Characterization of Xylazine-Related Overdose Deaths in Maryland (2020-2023)

Erin Y. Wang, BS[1], Rebecca Phipps, PhD[2], Stephanie A. Dean, MD[2], Ling Li, MD[2], Danielle Nestadt, PhD[3], Paul S. Nestadt, MD[1,4]

Institutional Affiliations:

1. Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.
2. Office of the Chief Medical Examiner, Baltimore, MD, USA.
3. Department of Health, Behavior and Society, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.
4. Department of Psychiatry and Behavioral Sciences, Johns Hopkins Hospital, Baltimore, MD, USA.

Corresponding Author:
Name: Paul Nestadt, MD
Address: 600 N. Wolfe Street, Meyer 114, Baltimore, Maryland 21287
Phone number: 410-955-8003
Email address: pn@jhmi.edu

References: 33
Tables: 3
Figures: 2
Appendices: 0

Manuscript Word Count (max 4000): 3955
Abstract Word Count (max 250): 244

Funding Sources:
EYW was supported by the NIH TL1 Predoctoral Clinical Research Program Fellowship. PSN was supported by NIDA grant K23DA055693.

Contributors:
Erin Wang: Formal analysis, funding acquisition, investigation, methodology, validation, visualization, writing - original draft.
Rebecca Phipps: Data curation, validation, writing - review and editing.
Stephanie Dean: Writing - review and editing.
Ling Li: Data curation, validation, writing - review and editing.
Paul Nestadt: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, visualization, writing - review and editing.
Danielle Nestadt: Writing - review and editing.

Declarations of Interest: All authors declare that they have no conflicts of interest.

Abstract

Background

Xylazine is a fentanyl contaminant which has been increasingly detected in drug overdose deaths in Maryland. This study explored risk factors and time trends of xylazine-related overdose deaths (XRODs) in Maryland from 2020-2023.

Methods

This serial cross-sectional study utilized data from the Maryland Office of the Chief Medical Examiner on fentanyl overdose deaths that occurred from 2020-2023. XROD was defined as someone who died from overdose and had a positive postmortem blood xylazine test. Multivariable logistic regression modeled associations between demographic variables and presence of co-occurring substances with XROD. Annual population-based XROD rates were calculated for the overall sample and by race, age group, and sex.

Results

There were 8,721 fentanyl overdose deaths in Maryland between 2020 and 2023. Among these, 1,798 (20.6%) were XRODs. Annual XROD rates peaked in 2021 and have declined since then. Although Black Marylanders experienced the highest overall burden of overdose, xylazine was significantly more likely to contribute to fentanyl overdose deaths among White individuals compared to Black individuals (aOR 1.18) and those aged 31-40 years compared to those 60 or older (aOR 1.25). Morphine (aOR 1.36), methadone (aOR 1.41), benzodiazepines (aOR 1.20), and tramadol (aOR 2.12) were associated with higher odds of XROD.

Conclusions

XRODs are a major problem in Maryland, and there are significant differences in XROD mortality by race, age, and co-occurring substance use. Efforts to reduce xylazine-related mortality in Maryland should provide overdose prevention education and harm reduction services to the most vulnerable populations.

Keywords (6 max)

xylazine, fentanyl, overdose, Maryland, death, forensic autopsy postmortem

1. Introduction

The opioid overdose epidemic continues to be one of the greatest public health challenges of our time, resulting in significant morbidity and mortality in the United States. Overdose deaths have steadily increased since 2015, and 2022 marked the deadliest year yet, with over 109,000 estimated deaths.[1,2] In this fourth wave of the overdose crisis, polysubstance use involving fentanyl and stimulants (e.g. methamphetamine and cocaine) and an increasingly toxic drug supply have driven the increase in overdose deaths.[3,4]

Xylazine is a non-opioid veterinary tranquilizer that is structurally similar to the alpha-2 adrenergic agonist clonidine. Xylazine is often added to illicit opioids such as fentanyl in order to prolong their sedating effects, and it has been linked to an increasing number of overdose deaths nationwide.[5,6] Xylazine, also known as "tranq," is a central nervous system depressant that can slow breathing, heart rate, and blood pressure to dangerously low levels.[7] Taking xylazine in combination with other depressants such as opioids, alcohol, or benzodiazepines can increase the risk of fatal overdose.[5] Xylazine use has also been associated with skin ulcers and abscesses.[6] Because xylazine is not an opioid, its physiological effects cannot be reversed with the opioid reversal medication naloxone, further increasing the risk of life-threatening overdose.[6]

Illicitly manufactured-fentanyls (IMFs) are present in 98.4% of xylazine-present-overdose-deaths, as well as cocaine (45.4%), benzodiazepines (28.4%), heroin (23.3%), and alcohol (19.7%).[6] Other substances involved in overdose deaths linked to both xylazine and fentanyl include gabapentin, methadone, and prescription opioids.[7]

Across the U.S., overdose deaths involving xylazine increased 34-fold from 2018 to 2021. During this time, males were twice as likely as females to die from overdose involving xylazine, and the rate of drug overdose deaths involving xylazine was highest among those aged 35-44.[8] Previous studies have found that males and non-Hispanic White and Black populations have been disproportionately impacted, with Black individuals experiencing the highest mortality rate.[3,8] The Northeast and Mid-Atlantic U.S. have been the epicenter of the xylazine overdose crisis. In 2020, the proportion of reported overdose deaths with xylazine present was highest in Philadelphia (25.8%), Maryland (17.1%), and Connecticut (10.2%).[6]

Overdose decedents in Maryland in 2020 were significantly more likely to be White (18.7% vs. 15.9% Black), living in Baltimore City (19.3% vs. 16.1% for all other counties combined), and 25-55 year olds (19% vs. 11.4% for those >55).[9] Among decedents who were xylazine-positive, >99% had IMF or heroin as a cause of death and 14.7% had prescription opioids as a cause of death.[10] Xylazine has been a pervasive adulterant in Maryland: 80% of syringe samples collected that tested positive for fentanyl were also contaminated with xylazine between July 2020 and June 2021.[11]

More work is needed to understand which communities in Maryland have been most vulnerable to xylazine-related overdose deaths and how these trends have changed over time. Our partnership with the Maryland Office of the Chief Medical Examiner (OCME) has enabled near real-time data collection to evaluate a rapidly evolving xylazine crisis. In this study, we explored the association between demographic variables, manner of death, and toxicology results among fentanyl overdose decedents with and without XROD in Maryland between 2020

and 2023. We then assessed temporal trends in XRODs by year, and by age group, race, sex, and manner of death.

2. Methods

2.1. Dataset

This analysis utilized data from the Maryland OCME on fentanyl-positive overdose deaths that occurred in Maryland between 2020 and 2023. The OCME is a statewide medical examiner system designated by law to investigate deaths that are sudden and unexpected, result from injury, occur under unexplained or suspicious circumstances, or when a person is not attended by a physician in the state of Maryland. Along with the medicolegal responsibility to determine cause and manner of death, OCME serves a critical public health role by identifying injury trends and emerging infectious diseases that may pose risks to Marylanders.[12] OCME data includes demographic information (e.g., race, age), cause and manner of death, and blood and urine toxicology. The OCME routinely conducts blood tests for xylazine as part of a standard autopsy, and Maryland is one of the few states with a centralized OCME, with consistent autopsy and toxicology protocols across all counties.[13] Fewer than 5% of decedents were missing conclusive bloodwork due to decomposition. These were excluded from analysis.

2.2 Variables

Xylazine-related overdose death (XROD) was defined as an individual who died from a fentanyl positive overdose and had a positive xylazine blood test at the time of autopsy. Five age groups were used to represent all adults in our sample: 18-30, 31-40, 41-50, 51-60, and >60. Race was categorized as White, Black, and other. Sex was categorized as male or female. Sex was derived from the medical examiner's characterization of the decedents' body, and therefore gender identity was not available. Manner of death was classified by the medical examiners as accident, suicide, or undetermined. The presence of a substance was defined as an individual having a positive blood test for that substance at time of autopsy and was coded as a binary variable.

2.3 Analytic Methods

We explored the association between the outcome variable of XROD and explanatory variables including demographics (e.g. age, race, sex), manner of death, and presence of co-occurring substances in blood toxicology (e.g. other illicit drugs, psychiatric medications) among all fentanyl-positive overdose decedents. First, we examined the means/distribution of each variable, stratified by XROD, and used chi-square or two sample t-tests to test for significant differences by group. Then, we used multivariable logistic regression models to estimate odds ratios for the adjusted associations between XROD and these explanatory variables. Year was included as an adjustment covariate.

We then assessed temporal trends in XROD by creating a histogram of XROD counts by month. We examined yearly XROD rates by race, age group, and sex. The most recent U.S. Census Bureau data from 2020 were used to calculate rates by race,[14] and data from 2022 to calculate rates by age and sex.[15]

3. Results

3.1. Risk Factor Analysis

Table 1: Fentanyl Positive Overdose Deaths in Maryland, by Presence of Xylazine, 2020-2023 (N=8,721)

		Total	Xylazine Absent (%)	Xylazine Present (%)	X^2 Test
		8,721 (100)	6,923 (79.4)	1,798 (20.6)	
Age	**18-30**	1,380 (15.8)	1,100 (15.9)	280 (15.6)	0.14
	31-40	2,081 (23.9)	1,621 (23.4)	460 (25.6)	
	41-50	1,787 (20.5)	1,416 (20.5)	371 (20.6)	
	51-60	2,209 (25.3)	1,754 (25.3)	455 (25.3)	
	>60	1,264 (14.5)	1,032 (14.9)	232 (12.9)	
Sex	**Male**	6,405 (73.5)	5,100 (73.7)	1,305 (72.6)	0.33
	Female	2,316 (26.5)	1,823 (26.3)	493 (27.4)	
Race	**White**	4,414 (50.6)	3,404 (49.2)	1,010 (56.2)	<0.001
	Black	3,808 (43.7)	3,074 (44.4)	734 (40.8)	
	Other	495 (5.7)	441 (6.4)	54 (3.0)	
Manner of Death	**Undetermined**	5,225 (59.9)	4,106 (59.3)	1,119 (62.2)	0.04
	Suicide	43 (0.5)	38 (0.5)	5 (0.3)	
	Accident	3,453 (39.6)	2,779 (40.1)	674 (37.5)	
Co-occurring Substances	**Oxycodone**	353 (4.0)	269 (3.9)	84 (4.7)	0.13
	Heroin	233 (2.7)	164 (2.4)	69 (3.8)	<0.001
	Morphine	1,325 (15.2)	956 (13.8)	369 (20.5)	<0.001
	Methadone	732 (8.4)	524 (7.6)	208 (11.6)	<0.001
	Buprenorphine	2 (0.0)	2 (0.0)	0 (0.0)	0.47
	Cocaine	4,097 (47.0)	3,261 (47.1)	836 (46.5)	0.65
	Benzodiazepines	853 (9.8)	622 (9.0)	231 (12.8)	<0.001
	Tramadol	568 (6.5)	349 (5.0)	219 (12.2)	<0.001
	Alcohol (>0.08)	3,030 (34.7)	2,581 (37.3)	449 (25.0)	<0.001
	Quetiapine	147 (1.7)	114 (1.6)	33 (1.8)	0.58

There were 8,721 fentanyl overdose deaths in Maryland between 2020 and 2023 (Table 1). Among these decedents, 1,798 (20.6%) tested positive for xylazine and were categorized as an XROD. The majority of XROD decedents were white (56.2%) and male (72.6%), with undetermined manner of death (62.2%) being more common than clear accidents or suicides. The most commonly co-occurring substances were cocaine (46.5%), alcohol (25.0%) and morphine (20.5%).

There were statistically significant differences in the distribution of race, manner of death, and toxicology results between XROD and non-XROD decedents. A greater proportion of XROD decedents were white compared to non-XROD decedents (56.2% vs. 49.2%), and

undetermined manner of death was more common among XROD decedents (62.2% vs. 59.3%). XROD decedents tested positive for morphine, methadone, benzodiazepines, tramadol, and heroin with significantly greater frequency than non-XROD decedents.

Table 2: Risk Factors Associated with Xylazine Presence in Fentanyl Positive Overdose Deaths

		Unadjusted OR	p-value	Adjusted OR	p-value
Age	**18-30**	1.13 (0.93, 1.37)	0.21	1.17 (0.95, 1.43)	0.14
	31-40	1.26 (1.06, 1.51)	**0.01 ****	1.25 (1.04, 1.51)	**0.02 ***
	41-50	1.17 (0.97, 1.40)	0.10	1.16 (0.96, 1.41)	0.13
	51-60	1.15 (0.97, 1.38)	0.11	1.16 (0.97, 1.40)	0.10
	>60	1	Ref	1	ref
Sex	**Male**	1	Ref	1	ref
	Female	1.06 (0.94, 1.19)	0.33	1.00 (0.89, 1.13)	0.977
Race	**White**	1	Ref	1	ref
	Black	0.80 (0.72, 0.90)	**<0.001 *****	0.85 (0.75, 0.95)	**0.005 ****
	Other Race	0.41 (0.31, 0.55)	**<0.001 *****	0.47 (0.35, 0.64)	**<0.001 *****
Manner of Death	**Accident**	0.89 (0.80, 0.99)	**0.03 ***	1.01 (0.90, 1.13)	0.90
	Suicide	0.48 (0.19, 1.23)	0.13	0.44 (0.17, 1.15)	0.10
	Undetermined	1	Ref	1	ref
Co-occurring Substances	**Oxycodone**	1.21 (0.94, 1.56)	0.13	1.02 (0.79, 1.32)	0.87
	Heroin	1.64 (1.24, 2.19)	**0.001 *****	1.17 (0.85, 1.61)	0.35
	Morphine	1.61 (1.41, 1.84)	**<0.001 *****	1.36 (1.17, 1.59)	**<0.001 *****
	Methadone	1.60 (1.35, 1.89)	**<0.001 *****	1.41 (1.18, 1.68)	**<0.001 *****
	Cocaine	0.98 (0.88, 1.08)	0.65	1.03 (0.92, 1.15)	0.62
	Benzodiazepines	1.49 (1.27, 1.75)	**<0.001 *****	1.20 (1.01, 1.42)	**0.04 ***
	Tramadol	2.61 (2.19, 3.12)	**<0.001 *****	2.12 (1.76, 2.56)	**<0.001 *****
	Alcohol (>0.08)	0.56 (0.50, 0.63)	**<0.001 *****	0.67 (0.58, 0.79)	**<0.001 *****
	Quetiapine	1.12 (0.76, 1.65)	0.58	0.96 (0.64, 1.44)	0.85

*≤0.05, **≤0.01, ***≤0.001

The results of univariate and multivariable logistic regression are shown in Table 2. Fentanyl overdose deaths had higher odds of being XRODs among white individuals (aOR 1.18, 1.05-1.33) compared to Black individuals, and those aged 31-40 years (aOR 1.25, 95% CI: 1.04-1.51) compared to those aged 60 years or greater. The presence of morphine (aOR 1.36, 1.17-1.59), methadone (aOR 1.41, 1.18-1.68), benzodiazepines (aOR 1.20, 1.01-1.42), and tramadol (aOR 2.12, 1.76-2.56) were associated with higher odds of XROD. High blood alcohol content was associated with lower odds of XROD (aOR 0.67, 0.58-0.79). While there was a significant association between the presence of heroin and XROD in the univariate model, this association became insignificant in the multivariable model. There was no significant difference in odds by sex, manner of death, or presence of oxycodone, cocaine, or quetiapine in the multivariable model.

3.2. Time Trend Analysis

Table 3: Annual XROD Rates (per 100,000) and Proportion of Fentanyl Deaths

Year	XRODs	XROD Rate	Fentanyl Deaths	XROD as Proportion of Fentanyl Deaths
2020	434	6.94	2360	18.4%
2021	699	11.32	2372	29.5%
2022	379	6.17	2048	18.5%
2023	286	4.66	1941	14.7%

The annual number of XRODs in Maryland increased from 434 in 2020 to 699 in 2021, then decreased to 379 in 2022 and 286 in 2023 (Fig. 1, Table 3). The XROD rate also increased to 11.32 per 100,000 in 2021, then decreased over the next two years to 4.66 per 100,000 in 2023. Lastly, XROD as a proportion of fentanyl overdose deaths reached a peak of 29.5% in 2021, then declined to 14.7% in 2023. XRODs per month reached a peak of 83 deaths in January 2021, and monthly numbers have trended down since then.

Annual XROD rates increased from 2020 to 2021 and then declined in 2022 and 2023 across most race, age, and sex sub-groups. Black individuals experienced the greatest increase in XROD rate in 2021, reaching 15.9 deaths per 100,000 and surpassing the rate for White individuals that year (Fig. 2a). Black individuals continued to have the highest rates in 2022 and 2023 and did not experience the same decrease as White individuals and individuals of other races in 2023.

People aged 51-60 years experienced the largest growth in XROD rate between 2020 and 2021, increasing from 11.9 to 22.7 per 100,000 and surpassing the rates for those aged 31-50 (Fig. 2b). While XROD rate decreased for all age groups between 18-60 years, people over 60 years of age experienced an increase in XROD rate in 2023. Males consistently had XROD rates that were 2 to 3 times greater than females across all years (Fig. 2c).

4. Discussion

This is the first study to analyze the risk factors and time trends associated with XRODs in Maryland from 2020 through 2023. Our results demonstrate that XRODs continue to be a major burden in Maryland compared to the rest of the country, and there are significant differences in XROD mortality by race, age, and co-occurring substance use.

There were 8,721 fentanyl overdose deaths in Maryland between 2020 and 2023, and 20.6% of these decedents had an XROD. Annual XROD rates increased from 6.9 per 100,000 in 2020 to 11.3 in 2021, then decreased in subsequent years. The increase in XROD rates in 2021 may be related to the overall spike in overdose mortality during the COVID-19 pandemic, which resulted in greater psychological stress and isolation, disruptions to substance use and mental health treatment, and disruptions in the illicit drug supply.[16] The Maryland Xylazine Workgroup published a report in 2023 which noted a slight decrease in the percentage of xylazine-positive drug samples tested at 15 syringe service programs across the state from May 2022 to April

2023.[10] Our findings confirm this drug supply contamination trend is also reflected in decedent toxicology.

This decrease may also be a result of focused efforts by public health agencies and community-based organizations to address xylazine morbidity and mortality over the past few years. The Maryland Overdose to Action program established the Maryland Xylazine Workgroup to specifically monitor xylazine trends in the state, share data, and make recommendations.[10] Maryland's Office of Overdose Response and Center for Harm Reduction Services (CHRS) have created public awareness campaigns about xylazine and expanded xylazine testing services at syringe service programs and community organizations across the state.[17,18]

4.1. Racial Disparities

The increasing and decreasing trend in XROD rate was observed across most race, age, and sex subgroups, although not to the same extent. Black Marylanders experienced the greatest increase in XROD rate in 2021, reaching 15.9 deaths per 100,000 and surpassing the rate for White Marylanders. Black individuals did not experience the same decrease in XROD rate as White individuals in subsequent years. This disparity was previously noted in the Maryland Overdose to Action Xylazine Report published in 2023, which stated that most xylazine-involved overdose deaths occurred in the greater Baltimore area, and a disproportionate percentage of XROD decedents were Black.[10] Across the U.S., Black, White, and Hispanic people experienced an increase in XRODs from 2020 to 2021, with the highest rate also seen among Black individuals at 1.82 per 100,000 in 2021. Whites had the second-highest rate at 1.21 per 100,000.[8]

The growing disparity in XROD rates between Black and White Marylanders mirrors trends in fentanyl overdose death rates, which have been steadily declining for White Marylanders but remained relatively constant for Black Marylanders over the past 4 years (data not shown). These findings are also part of a broader trend in all drug overdose deaths across the U.S. By 2022, the overdose death rate among Black Americans had reached 1.4 times the rate seen among White Americans, at 49.5 per 100,000 compared to 34.6 per 100,000.[16] In 2022, deaths among White Americans decreased relative to 2021, while rates among all other groups continued to rise. There are many factors contributing to the racial disparity in XROD and fentanyl overdose death rates, including decreased access to harm reduction services and medications for opioid use disorder, as well as higher rates of incarceration and post-release overdose deaths for Black individuals compared to White individuals.[16]

While Black Marylanders experienced the greatest burden of xylazine-related mortality overall, corresponding to higher rates of fentanyl overdose mortality, we also found that among fentanyl overdose decedents only, xylazine was more likely to be detected at the time of fatal overdose among White individuals compared to Black individuals. Geographic variations in the drug supply and in demographic composition may explain these results. Geographic factors influence the social and economic conditions that individuals experience, which in turn affect their social networks, drug supply sources, access to harm reduction education and services, and individual substance use behaviors.[3,19,20] Rural areas, in particular, have faced unique challenges including economic decline, barriers to substance use treatment and recovery services, and varying levels of stigma towards drug use.[21]

Geographic, socioeconomic, and urban-rural factors likely play a major role in the XROD trends observed in Maryland. Although our limited data set precluded formal analyses of the relationships between these factors, we have several hypotheses for how they may explain our results. Racial composition varies drastically by county in Maryland. The population of Baltimore City is 57.8% Black and 27.8% White, while the population of rural Garrett County is over 95% White.[22] White Marylanders may be more frequently exposed to fentanyl mixtures that contain xylazine. Indeed, the statewide CHRS drug testing program found that xylazine-positive samples have been most prevalent in Calvert, Cecil, Frederick, Howard, and Wicomico counties, all of which are considered rural and have predominantly White populations, with the exception of Howard County.[10] Additionally, residents of these rural counties may experience barriers to accessing harm reduction services such as xylazine testing, naloxone provision, and substance use treatment.

At the same time, Black Marylanders had greater overall rates of XRODs. In 2023, the fentanyl overdose death rate for Black Marylanders increased (data not shown), while the XROD rate decreased. This suggests that Black individuals may be exposed to more potent fentanyl mixtures or non-xylazine adulterants which are contributing to overdose deaths. Baltimore's drug market has been known for "scramble," which refers to a mixture of substances that may include fentanyl, benzodiazepines, crushed pills, xylazine, and other adulterants.[23] Thus, it is possible that Black individuals who live in urban areas such as Baltimore are exposed to a more contaminated drug supply than people living in rural or suburban areas, potentially including other dangerous contaminants aside from xylazine.

Unfortunately, the dataset we used did not include geographic data, so geographic associations between demographic characteristics and XROD could not be assessed. Geographic location is a key variable and possible confounder that should be studied in the future, as it may reveal important associations and potential hotspots for targeted interventions.

4.2. Age Disparities

Middle-aged adults were most significantly impacted by XRODs compared to those aged 18-30 and those older than 60 years old over this time period, but the increasing rates in those older than 60 warrant special attention. Overdose deaths among Black Marylanders aged 55 and older have increased by 119.7% percent since 2016.[24] Across the U.S., fatal overdoses have quadrupled among older adults in the past 20 years, and the highest overdose rates have emerged among older Black adults in the 55-64-year-old age group, representing 2.4 times the rate of White adults of the same age.[16,25] Previously, overdose deaths have tended to affect younger individuals, but the data show that older adults are increasingly at risk of fatal drug overdose, including those which involve xylazine or other adulterants. One reason for this is because many older adults began using opioids decades ago, when heroin was more common than fentanyl.[26] Their unique health and social needs must be considered in overdose prevention policies and outreach efforts. Information about xylazine and overdose prevention may be more effectively disseminated to older adults through partnerships with faith-based organizations and senior centers, as well as printed media and radio channels.

4.3. Sex Disparities

Males consistently had XROD rates that were 2-3 times greater than females. This aligns with the findings of a national study which found that men had a 2-3 times greater rate of overdose mortality from opioids and psychostimulants.[27] While men are known to use drugs at higher rates than women, this alone did not explain the gap in overdose deaths. The researchers hypothesized that a combination of behavioral (e.g. men may use drugs in a riskier way than women), biological (e.g. men may be more vulnerable to the toxicity of drugs than women), and other social- and gender-related factors contribute to this observed difference.[28] More research is needed to understand the unique risk factors that men experience and to develop targeted prevention and harm reduction interventions for men.

4.4. Co-occurring Substance Use

XROD was associated with the co-occurrence of morphine, methadone, benzodiazepines, and tramadol among fentanyl decedents. Benzodiazepines, methadone, and opioids are known to be present in a significant portion of overdose deaths involving both xylazine and fentanyl.[6,7]

Tramadol is an opioid analgesic which is FDA-approved for the treatment of moderate to severe pain.[29] It has been reported to be present in illicit fentanyl products.[30] While the only published reports about the combination of xylazine and tramadol come from veterinary journals where this mixture was used as a novel anesthetic in animals, it is possible that drug distributors are combining xylazine and tramadol with opioids such as fentanyl and heroin for their comparable psychoactive properties at a lower price point.[31,32]

The statistically significant association between heroin and XROD in the univariate model became insignificant after adjusting for other covariates included in the multivariable model. We hypothesize that this could be due to collinearity between heroin and morphine in toxicology testing.

In general, these findings show that higher odds of XROD were associated with the presence of these specific other substances in blood toxicology, which may or may not indicate simultaneous consumption. Data from drug testing services such as the Rapid Analysis of Drugs program in Maryland can provide valuable information about the composition of local drug supplies and should be used to corroborate toxicology data.

4.5. Policy and Public Health Implications

Our results highlight the increased odds of XROD among fentanyl decedents who were middle-aged, White, or used morphine, methadone, benzodiazepines, or tramadol. We also found that, overall, older adults, Black individuals, and males have experienced an increasing burden of xylazine-related overdose deaths compared to other populations in Maryland over the study period. Efforts to reduce xylazine-related mortality in Maryland should focus on providing overdose prevention education and harm reduction services tailored to the most vulnerable populations.[33] It is important to acknowledge that the following interventions will not automatically address disparities in overdose risk; thus, it is critical to formally direct programmatic funding for substance-use related services towards marginalized communities who face the greatest barriers to accessing these services.[16] Leadership and peer services from

individuals who belong to minoritized communities should be incorporated into all overdose prevention efforts.

Community-based organizations and public health departments should increase access to xylazine test strips and other drug checking services to people who use drugs (PWUD) and utilize this opportunity to educate the community about the increasing presence of xylazine and harm reduction strategies. Overdose prevention training and take-home naloxone should also be made available to PWUD. Although naloxone does not directly reverse the effect of xylazine, it should be given in the case of any suspected overdose to reverse any possible opioid effects. Lastly, community organizations should link people at risk for overdose with healthcare and social services, especially timely wound care for xylazine-related skin infections. In addition to increasing access to harm reduction and treatment services for PWUD, it is important for healthcare providers and first responders to increase their own knowledge of the risks of xylazine to provide appropriate treatment and referrals.

More comprehensive public health surveillance efforts are also needed across the country to monitor trends in xylazine mortality, morbidity, and presence in local drug supplies and better inform public health interventions and policy development. Xylazine databases should include metrics such as racial/ethnic background, geographic region, rurality, socioeconomic status, clinical comorbidities, and concurrent mental health and substance use disorder diagnoses to guide interventions for medically underserved populations.[3] It will also be important to understand the burden of non-fatal xylazine overdoses using data from emergency medical services and emergency departments. Drug checking data can shed light on the composition of local drug markets and which substances are being consumed simultaneously with xylazine. Finally, qualitative studies can deepen our understanding of the root causes of the xylazine crisis and how to best address it by answering questions like, "Where is xylazine coming from?" and "What do PWUD know about xylazine, and what are their perceptions of it?"[10]

4.6. Limitations

While there are many advantages of using data from the state medical examiner's office, one limitation is that it can be difficult to draw conclusions about contaminants in the drug supply using solely mortality data, as there are many factors that predispose an individual to a fatal overdose that may not be fully captured by toxicology results and basic demographic characteristics (e.g. substance use behaviors, knowledge of adulterants, access to harm reduction services, biological vulnerabilities, incarceration, etc.). Additionally, while we can assess whether xylazine and other substances were present in an individual's system at the time of autopsy, we cannot determine the relative contribution of each identified substance to the subject's death. Moreover, toxicology only reveals which substances were consumed within its window of detection, but not the combinations of drugs consumed simultaneously. In order to accurately evaluate the risk of xylazine and other drug contaminants, it is important to supplement overdose fatality data with real-time drug checking data from the Maryland Rapid Analysis of Drugs program and community-level point-of-care drug checking services, emergency medical services, and hospital emergency departments.[11] Finally, manner of death is the medical opinion of the medical examiner, taking into account the known circumstances, and can vary between individual medical examiners. Therefore, conclusions regarding manner of drug overdose deaths should be interpreted with caution.

Another limitation of our data was the exclusion of geographic and socioeconomic data for each individual, which prevented us from studying how sociodemographic characteristics and geographic location interact to influence the risk of XROD. Additionally, in our study, we categorized race into White, Black, and all other races due to small numbers. However, this may obscure differences in XROD mortality within other racial/ethnic groups such as Asian and Hispanic populations.

4.7. Strengths

Despite these limitations, this study is the only study to analyze xylazine mortality data from 2020-2023 in Maryland, providing a timely picture of the magnitude of the xylazine overdose crisis and how it has evolved in the post-COVID era. Maryland is one of the few states with a centralized OCME, with consistent autopsy and toxicology protocols across all counties, and it has performed routine testing for xylazine since the early 2000s, making this a highly reliable data source.

4.8. Conclusions

Our study emphasizes the importance of having access to current overdose data in fighting the most recent wave of the opioid epidemic. Reducing the morbidity and mortality of drug overdose and mitigating the harms of new drug contaminants such as xylazine will require real-time data as well as cross-sector collaboration between people who use drugs, harm reduction organizations, public health departments, and healthcare providers.

References

1. Products - Vital Statistics Rapid Release - Provisional Drug Overdose Data. January 17, 2024. Accessed January 27, 2024. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

2. National Institute on Drug Abuse. Drug Overdose Death Rates | National Institute on Drug Abuse (NIDA). June 30, 2023. Accessed November 14, 2023. https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates

3. Zhu DT. Public health impact and harm reduction implications of xylazine-involved overdoses: a narrative review. *Harm Reduct J*. 2023;20(1):131. doi:10.1186/s12954-023-00867-x

4. Ciccarone D. The rise of illicit fentanyls, stimulants and the fourth wave of the opioid overdose crisis. *Curr Opin Psychiatry*. 2021;34(4):344. doi:10.1097/YCO.0000000000000717

5. National Institute on Drug Abuse. Xylazine | National Institute on Drug Abuse (NIDA). April 21, 2022. Accessed January 27, 2024. https://nida.nih.gov/research-topics/xylazine

6. Friedman J, Montero F, Bourgois P, et al. Xylazine spreads across the US: A growing component of the increasingly synthetic and polysubstance overdose crisis. *Drug Alcohol Depend*. 2022;233:109380. doi:10.1016/j.drugalcdep.2022.109380

7. 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. doi:10.1016/j.forsciint.2014.03.015

8. New Analysis Looks at Drug Overdose Deaths Involving Xylazine | Blogs | CDC. June 30, 2023. Accessed January 27, 2024. https://blogs.cdc.gov/nchs/2023/06/30/7408/

9. Schneider KE. Xylazine among Maryland opioid overdose decedents, 2020. In: APHA; 2022. Accessed January 27, 2024. https://apha.confex.com/apha/2022/meetingapp.cgi/Paper/514871

10. Maryland Xylazine Workgroup. Xylazine in Maryland: An Initial Report of the Maryland Xylazine Workgroup, 2023. Published online 2023.

11. Russell E. Rapid Analysis of Drugs: A Pilot Surveillance System To Detect Changes in the Illicit Drug Supply To Guide Timely Harm Reduction Responses — Eight Syringe Services Programs, Maryland, November 2021–August 2022. *MMWR Morb Mortal Wkly Rep*. 2023;72. doi:10.15585/mmwr.mm7217a2

12. Maryland Department of Health Office of the Chief Medical Examiner. Maryland.gov Enterprise Agency Template. Accessed January 27, 2024. https://health.maryland.gov/ocme/Pages/default.aspx

13. CDC - Death Investigation Systems - Coroner/Medical Examiner Laws - Publications by Topic - Public Health Law. February 8, 2023. Accessed January 27, 2024. https://www.cdc.gov/phlp/publications/coroner/death.html

14. P9: HISPANIC OR LATINO, AND NOT ... - Census Bureau Table. Accessed April 13, 2024. https://data.census.gov/table/DECENNIALDHC2020.P9?g=040XX00US24

15. S0101: Age and Sex - Census Bureau Table. Accessed April 13, 2024. https://data.census.gov/table/ACSST1Y2022.S0101?q=sex%20maryland

16. Friedman JR, Nguemeni Tiako MJ, Hansen H. Understanding and Addressing Widening Racial Inequalities in Drug Overdose. *Am J Psychiatry*. 2024;181(5):381-390. doi:10.1176/appi.ajp.20230917

17. Xylazine “tranq” is in Maryland: What you need to know to stay safe. Maryland’s Office of Overdose Response. Accessed April 14, 2024. https://stopoverdose.maryland.gov/xylazine/

18. Brown DJ. Md. workgroup highlights increase of xylazine in opioid crisis, overdoses in recent years. Maryland Matters. November 30, 2023. Accessed April 14, 2024. https://www.marylandmatters.org/2023/11/30/md-workgroup-highlights-increase-of-xylazine-in-opioid-crisis-overdoses-in-recent-years/

19. Friedman J, Shover CL. Charting the fourth wave: Geographic, temporal, race/ethnicity and demographic trends in polysubstance fentanyl overdose deaths in the United States, 2010–2021. *Addiction*. 2023;118(12):2477-2485. doi:10.1111/add.16318

20. MONNAT SM. Demographic and Geographic Variation in Fatal Drug Overdoses in the United States, 1999–2020. *Ann Am Acad Pol Soc Sci*. 2022;703(1):50-78. doi:10.1177/00027162231154348

21. Wilson AM, Brown AR. Barriers to utilizing substance use disorder treatment and harm reduction services in Appalachia. *J Rural Ment Health*. 2024;48(1):15-25. doi:10.1037/rmh0000248

22. Bureau UC. Maryland’s Population Grew 7% to 6,177,224 Last Decade. Census.gov. Accessed April 13, 2024. https://www.census.gov/library/stories/state-by-state/maryland-population-change-between-census-decade.html

23. Mars SG, Ondocsin J, Ciccarone D. Sold as Heroin: Perceptions and Use of an Evolving Drug in Baltimore, MD. *J Psychoactive Drugs*. 2018;50(2):167-176. doi:10.1080/02791072.2017.1394508

24. Maryland Opioid Operational Command Center. *Review of Demographic Overdose Trends in Maryland by Local Jurisdiction*. Accessed April 14, 2024.

https://stopoverdose.maryland.gov/wp-content/uploads/sites/34/2023/03/OOCC-Grants-Reference-Demographic-Information-.pdf

25. Humphreys K, Shover CL. Twenty-Year Trends in Drug Overdose Fatalities Among Older Adults in the US. *JAMA Psychiatry*. 2023;80(5):518-520. doi:10.1001/jamapsychiatry.2022.5159

26. Mason M, Post LA, Aggarwal R. Health care and harm reduction provider perspectives on treating older adults who use non-medical opioids: a qualitative study set in Chicago. *BMC Health Serv Res*. 2023;23:876. doi:10.1186/s12913-023-09843-4

27. Butelman ER, Huang Y, Epstein DH, et al. Overdose mortality rates for opioids and stimulant drugs are substantially higher in men than in women: state-level analysis. *Neuropsychopharmacology*. 2023;48(11):1639-1647. doi:10.1038/s41386-023-01601-8

28. Men died of overdose at 2-3 times greater a rate than women in the U.S. in 2020-2021. National Institutes of Health (NIH). June 14, 2023. Accessed April 14, 2024. https://www.nih.gov/news-events/news-releases/men-died-overdose-2-3-times-greater-rate-women-us-2020-2021

29. Dhesi M, Maldonado KA, Maani CV. Tramadol. In: *StatPearls*. StatPearls Publishing; 2024. Accessed April 14, 2024. http://www.ncbi.nlm.nih.gov/books/NBK537060/

30. Ruhter L, Juhascik M, Watson J, Sweeney K, Daniulaityte R. Tramadol in seized drugs containing non-pharmaceutical fentanyl: Crime lab data from Ohio, USA. *Emerg Trends Drugs Addict Health*. 2022;2:100042. doi:10.1016/j.etdah.2022.100042

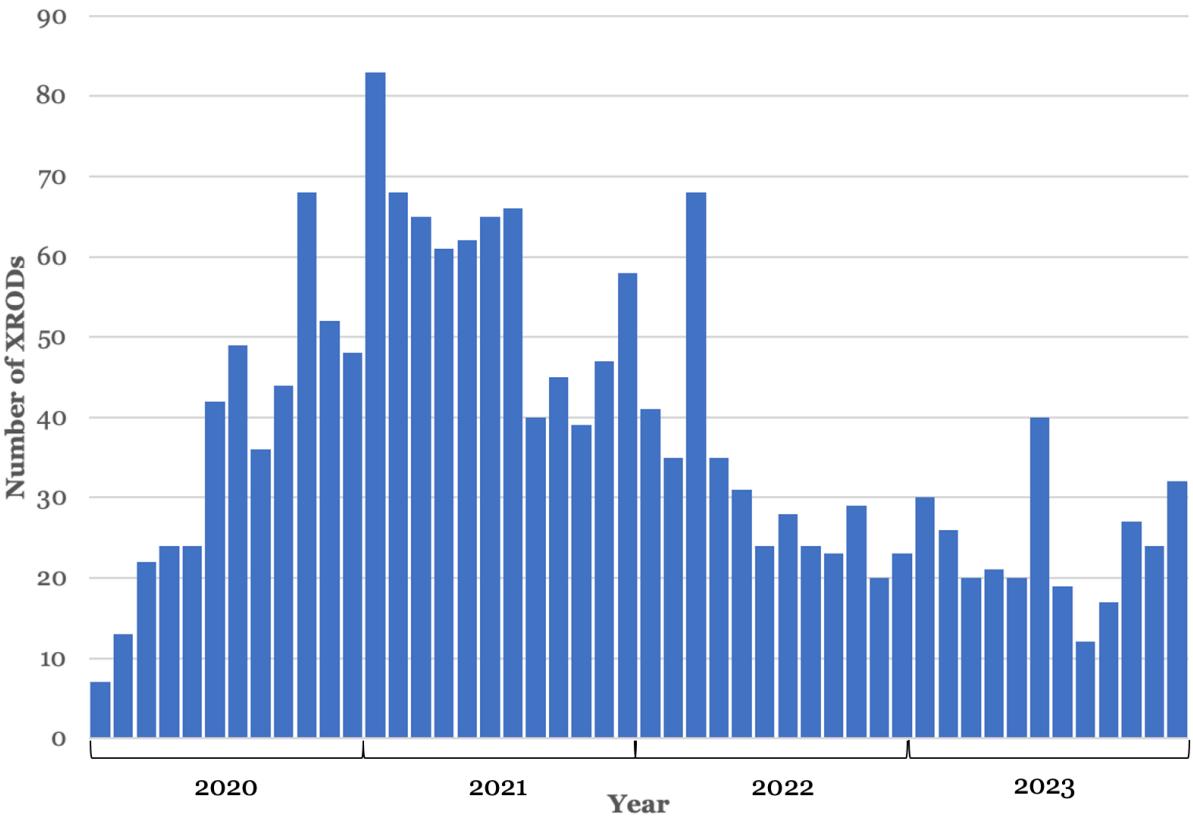
31. Seo J pil, Son W gyun, Gang S, Lee I. Sedative and analgesic effects of intravenous xylazine and tramadol on horses. *J Vet Sci*. 2011;12(3):281-286. doi:10.4142/jvs.2011.12.3.281

32. Lu D zhang, Fan H gang, Jiang S, et al. Cardiopulmonary, Biochemical and Haematological Effects of the Tiletamine/Zolazepam-Xylazine-Tramadol Combination to Provide Anaesthesia in Miniature Pigs. *J Integr Agric*. 2012;11(8):1340-1346. doi:10.1016/S2095-3119(12)60132-4

33. What You Should Know About Xylazine | Drug Overdose | CDC Injury Center. February 22, 2024. Accessed March 24, 2024. https://www.cdc.gov/drugoverdose/deaths/other-drugs/xylazine/faq.html

Figure 1: Monthly XRODs from 2020-2023

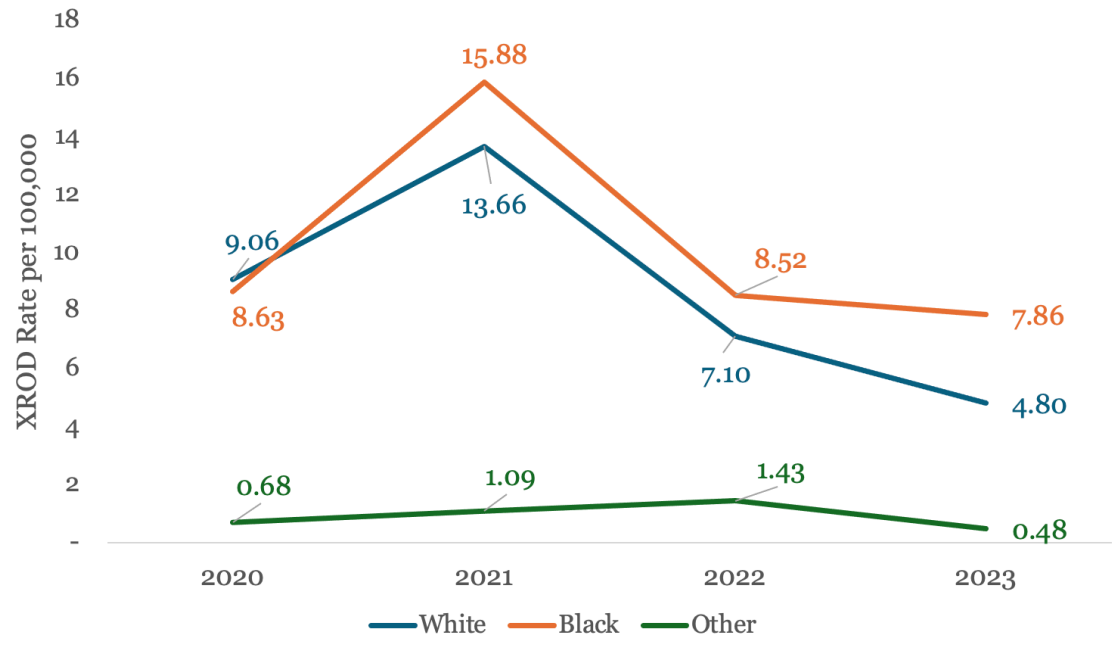
This histogram shows the number of xylazine-related overdose deaths (XRODs) per month between January 2020 and December 2023.



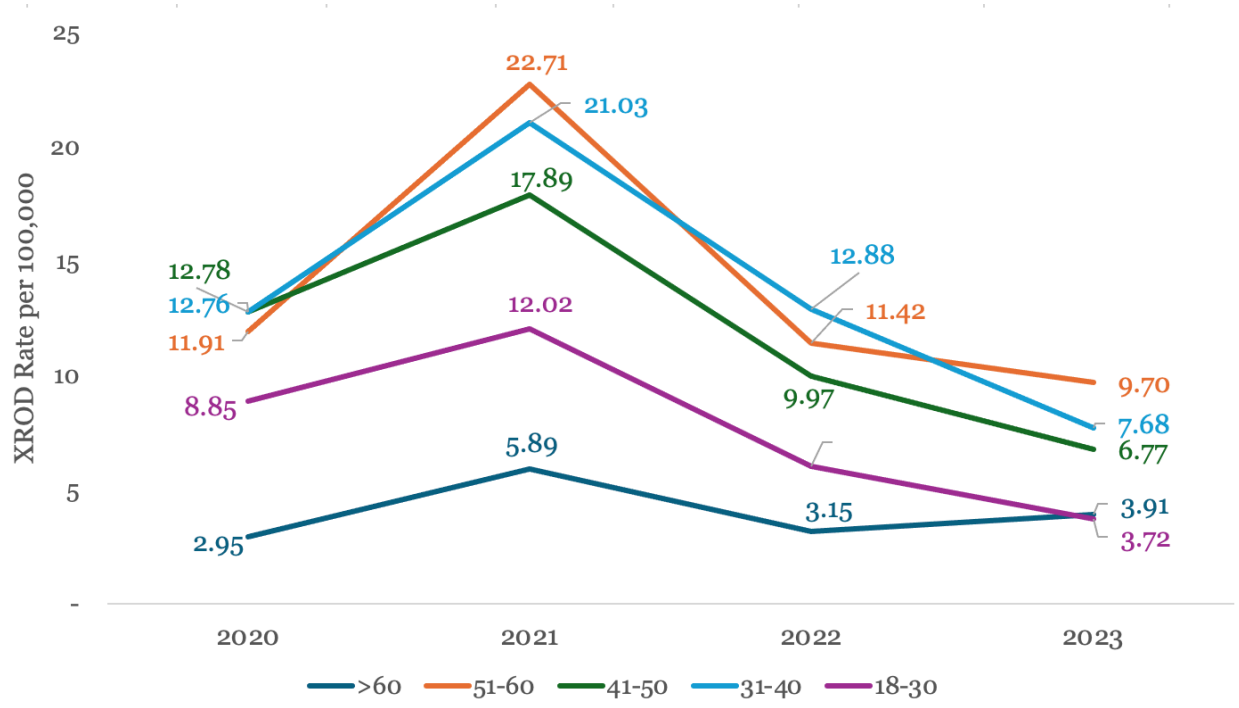
Figures 2a-c: Annual XROD Rates

Annual xylazine-related overdose death rates per 100,000 are shown, stratified by (a) race, (b) age group, and (c) sex.

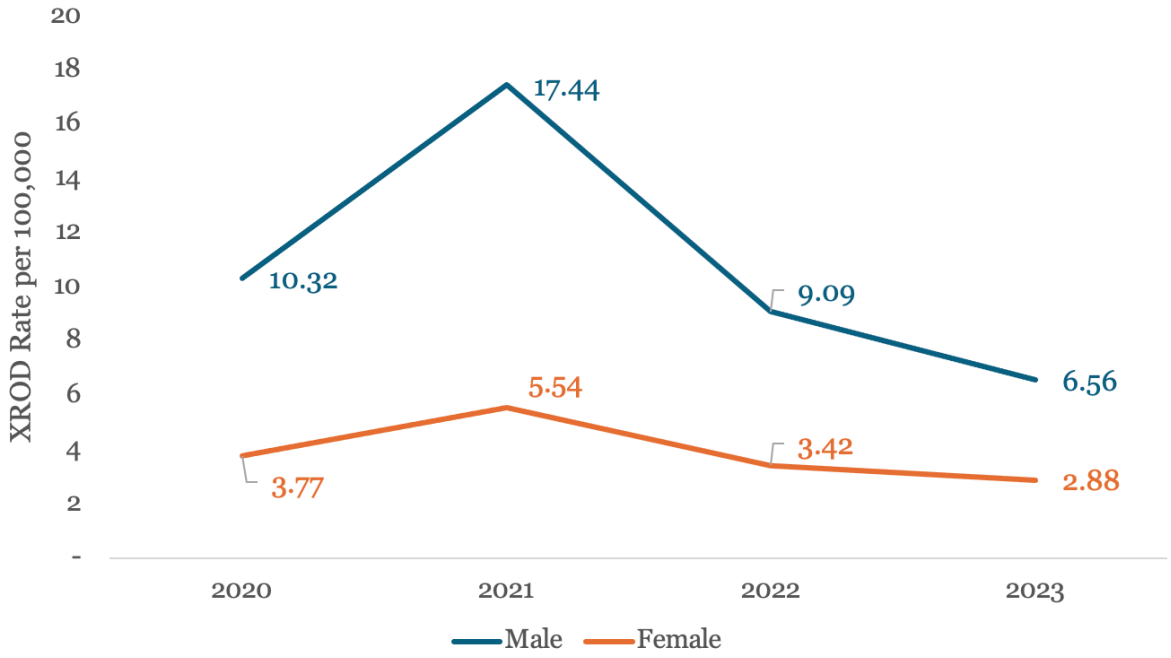
(a)



(b)



(c)


20
18
16
14
12
10
8
6
4
2
-
XROD Rate per 100,000
17.44
10.32
9.09
6.56
5.54
3.42
3.77
2.88
2020
2021
2022
2023
Male
Female