal relationship was tested using the gamma statistic. Gamma values that are positive reflect a positive correlation of xylazine usage to the drug of choice, while negative gammas denote the opposite effect. All tests were conducted as one-tailed tests, with significance denoting a significant positive relationship.

Results

Out of 147 participants (1 response excluded), 53% of participants had heard of xylazine, 42% had not and 5% were unsure if they had. Sixteen percent reported xylazine usage, 66% had not used xylazine, and 18% were unsure if they had used xylazine. Out of the participants that said they had used or were unsure if they had used xylazine (n= 37), 76% said it was unintentional use. Eighty-three percent of participants reported they had never used xylazine testing strips while only 14% said they had. No participants selected xylazine as their primary drug of choice. The four most selected drugs of choice were fentanyl, heroin, methamphetamine, and THC. If more than one drug was selected for drug of choice, the response was excluded from analysis (n=10). Table 2 displays the complete distribution of participants' primary drug of choice (n=137).

Table 2. Primary Drug of Choice Distribution. The table depicts the distribution of what respondents selected as their primary drug of choice (n=137).

Primary Drug of Choice	Frequency, n (%)
Alcohol	3 (2.2)
Cocaine	1 (0.7)
Crack	1 (0.7)
Ecstasy/MDMA	3 (2.2)
Fentanyl	38 (27.7)
Heroin	15 (10.9)
Ketamine	1 (0.7)
LSD	2 (1.5)
Meth	49 (35.8)
Psilocybin	1 (0.7)
THC	20 (14.6)
Other Opioids	1 (0.7)
Other	2 (1.5)

Those that selected fentanyl as their primary drug of choice were significantly more likely to use xylazine with 58.3% of them responding “yes” to xylazine use, 39.8% responding “unsure” to

xylazine use and 16.5% responding “no” to xylazine use, demonstrating a statistically significant positive relationship ($\gamma= 0.5878$, $p=0.0001$). A similar positive association was found for those choosing heroin with 20.8% of them responding “yes” to xylazine use, 15.4% responding “unsure” to xylazine use and 6.2% responding “no” to xylazine use ($\gamma= 0.4852$, $p=0.0027$). Conversely, those who listed methamphetamine as their primary drug of choice had reverse associations with xylazine usage with only 4.17% of them responding “yes” to xylazine use, 34.62% responding “unsure” to xylazine use and 39.18% responding “no” to xylazine use, demonstrating a statistically significant negative relationship ($\gamma= -0.4799$ $p=0.9996$). Those who listed THC also demonstrated a significant negative relationship with 0% of them responding “yes” or “unsure” to xylazine use and 20.62% responding “no” to xylazine use ($\gamma= -1.0000$, $p=1.0000$) (Figure 1).

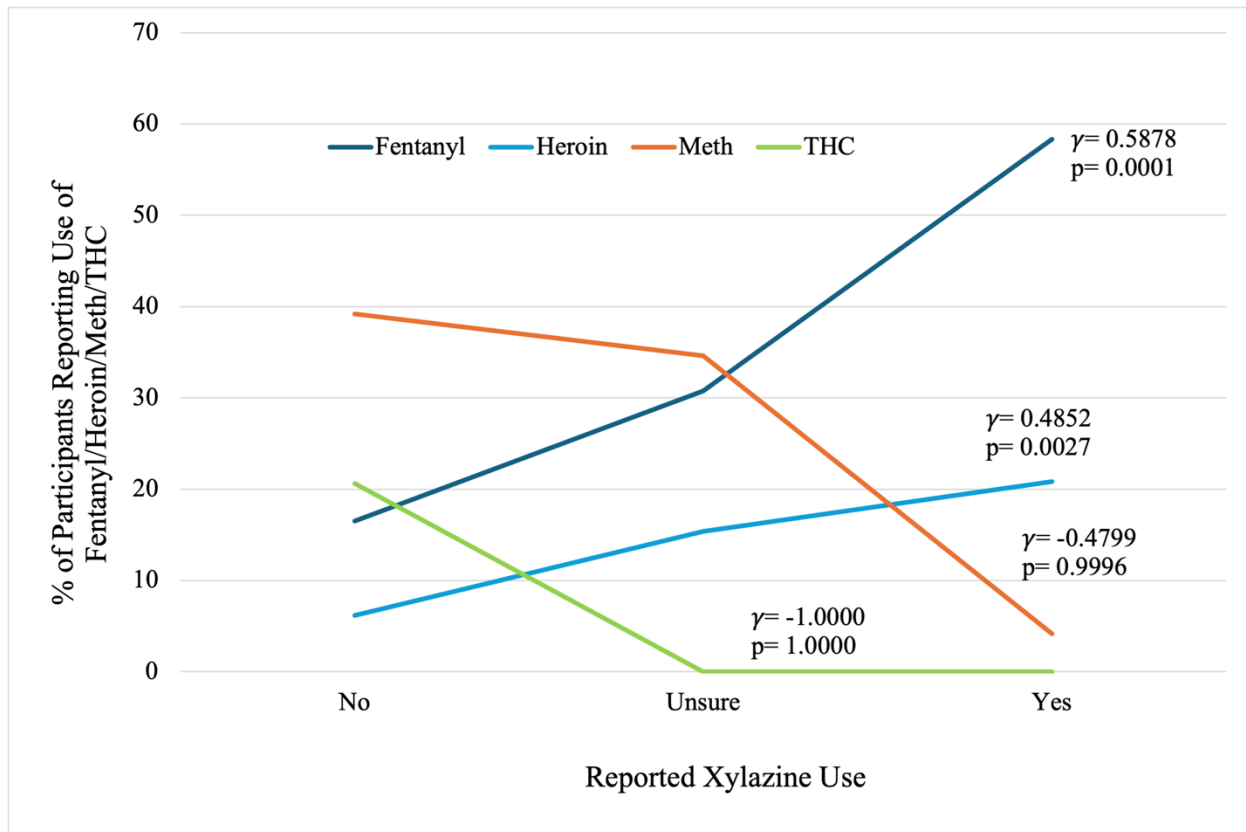


Figure 1. Association of Primary Drug of Choice with Xylazine Usage. Dark blue line represents fentanyl use as it relates to reported xylazine use. Light blue line represents heroin use as it relates to reported xylazine use. Orange line represents methamphetamine use as it relates to reported xylazine use. Green line represents THC use as it relates to reported xylazine use. Note that participants who chose fentanyl or heroin as their primary drug of choice were significantly more likely to have used xylazine than participants who selected methamphetamines or THC. ($p=0.0001$ and $p=0.0027$, respectively).

Discussion

Xylazine usage has greatly increased⁴ in the United States since 2019. Subsequently, there has been an increase in the detection of xylazine in fatal and non-fatal overdoses¹⁷ since 2020. To our

knowledge, this study is the first to survey PWUD's awareness and usage of xylazine in Colorado. This study showed that nearly half of the participants had not heard of xylazine, and the majority had never used xylazine testing strips. While the HRAC and the Colorado Department of Public Health and Environment (CDPHE) have been expanding access to free xylazine testing strips, use remains low. This could be due to the lack of awareness surrounding the presence of xylazine in the drug supply and the benefits of using xylazine testing strips.

Other studies have found that xylazine is often added to fentanyl and other opioid drugs to prolong the characteristically short high of fentanyl.³ Xylazine does not give the same euphoria as opioids, which could explain why xylazine is not being frequently used on its own or being used intentionally.³ None of the participants in this study reported that xylazine was their primary drug of choice, indicating that xylazine use was largely unintentional.

Limitations

The limitations of this study included the data's self-reported nature, the minimal usage of xylazine testing strips, and the possible intoxication of participants. Since this study relied on self-reported data, we were unable to test drug samples or used syringes for the presence of xylazine to more accurately assess the extent of xylazine presence in Denver, Colorado. Additionally, this study was limited to only one public health agency in Denver; therefore, xylazine presence and awareness in the rest of the state remains unknown. Further studies should be conducted to better understand xylazine pharmacokinetics in humans. There are some data on the metabolism and elimination of the drug; however, pharmacokinetic data regarding different methods of administration is lacking in humans.¹⁷ These data are important to obtain because PWUD administer drugs through a variety of routes including, but not limited to, injecting and smoking. Since there is currently no treatment protocol for xylazine-involved overdose, studies should be done to assess possible treatments for xylazine and multidrug overdose/withdrawal. Expanding research efforts with xylazine presence, pharmacokinetics, and treatments will be pivotal in educating PWUD and healthcare providers about the effects of xylazine (such as necrotic wounds and sedation) and in reducing the rates of fatal overdose.

Conclusion

Despite xylazine's increasing prevalence in the United States, awareness of it amongst PWUD in Denver, Colorado, remains limited. Xylazine use was strongly associated with PWUD whose primary drug of choice was fentanyl or heroin, and most xylazine use was unintentional. Xylazine's recent appearance in the Denver drug supply could impact overdose treatment in health care settings if providers are not aware of its effects. More research is warranted to determine healthcare providers' and first responders' knowledge of managing xylazine complications and awareness of harm reduction strategies. Harm reduction and other public health agencies should focus on raising awareness of xylazine and its adverse effects and promote use of xylazine testing strips among PWUD, especially to those who preferentially use fentanyl or heroin.

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