Maryland Overdose Data to Action | OD2A

Xylazine in Maryland: An Initial Report of the Maryland Xylazine Workgroup, 2022

Prepared by the Maryland Xylazine Workgroup and Maryland Overdose Data to Action Team

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ACRONYMS

CDC: Centers for Disease Control and Prevention and Prevention
CHRS: Maryland Center for Harm Reduction Services
COD: Cause of Death
CRISP: Chesapeake Regional Information System for our Patients
DART-MS: Drug Analysis in Real Time Spectrometry
DEA: Drug Enforcement Administration
EHR: Electronic Health Record
IMF: Illicitly-Manufactured Fentanyl
MDH: Maryland Department of Health
MODC: Maryland Overdose Data Collaborative
MOUD: Medication for Opioid Use Disorder
NIST: National Institute of Standards and Technology
OCME: Office of the Chief Medical Examiner
OCSA: Maryland Office of Controlled Substances Administration
OTC: Over the Counter
OD2A: Overdose Data to Action
OUD: Opioid Use Disorder
PHSA: MDH Public Health Services Administration
PWUD: People who use drugs
RAD: Rapid Analysis of Drugs
SUDORS: State Unintentional Drug Overdose Reporting System
SSPs: Syringe Services Programs
VSA: Maryland Vital Statistics Administration

CONTENTS

EXECUTIVE SUMMARY

Background

Xylazine is an emerging public health threat that could exacerbate the overdose crisis and complicate overdose prevention. The growth of xylazine in Maryland would result in more death and suffering and would further drain public health resources. To respond to the potential threat of xylazine, we developed the Maryland Xylazine Workgroup to address questions, share data, and make recommendations. The Workgroup is an interagency and multidisciplinary team of professionals with a stake in overdose prevention. This report summarizes the efforts of the Workgroup and presents critical information about xylazine in Maryland.

Organization of this Report

This report contains six chapters, including an introduction to the problem in Chapter 1. Chapter 2 uses 2020 data from Maryland's State Unintentional Drug Overdose Reporting System (SUDORS) to describe the number of overdose decedents in Maryland who tested positive for xylazine, and compares xylazine positive versus negative decedents on death and drug use circumstances. Chapter 3 introduces the role of Maryland Vital Statistics Administration (VSA) in monitoring xylazine; it includes: a description of the agency's procedures for reporting xylazine-related deaths, a summary of xylazine-related overdose fatalities, and a discussion of considerations that will be used to determine whether xylazine should be included in the Administration's quarterly and annual reports. Chapter 4 uses data from the "Rapid Analysis of Drugs Project," (RAD) an initiative of the MDH's Center for Harm Reduction Services. RAD involves chemical analysis of drug paraphernalia donated from volunteers who use drugs; there are collection sites at Syringe Services Programs (SSPs) across Maryland. The paraphernalia are being tested for xylazine and results offer insights about its prominence in the drug supply. Chapter 5 presents findings from the "Xylazine Toxicology Project," which aims to quantify the concentration of xylazine in post-mortem toxicology of opioid overdose decedents. Findings provide new information about xylazine as a contributor to overdose death. In the final chapter, Chapter 6, we integrate knowledge across all studies to summarize what is known about xylazine as a public health threat in Maryland. We also present recommendations for practice, surveillance, and policy development.

Major Findings & Recommendations

The number of xylazine-positive overdose decedents in Maryland has grown in recent years. Seventeen percent of Maryland opioid overdose decedents in 2020 were xylazine positive; most had fentanyl as a cause of death (Chapters 2 and 3). Preliminary information from the RAD study complements overdose fatality data; xylazine was detected in drug paraphernalia, often along with

opioids (Chapter 4). In Chapter 5 we summarized a pilot conducted on 30 overdose decedents who tested positive for xylazine and findings showed that xylazine-positive decedents usually had fentanyl as a cause of death. Xylazine concentrations ranged widely – most decedents had concentrations between 3.3 to 125ng/mL, and two had concentrations above 200 ng/mL.

Based on these findings, the Workgroup notes the importance of continuing this work. We established 4 recommendations for future work. We plan to continue to meet as a Workgroup to carry out these recommendations.

1. Build and maintain an infrastructure to respond to the problem.
2. Continue to monitor the issue.
3. Disseminate information about the problem to stakeholders in Maryland and beyond.
4. Investigate factors underlying the emergence of xylazine in the drug supply.

Chapter 1. Introduction to this Report

Authors: Renee M. Johnson, Sharmin Hossain, Madison Nuzzo, Rachel Alinsky, Taylor Parnham, Marie Stratton, Kristin Schneider

Overview

This Chapter provides detailed information about the emergence of xylazine across the US, potential public health impacts, and early steps toward a public health response. It also describes the rationale for the establishment of the Maryland Xylazine Workgroup. The Chapter ends with a description of the purpose of the Report and the focus of each Chapter.

Background

This Report addresses xylazine in Maryland, including its misuse, potential consequences of misuse, and public health response strategies. Xylazine is a respiratory depressant that is used clinically as a sedative and analgesic for animals, and also to assist in euthanizing dogs.[1,2] It is not classified federally as a controlled substance, and legally is limited to use by or on the order of a licensed veterinarian. Xylazine can enhance and extend the sedative and euphoric effects of opioids, and there is a growing body of evidence indicating that it is being used in combination with illicitly-manufactured fentanyl (IMF).[3–7] Reasons for an increase in xylazine are not well known, but it has been suggested that traffickers may have begun using it as an adulterant in IMF after COVID-19 restrictions (e.g., border closures, stay-at-home orders) disrupted the availability of specific drugs across North America.[3–5]

There have been reports of xylazine being used in combination with opioids in the US for more than a decade. Early reports highlighted its use in Puerto Rico, whereas more recent work notes its emergence in overdose deaths in several US cities and states.[7–9] Recent data from Cook County, IL show that 10% of decedents with IMF as a cause of death from 2017-2021 were xylazine-positive.[10] A study from the Philadelphia Medical Examiner's Office showed that xylazine was detected in 2% of IMF/heroin overdose deaths from 2010 to 2015, and in 31% of deaths in 2019.[11] There is evidence of an increase in xylazine among overdose decedents in Maryland. From 2006-2018, there were 83 overdose decedents who were positive for xylazine. In 2018 alone, there were 56 cases, a 331% increase from the year before. IMF was detected in nearly all of the xylazine positive cases (i.e., 80 of 83).[12]

Xylazine is an emerging public health threat that could exacerbate the overdose crisis, complicate overdose prevention, and further drain already limited public health resources. The combination of xylazine and IMF can overpower the autonomic nervous system and increase respiratory distress to the point of overdose. In addition to increasing risk for overdose, xylazine is resistant to overdose reversal with naloxone. Therefore, xylazine could lead to increases in non-fatal and fatal overdose and decrease the efficiency of naloxone distribution, which is among the most effective

population-based strategies for overdose prevention. Additionally, xylazine contributes to severe skin and soft tissue infections (SSTIs), which are costly and difficult to treat – especially for people who are actively injecting drugs. Xylazine-related SSTIs are also painful and can be life-threatening.[13] Unlike with other injected drugs, SSTIs resulting from xylazine use can develop all over, not just around the injection site. Finally, xylazine can be addictive and little is known about effective medical care for management of withdrawal or options for pharmacotherapy for people with xylazine dependence.[14,15]

The presence of xylazine in illicit opioids and in the toxicology of opioid overdose decedents has led to several public health advisories and law enforcement alerts in the past five years, and law enforcement officials have uncovered xylazine in their monitoring of drug trafficking.[16] CDC published the first 'notes from the field' article on xylazine in *Morbidity & Mortality Weekly Report* in 2019.[17] In 2021, the police department in Frederick County, MD, published a report on opioid use trends in the county, describing a rise in xylazine being used as an adulterant in IMF,[18] and Vermont Department of Health issued an advisory with guidance on harm reduction.[19] In Massachusetts, the Berkshire County District Attorney recently issued a Public Health Advisory about xylazine;[20] that advisory was issued after a drug checking surveillance project reported detecting the drug in a large number of samples of street drugs.[21] The District Attorney for Worcester County, Maryland issued a warning about xylazine in September 2022.[22]

Maryland Xylazine Workgroup

The Maryland Xylazine Workgroup was established as part of Overdose Data to Action (OD2A) implementation. Funded by the CDC, OD2A supports jurisdictions – including Maryland – with collection of high-quality, comprehensive, and timely data on nonfatal and fatal overdose and supports the use of those data for overdose prevention and response efforts. Evaluation goals for Maryland's OD2A initiative are to: demonstrate achievement of program outcomes; build a stronger evidence base for specific program interventions; clarify applicability of the evidence base to different populations, settings, and contexts; drive continuous program improvement; and determine whether program strategies are scalable and effective at reaching the target or intended populations.

Members of the Maryland Department of Health (MDH), the Vital Statistics Administration (VSA), the Office of the Chief Medical Examiner (OCME), and the Maryland Overdose Data Collaborative (MODC) met for the first time in December of 2021 to discuss the topic of xylazine and overdose in Maryland. OCME was considering whether and under what circumstances xylazine should be designated as a cause of death (COD) in fatal overdose cases. VSA relies on the OCME data and COD designations for the issuance of quarterly and annual vital statistics reports, and a primary VSA question was whether

xylazine made enough of an impact to be included in regular reports. MDH OD2A team members were interested in incorporating public health response efforts for xylazine into the ongoing work of OD2A.

The Maryland Xylazine Workgroup was formally established after that first meeting, and the Workgroup's activities were subsumed under the auspices of OD2A implementation. Workgroup leadership was provided by OD2A and MODC, and workgroup members met in their professional capacities to establish a scope of work, identify key stakeholders and ongoing related work, and develop recommendations for Maryland. Meetings were held twice monthly, with additional discussions as needed. Given the relevance of xylazine to their work, MDH's Center for Harm Reduction Services (CHRS), Baltimore County OD2A, and the team working on the State Unintentional Drug Overdose Reporting System (SUDORS) were invited to participate. The Workgroup reviewed the science on xylazine, leveraged datasets across the state, and began new data collection projects to estimate the scope of the xylazine problem and consider implications for Maryland.

Purpose of this Report

This report summarizes the efforts of Maryland Xylazine Workgroup and presents critical information about xylazine in Maryland. In addition to this chapter (Chapter 1. Introduction), five chapters are included. Chapter 2 uses SUDORS data to describe the number of overdose decedents in Maryland (2020) who tested positive for xylazine and compares xylazine positive versus negative decedents on death and drug use circumstances. Chapter 3 introduces the role of Maryland VSA in monitoring xylazine; it includes a description of the agency's procedures on reporting xylazine-related deaths, a summary of fatality data, and a discussion of considerations that will be used to determine whether xylazine should be included in quarterly and annual reports. Chapter 4 uses data from the "Rapid Analysis of Drugs Project," (RAD) an initiative of the MDH's CHRS. RAD involves testing drug paraphernalia donated from Syringe Services Programs (SSPs) in Maryland. The paraphernalia are tested for xylazine and offer insights about its prominence in the drug supply. Chapter 5 presents findings from the "Xylazine Toxicology Project," an OCME-led project that aims to quantify the amount of xylazine in post-mortem toxicology screening of overdose decedents. Findings will provide new information about the role of xylazine in overdose deaths. In the final chapter, Chapter 6, we integrate knowledge across all studies to summarize what is known about xylazine as a public health threat in Maryland. We also present recommendations for practice, surveillance, and policy development.

Chapter 2. Xylazine in Post-Mortem Toxicology Screening of Overdose Decedents: Maryland, 2020

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Overview

This chapter presents descriptive information about the presence of xylazine in the toxicology of opioid overdose decedents in Maryland. Data are from the 2020 State Unintentional Drug Overdose Reporting System (SUDORS). Seventeen percent of opioid overdose decedents were positive for xylazine, nearly all of whom had IMF as a cause of death. There was notable variation across the state's regions. Xylazine-positive decedents were more likely than xylazine-negative decedents to have evidence of drug injection at the scene of overdose. Findings highlight the importance of considering xylazine as part of Maryland's coordinated efforts to prevent overdose.

Introduction

Data from the Maryland Vital Statistics Administration show that there were 56 overdose decedents who screened positive for xylazine in 2018, a 331% increase from the prior year.[12] Xylazine is an emerging public health threat that could exacerbate the overdose crisis, complicate overdose prevention, and further drain public health resources in the state. Analysis of overdose death data can provide needed information on a possible increase in xylazine in Maryland, and provide data to inform prevention strategies. The purpose of this chapter is to present information about the presence of xylazine in the post-mortem toxicology of opioid overdose decedents in Maryland. We used data from the State Unintentional Drug Overdose Reporting System (SUDORS). The work presented here addresses Maryland OD2A's evaluation question 4.14, "What drug combinations have been used by overdose decedents?".

Methods

Data: Maryland SUDORS

Data are from the State Unintentional Drug Overdose Reporting System (SUDORS), which provides detailed information on unintentional and undetermined drug poisoning deaths in US states.[1] A main goal of SUDORS is to improve the public health response to drug overdose by collecting detailed death data and ensuring use of those data to inform prevention strategies and policy development. SUDORS was initiated in 2016 in several states as part of the CDC's Enhanced State Opioid Overdose Surveillance (ESOOS) program to abstract opioid overdose death data in states. In 2019, CDC expanded

[1] We analyzed the Maryland SUDORS 2020 dataset from Fall 2021.

SUDORS to include all drug overdose deaths, and incorporated it into OD2A. Data for this brief are from the Maryland SUDORS program, which was initiated in 2017.

The case criteria for SUDORS included all drug poisoning deaths, i.e., deaths with ICD-10 codes X44-X44 and Y10-14. Decedents with alcohol as a COD, i.e., those coded as X45 (accidental poisoning by and exposure to alcohol) or Y15 (poisoning by and exposure to alcohol, undetermined intent), are included in SUDORS if and only if they had a qualifying ICD-10 code. To populate the SUDORS dataset, abstractors pull data from multiple sources, including: law enforcement reports, medical examiner (ME) reports, and death certificates. SUDORS contains data on decedent demographic factors, event data (e.g., location of injury and death), death scene investigation findings (e.g., route of administration, evidence of substances used, response efforts), post-mortem toxicology results (e.g., substances present, substances designated by medical examiners as causes of death), circumstances of fatal overdose events (e.g., diagnosed mental health problem, mental health/substance use treatment), and other risk factors including current or acute critical events within two weeks of death that might be potential contributors to fatal overdose, such as job-related crises. The completeness of SUDORS is subject to the completeness of source data, meaning that a circumstance variable can be endorsed if and only if it was recorded in one or more of the source documents.

Variables

Decedents were classified as xylazine-positive or xylazine-negative, and we examined specific types of opioids designated as CODs (i.e., prescription opioid medications, IMF, heroin, and all other opioids). We also classified decedents into three categories based on their causes of overdose death, i.e., opioids only; opioids and psychostimulants (i.e., cocaine, methamphetamine, or amphetamines); and opioids and alcohol. The latter two categories included decedents regardless of whether there were any other drugs designated as CODs.

Death circumstances included: [1] overdose took place at a residence, [2] decedent was attended by EMS personnel, [3] potential bystander was present at the time of the overdose, [4] naloxone was administered, and [5] evidence of injection (defined as found with cookers, filters, syringes, tourniquets, or other injection evidence). Overdose deaths were designated as EMS-attended if personnel were present at the scene of the injury accident, regardless of whether they provided any type of treatment/resuscitative efforts. Potential bystanders were defined as a person aged ≥11 years who was physically nearby either during or shortly preceding a drug overdose and potentially had an opportunity to intervene or respond to the overdose.

We examined decedents by age category (i.e., <25 years, 25-55 years, >55 years), sex (male, female), and race/ethnicity. To preserve confidentiality, we reported race/ethnicity as White,

non-Hispanic; Black, non-Hispanic; and all other groups, combined. We also reported on county and region of residence, with out-of-state as an option. Regions were Capital, Central, Southern, Upper Eastern Shore, Lower Eastern Shore South, and Western (Table 2.1). Location was based on place of overdose, not place of death.

Table 2.1. Maryland Counties and Regions

Western	Capital	Central	Southern	Upper Eastern Shore	Lower Eastern Shore
Allegany	Frederick	Anne Arundel	Calvert	Caroline	Dorchester
Garrett	Montgomery	Baltimore City	Charles	Cecil	Wicomico
Washington	Prince George's	Baltimore	St. Mary's	Kent	Somerset
		Carroll		Queen Anne's	Worcester
		Harford		Talbot	
		Howard			

Analysis

The 2020 Maryland SUDORS dataset included 2,722 overdose decedents. Our analytical team restricted it to decedents who were 18 years or older and whose overdose took place in Maryland (n=2,700). We further restricted analysis to the 2,511 cases in which opioids were listed as a COD. We employed basic analytic measures such as counts and proportions to describe the sample. An omnibus chi-square test was performed to statistically test the distribution of xylazine-positive cases by demographic subgroups and drugs that contributed to the death. For the subgroups with more than two categories (i.e., race/ethnicity, location, and age groups), we used logistic regression to examine pairwise differences across categories.

Results

Demographic and Geographic Factors

There were 2,511 overdose decedents; 17.1% were positive for xylazine in post-mortem toxicology (n=429). As Table 2.2 shows, fewer decedents in the 'other' race/ ethnicity group were xylazine-positive compared to White decedents (10.3% vs. 18.7%, p=0.011). There was no difference in the percentage of Non-Hispanic Black and Non-Hispanic White decedents who were xylazine-positive (15.9% vs. 18.7%, p=0.075). Among decedents aged 25-55, 19% were xylazine-positive, compared to 11.4% of decedents aged 55 and older ($p<0.001$).

Table 2.2. Demographic factors of Maryland opioid overdose decedents by xylazine toxicology (n=2,511)

	N	Xylazine Toxicology		*p*
		Positive (*n* = 429)	Negative (*n* = 2,082)	
Total	2,511	17.1%	82.9%	Ref.
Sex				
Male	1,820	17.0%	83.0%	Ref.
Female	691	17.2%	82.8%	0.911
Race/Ethnicity				
White, Non-Hispanic	1,391	18.7%	81.3%	Ref
Black, Non-Hispanic	965	15.9%	84.2%	0.075
All other	155	10.3%	89.7%	0.011
Age Category				
<25	121	16.5%	83.5%	0.118
25-55	1,801	19.0%	81.0%	<0.001
>55	589	11.4%	88.6%	Ref.

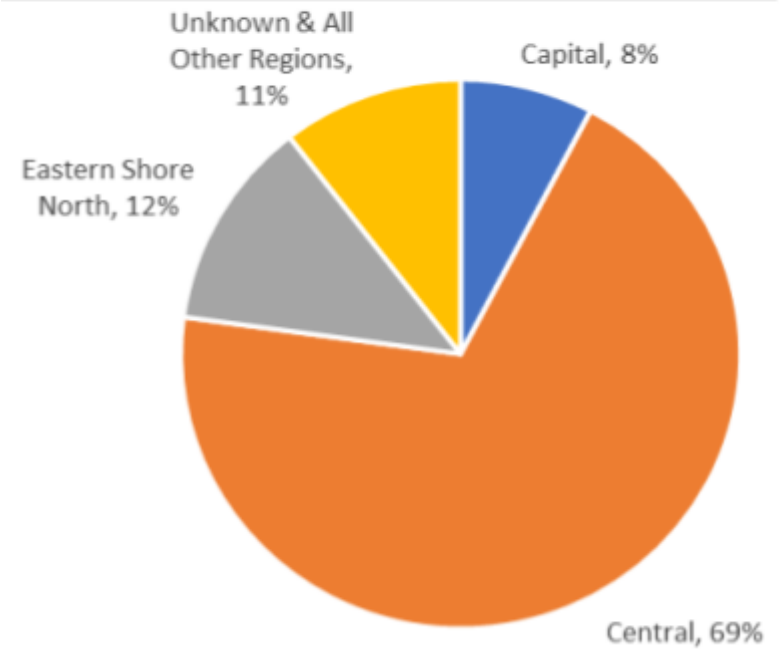
Descriptive data on xylazine-positive decedents by geographic factors is provided in Table 2.3. Compared to Maryland-born decedents, decedents born outside of Maryland and outside of the US were significantly less likely to be xylazine-positive. Seventeen percent of decedents whose residence was in Maryland were positive for xylazine, compared to 13.8% who resided out-of-state and 20.3% for those whose residence was unknown; these differences were not statistically significant. Nearly one-fifth (19.3%) of decedents whose overdose occurred in Baltimore City were xylazine-positive, which was higher than the percentage for Baltimore County (14.4%, p=0.044).

Table 2.3. Geographic factors of opioid overdose decedents, by xylazine toxicology (n=2,511)

		Xylazine Toxicology		
	N	Positive (*n* = 429)	Negative (*n* = 2,082)	*P*
Location of Birth				
In Maryland	1,656	18.6	81.4	Ref.
Outside of Maryland, in US	678	14.5	85.5	0.008
Outside of US	85	5.9	94.1	0.003
Not Known	92	19.6	80.4	0.946
County of Residence				
In Maryland	2,271	17.0	83.0	Ref.
Outside of Maryland	87	13.8	86.2	0.475
Unknown	153	20.3	79.7	0.205
Location of Overdose				
Baltimore City	960	19.3%	80.7%	Ref.
Baltimore County	341	14.4%	85.6%	0.044
All Other/unknown	1,210	16.1%	83.9%	0.055

There was notable variation in the proportion of decedents who were xylazine-positive by region. Regions with the highest proportions of xylazine-positive decedents were Upper Eastern Shore (41.1%), Lower Eastern Shore (17.8%), and Central (17.5%); proportions for all other regions were below 15%. More than two-thirds of all xylazine-positive decedents in the state had their fatal overdose in the Central Region (*n*=298), which includes Anne Arundel County, Baltimore City, Baltimore County, and Harford County (Figure 2.1).

Figure 2.1. Location of Overdose for Maryland Opioid Overdose Decedents, 2020



Drug Use Circumstances & Substances Involved

Table 2.4 demonstrates the circumstances surrounding drug use and opioid overdose. Xylazine-positive (vs. negative) decedents were significantly more likely to have a higher prevalence of evidence of injected drugs compared to xylazine-negative decedents (29.6% vs. 21.9%). There were no statistically significant differences with regard to whether the overdose occurred at a residence, naloxone administration, presence of potential bystanders, or whether EMS was called to the scene.

Table 2.4. Drug use circumstances by post-mortem xylazine toxicology (n=2,511)

	Xylazine Positive *n* = 429	**Xylazine Negative *n* = 2082**	***p***
Evidence of injection	127 (29.6%)	456 (21.9)%	0.001
Overdose took place at a residence	244 (56.9%)	1,196 (57.4%)	0.828
Administered Naloxone	82 (19.1%)	375 (18.0%)	0.590
Potential Bystanders	305 (71.1%)	1426 (68.5%)	0.289
EMS present	412 (96.0%)	1,999 (96.0%)	0.982

The most common opioid listed as a cause of death among decedents was IMF, regardless of xylazine toxicology. Among decedents who were xylazine-positive (n=429), >99% had IMF and/or heroin as a cause of death and 14.7% had prescription opioids as a cause of death (Table 2.5). Corresponding estimates for xylazine-negative decedents were 91.5% and 18.9%. Both IMF/heroin and prescription opioids were causes of death for 14.5% of the xylazine-positive decedents and 11.9% for the xylazine-negative decedents. Prescription opioids, including methadone and buprenorphine, were rarely noted as single contributors to death among xylazine-positive decedents (<1%), but were the sole causes of death for 7.0% of xylazine-negative decedents.

Table 2.5. Substances that Contributed to Opioid Overdose Death

	Xylazine Positive *n* = 429	**Xylazine Negative *n* = 2082**
Type of Opioids		
Any Prescription Opioids	14.7%	18.9
Prescription Opioids, Only	<1%	7.0
Any IMF and/or Heroin	99.1%	91.5%
Any IMF	*99.8%*	*91.6%*
Any Heroin	*6.1%*	*4.5%*
IMF and/or Heroin, Only	37.5%	34.2%
Both IMF/Heroin & Prescription Opioids	14.5%	11.9%
IMF/Heroin & other opioids	47.1%	45.4
Types of Drugs		
Opioids, Only	44.8%	44.2%
Opioids & Psychostimulants (with or without any other drugs)	35.2%	34.1%
Opioids & Alcohol (with or without any other drugs)	9.1%	18.4%

The proportion of decedents with opioids as the only cause of overdose death was similar among xylazine-positive and xylazine-negative decedents (44.8% vs. 44.2%), as were the proportions with both opioids and psychostimulants as causes of death (35.2% vs. 34.1%). It is worth noting that most psychostimulants represented cocaine. By contrast, a smaller percentage of xylazine-positive decedents had both alcohol and opioids as causes of death (9.1% vs. 18.4%).

Conclusion

Our data analysis from Maryland SUDORS suggests that xylazine is common among opioid decedents in Maryland and a public health concern. In 2020, 17.1% of opioid overdose decedents in Maryland tested positive for xylazine in post-mortem toxicology. These findings highlight the importance of considering xylazine as part of Maryland's coordinated efforts to prevent overdose. Consistent with CDC's analysis of multi-state SUDORS data, there was modest variation in the proportion of Maryland decedents who were xylazine-positive by sex, race/ethnicity, and age category.[17]

The proportion of xylazine-positive decedents in Maryland is substantially higher than the estimate of 1.8% reported in 2019 SUDORS data from 38 states and the District of Columbia.[17] CDC notes that xylazine estimates in overdose deaths may be underestimated due to lack of testing or lack of standardization with regard to testing and highlight the importance of implementing standardized protocols.

Our findings on xylazine and alcohol offer additional insights about the drugs used by overdose decedents. Consistent with existing research, nearly all of the xylazine-positive decedents in Maryland had IMF as a cause of death.[17] Alcohol and prescription opioids were less commonly detected among xylazine-positive decedents than among xylazine-negative decedents, whereas xylazine-positive decedents were more likely to have evidence of injection than xylazine-negative decedents.

The multi-state SUDORS from 2019 data suggests that xylazine-positivity is more common in Northeast states than states in other Census regions.[17] Maryland may look more like the Northeastern states in terms of the presence of xylazine among overdose decedents, despite being located in the South. A caveat to this conclusion relates to completeness of the data. Four states in CDC's multi-state study contributed just 6 months of data to the analysis, i.e., Florida, Louisiana, Michigan, and Maryland. If the data were complete for those states, the geographical distribution of xylazine-positive decedents might have been different.

Chapter 3. Tracking of Xylazine Intoxication Fatality Data: Vital Statistics Administration

Authors: Jeanetta Churchill, Monique Wilson

Overview

The Maryland Vital Statistics Administration (VSA) uses OCME data to report on trends in drug- and alcohol-related intoxication deaths. The purpose of this Chapter is to determine whether it is advantageous for VSA to include the number of deaths from xylazine across time, either occurring alone, or in conjunction with another substance in annual reports. VSA data from 2012 through 2021 indicate that there were very few xylazine deaths that did not involve IMF. The main conclusion is that there is little value in reporting xylazine as an individual substance. Because data on xylazine in fentanyl-related deaths offer important information, regular reporting by VSA of fentanyl deaths that occur with xylazine is warranted to monitor the expansion of xylazine among overdose decedents in Maryland.

Introduction

The Maryland Vital Statistics Administration (VSA) is responsible for tracking data trends resulting from unintentional drug- and alcohol-related intoxication deaths. The data on all intoxication deaths are reported in VSA's *Annual Report on Unintentional Drug and Alcohol-Related Intoxication Deaths in Maryland*.[23] The purpose of this report is to describe trends in the number of unintentional drug and alcohol-related intoxication deaths occurring in Maryland during a 10-year period. Trends are examined by age at time of death, race/ethnicity, sex, place of death, and substances related to death. These data are also used for VSA quarterly reports, dashboards (e.g., the Maryland Opioid Operational Command Center [OOCC]),[24] weekly and monthly reporting to local health departments and other stakeholders.

In this Chapter we present descriptive information on xylazine-related deaths over time as a contributing factor to cause of overdose death, independently and in combination with other substances. Cause of death and toxicology determinations are made by the Office of the Chief Medical Examiner (OCME), and the VSA uses OCME designations to summarize overdose trends for a variety of substances including heroin, IMF, prescription opioids, other prescribed drugs (e.g., benzodiazepines), phencyclidine (PCP), and alcohol. The substances that are currently tracked annually by VSA as independent causes of overdose death are listed in Table 3.1. Although xylazine is captured as contributing to the cause of death by the OCME, VSA is not currently tracking the trends for this substance as an independent cause of death.

Table 3.1. Substances Monitored in Annual Reporting by VSA		
Alcohol	Benzodiazepine	Carfentanil
Cocaine	IMF	Heroin
Methadone	Methamphetamine	Oxycodone
Phencyclidine	Prescriptions Opioids	Tramadol

The purpose of this report is to determine whether it is advantageous for VSA to report the number of deaths from xylazine across time, either occurring alone, or in conjunction with another substance. A main factor that influences the decision to report is an increase in the OCME reporting xylazine as a cause of death or contributor to the cause of death on the death certificates, which is based on OCME toxicology reports. For example, VSA began reporting carfentanil following large spikes in its presence as a cause of death or contributor to the cause of death.

Methods

Designating Deaths as Drug-Related

Data on substances involved in fatal overdose are housed in a registry developed and maintained by VSA. The methodology for reporting on drug-related intoxication deaths in Maryland was developed by VSA with assistance from the MDH Behavioral Health Administration, OCME, and the Maryland Poison Control Center. Assistance was also provided by authors of a Baltimore City Health Department report on intoxication deaths.[25]

Data used to investigate xylazine intoxication deaths were obtained from the OCME. Maryland law requires the OCME to investigate all drug deaths occurring in the State, as well as non-natural and unattended deaths. In these instances, information compiled during an investigation is used to determine the cause or causes of death. Depending on the circumstances, an investigation may involve a combination of scene examination, review of witness reports, review of medical and police reports, autopsy, and toxicological analysis of autopsy specimens. Toxicological analysis is routinely performed when there is suspicion that a death was the result of drug or alcohol intoxication. A small number of death records involving intoxication deaths were filed by sources other than OCME and were identified through death records maintained by VSA. This included records filed by medical facilities rather than OCME, and records filed by federal investigators following deaths involving US military personnel. Information available on these cases was included in the registry. Information on place of death and race/ethnicity was missing for a small number of records provided by OCME and was obtained through death certificate data. Death certificate data were also used to update demographic information on records that were amended after the records were filed with the Division of Vital Records.

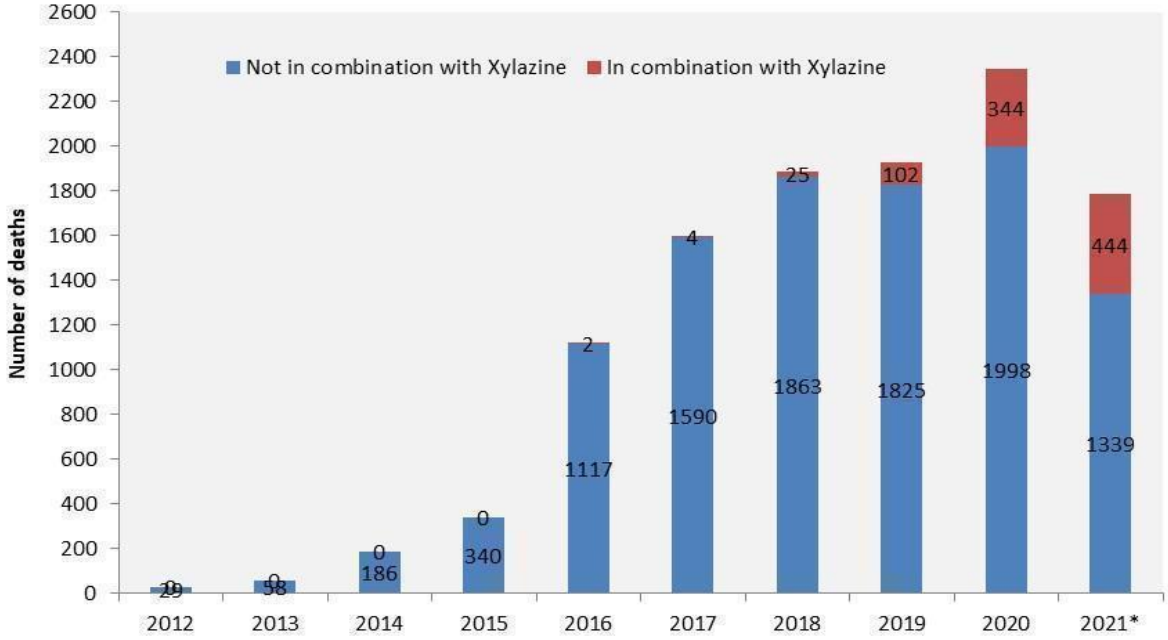
Statistical Analysis

For the purpose of this report, a xylazine-related intoxication death was defined as a death that was the result of recent ingestion or exposure to xylazine alone or in combination with another type of drug, such heroin, fentanyl, cocaine, prescription opioids, benzodiazepines, phencyclidine (PCP), methamphetamines, or other prescribed and unprescribed drugs (including over the counter drugs). OCME provided all records to VSA for which the text of the cause of death included one or more of the following terms: poisoning, intoxication, toxicity, inhalation, ingestion, overdose, exposure, chemical, effects, or use. Any records provided by OCME that were not unintentional drug related intoxication deaths, such as deaths due to smoke inhalation, carbon monoxide intoxication, cold exposure, and chronic use of alcohol or other drugs, were excluded from the registry. Also excluded from the registry were deaths for which the manner of death was determined to be natural, suicide, or homicide. Maryland VSA data from 2012 through the third quarter of 2021 was reviewed. Data from 2021 are preliminary and based on estimates as of March 2022.

Results

There were 926 xylazine-related deaths in Maryland from 2012 through Q3 of 2021. Nearly all occurred in 2020 (n=344,37.1%) or 2021 (48.2%, n=446). IMF was a COD in nearly all xylazine-related deaths (921 out of 926). Figure 3.1. shows an upward trend in the number of xylazine-related deaths where fentanyl was a cause of death. There were 0 such deaths from 2012-2015, 31 from 2016-2018, and 102 in 2019. The number more than tripled from 2019 to 2020, i.e., from 344 to 444.

Figure 3.1. Number of xylazine-related deaths in combination with IMF; MD, 2012-Q3 2021.



There was a sharp contrast between the number of xylazine-related deaths where fentanyl was present compared to the number of fentanyl-related deaths where xylazine was present. The number of fentanyl deaths has increased since 2016, and so have the number of fentanyl-related deaths in which xylazine was present (Figure 3.2). The proportion of fentanyl-related deaths where xylazine was present was negligible from 2012 through 2018 and rose to 5.3% by 2019. The proportion increased to 14.7% in 2020 and 24.9% for Q1-Q3 of 2021.

Figure 3.2. Number of fentanyl-related deaths in combination with xylazine; MD, 2012-Q3 2021.

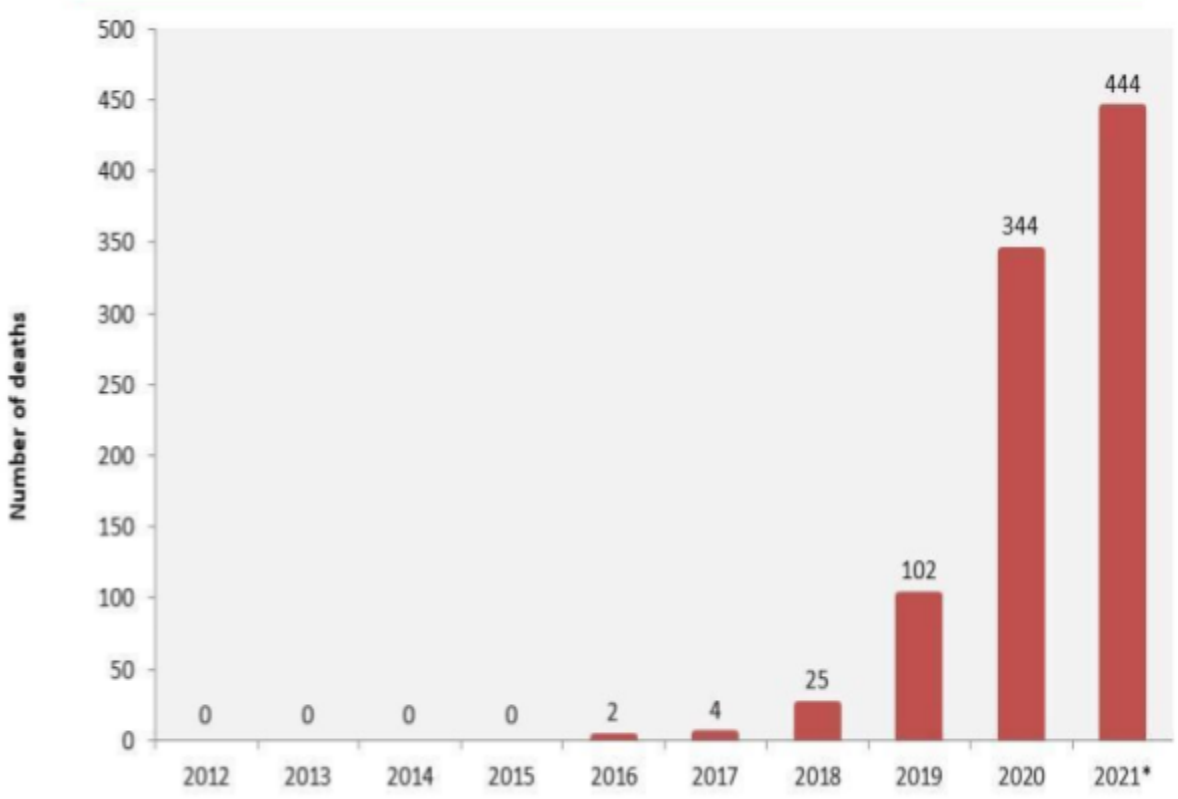
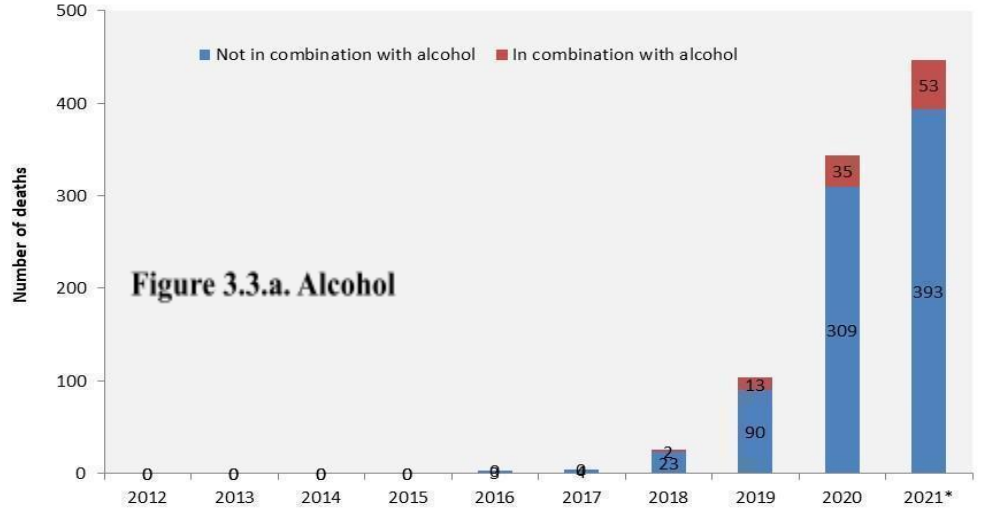
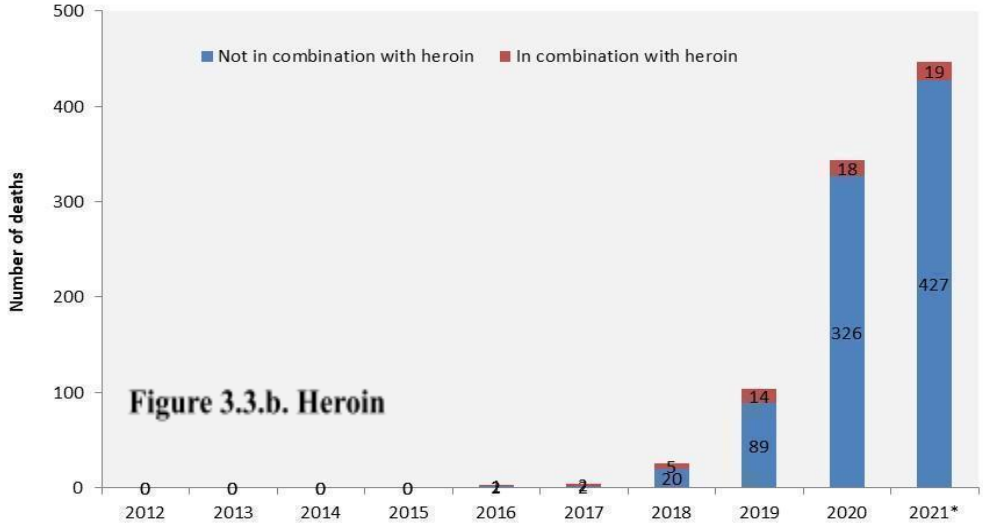
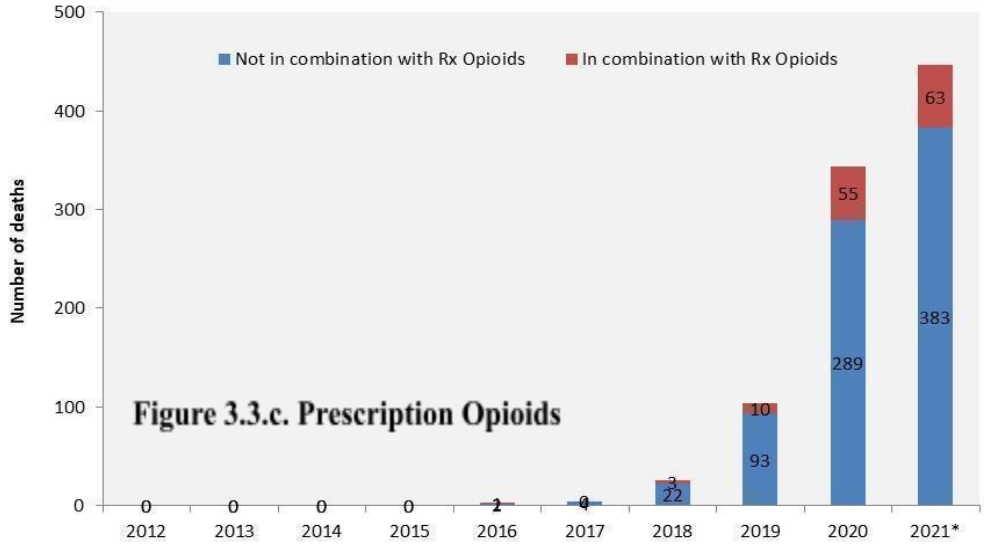


Figure 3.3 shows the number of xylazine-related deaths where another drug was also used. alcohol (3.3.a), heroin (3.3.b), or prescription opioids (3.3.c) were also used, with Maryland data from 2012 through Q3 of 2021. There were fewer than 20 xylazine deaths for alcohol-, heroin-, and prescription opioid-related deaths annually from 2012-2019. For2020, the percentage of xylazine-related deaths in which alcohol, heroin, and prescription opioids were causes of death were lower than for IMF, respectively 10.2%, 5.2%, and 16.0%. Similarly, from Q1-Q3 of 2021, the percentage of xylazine-related deaths in which alcohol, heroin, and prescription opioids were causes of death were, respectively 11.9%, 4.3%, and 14.1%.

Figure 3.3. Number of xylazine-related deaths in combination with other drugs; Maryland, 2012-Q3 2021.







Conclusion

The goal of this analysis was to determine whether VSA should report xylazine as an independent cause of death. We observed that IMF is a contributor of death in nearly all xylazine-related deaths, but xylazine-related deaths comprise a small percentage of all IMF deaths. Our findings are consistent with additional studies indicating that people who use drugs rarely use xylazine alone, as the acute effects are most powerful in combination with opioids.[26] The IMF-xylazine combination is important to monitor, as IMF and xylazine overdose may be resistant to reversal from naloxone.[7]

As there are few xylazine deaths that do not involve IMF, there may be little value added by VSA reporting xylazine as an individual substance. However, data on xylazine in fentanyl-related deaths offer important information. Regular reporting by VSA of fentanyl deaths that occur with xylazine is warranted to monitor the expansion of xylazine among overdose decedents in Maryland.

Chapter 4. Preliminary Findings from the Center for Harm Reduction Services' Rapid Analysis of Drugs Project (RAD)

Authors: Allison Thomson, Jasmine Lopes, Margaret Rybak, Erin Russell

Overview

MDH's Center for Harm Reduction Services (CHRS) implemented the Rapid Analysis of Drugs (RAD) Project in October 2021, with the goal of enhancing what is known about specific drugs being used. Drug checking studies serve the important role of providing information about the drug supply before health problems are observed. Data for the study come from an analysis of paraphernalia voluntarily provided by clients at syringe services programs (SSPs). The Maryland State Police (MSP) also implemented drug checking using the same partnership as CHRS. In this report, the aggregate data on xylazine from both sources are compared.

Introduction

Maryland Department of Health (MDH) identified a need for drug checking to benefit public health surveillance efforts and people who use drugs (PWUD). Drug checking empowers PWUD with knowledge about the drug supply. This knowledge allows PWUD to make informed decisions and utilize various risk reduction strategies. Emerging substances in the drug supply can worsen the overdose crisis by increasing risk for overdose. Surveillance of the illicit drug market fills a gap by monitoring the supply before health outcomes are observed, aligning with the following evaluation question from Maryland OD2A: 8.4 *"How can information about the drug combinations used by clients at syringe services programs be used to inform provider education/academic detailing, target setting for naloxone distribution, and Maryland's response to overdose events including spikes and the emergence of novel substances?".*

MDH's Center for Harm Reduction Services (CHRS) implemented the Rapid Analysis of Drugs (RAD) Project in October 2021. RAD is provided through a partnership with the National Institute of Standards and Technology (NIST).[27] Paraphernalia voluntarily provided by SSP participants are tested utilizing the Direct Analysis in Real Time Mass Spectrometry (DART-MS)[28,29] to better understand the drug market landscape in Maryland, empower PWUD with knowledge about the drug supply to inform decisions and reduce risks, and provide critical information about new and emerging trends in the drug supply to inform harm reduction education and interventions. RAD provides valuable information to SSPs, PWUD, and various public health partners. The Maryland State Police also partner with NIST, giving them the ability to sample items they find in their work and have them analyzed via DART-MS. This chapter will use their xylazine data to provide additional context of the drug market landscape in

Maryland. The purpose of this chapter is to summarize the presence of xylazine detected from samples of paraphernalia supplied by PWUD.

Methods

Maryland currently has 21 SSPs spanning 14 jurisdictions and offering comprehensive services to PWUD, including safer injection supplies, overdose education, and naloxone distribution, wound care, HCV/HIV testing, linkage to care, wellness services, peer support, and more.[30] RAD was piloted at eight SSPs located throughout seven jurisdictions of Maryland. RAD builds on existing policy and infrastructure allowing for Syringe Services Programs (SSP) statewide. Specifically, a statute that protects SSP staff and participants against being arrested, charged, or prosecuted for possession or distribution when it is a direct result of the activities of the program. SSPs have trusting and long-standing relationships with participants, allowing for the integration of drug checking services.

Participating SSPs promote the availability of RAD to their participants and collect samples by swabbing various types of paraphernalia including pipes, cookers, baggies, capsules, and others. These samples are shipped directly to NIST for testing to determine the contents of the sample. Results are made available to SSPs, who share individualized and aggregate results back to participants along with tailored educational materials based on findings. Programs may also choose to use aggregate results to tailor wound care and inform stakeholders of trends. Additionally, CHRS staff hosted monthly collaborative calls with participating programs to share program implementation methods, provide feedback, and talk through RAD findings. These calls gave participating SSPs an opportunity to discuss emerging statewide trends and tailored prevention and infection- related wound care efforts.

Results

From October 2021 to June 2022, 448 samples have been collected and analyzed. As Figure 4.1 shows, RAD samples provided a wide variety of polysubstance results, with 31% (n=139) having only one active ingredient, 58.04% (n=260) having two active ingredients, 4.9% (n=22) having three active ingredients, and 0.7% (n=3) having four active ingredients.

Xylazine was identified in 62.7% (n=281) of the samples. Of those only 6.1% (17 out of 281) contained only xylazine (Table 4.1). Additionally, 85.1% of the samples contained xylazine and one other substance, e.g., opioids, cocaine, cannabinoids, methamphetamine, anabolic steroids, and anticonvulsants. Xylazine was most prevalent in samples that also included opioids; 82.6% of the xylazine samples also contained opioids (232 out of 281).

Table 4.1. Combinations of substances present with xylazine in samples of drug paraphernalia; Rapid Analysis of Drugs Project, MD, October 2021 - June2022			
Xylazine	**Opioids**	**Cocaine**	**Combination of Substances, %, (*n*)**
x			6.1% (17)
x	x		82.6% (232)
x	x	x	5.3% (15)
Note. Polysubstance samples <5 five were suppressed for privacy.			

Xylazine was identified in drug samples collected from each jurisdiction participating in RAD including Baltimore City, Baltimore County, Calvert County, Cecil County, Frederick County, Washington County, and Wicomico County. Figure 4.2 shows that Cecil and Calvert Counties collected the largest number of samples during the pilot. Eighty-six percent of samples in Cecil County contained xylazine (n=154), as did 64.8% of samples from Calvert County 64.8% (n=83).

Figure 4.2. Number of total samples and samples with xylazine in seven counties; Rapid Analysis of Drugs Project, MD, Oct. 2021-Jun. 2022

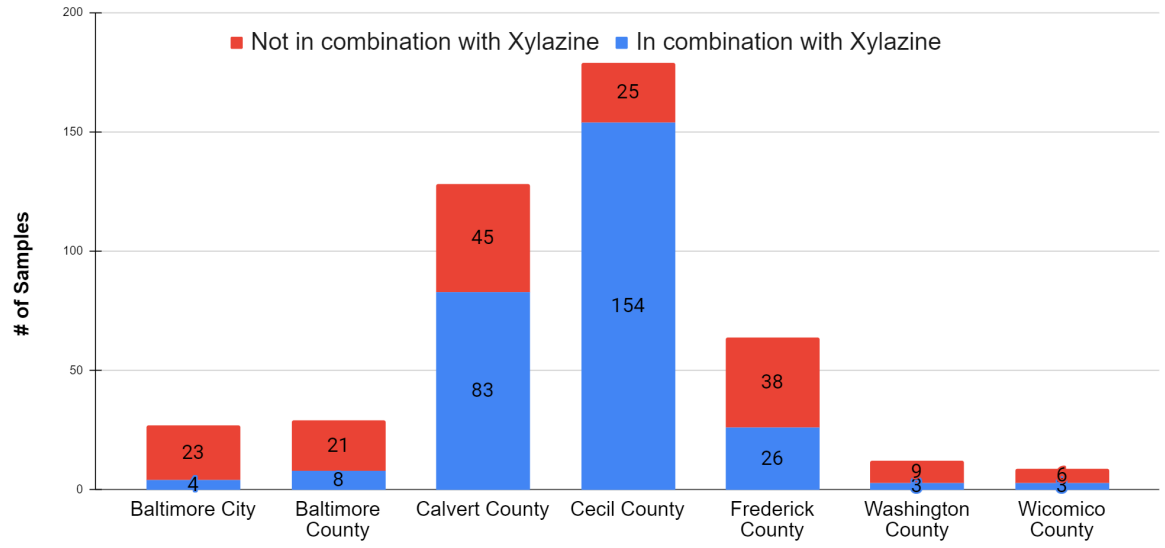
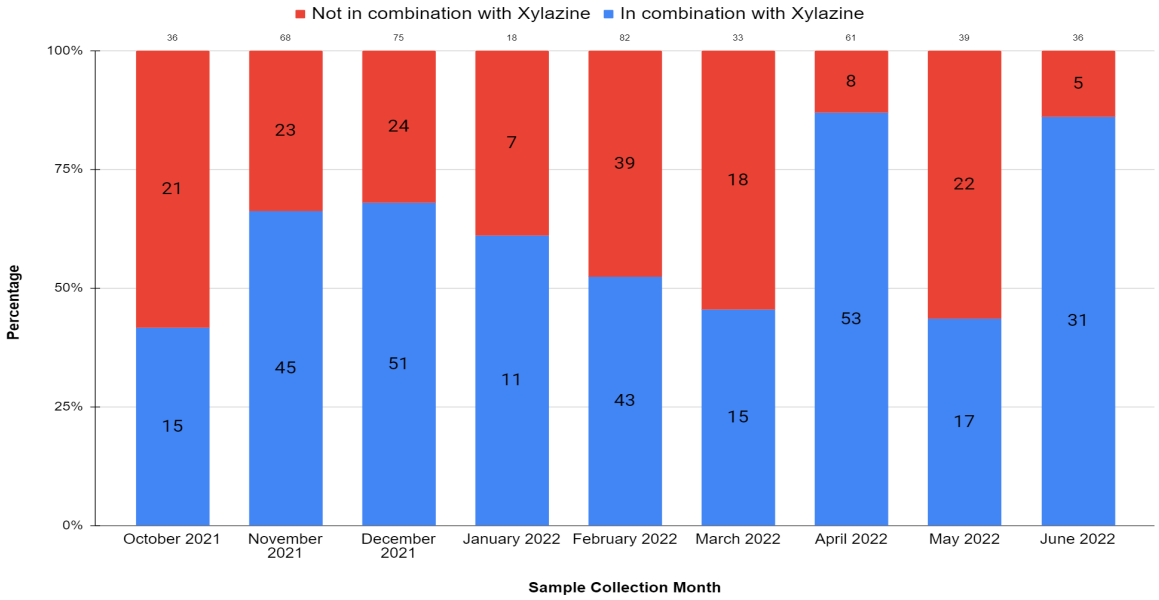


Figure 4.3 shows the number of samples per month, as well as the number that were positive for xylazine over the study period. The percentage of samples containing xylazine increased from October

2021 (41.7%, n=15) to December 2021 (68%, n=51). Later in the pilot, the percentage of samples with xylazine increased, to 86.9% (n=53) in April 2022 and 86.1% (n=31) in June 2022. Six months into the nine-month pilot, more than 50% of all the RAD samples collected contained xylazine.

Figure 4.3. Percentage of Samples in Combination with Xylazine in Maryland from October 2021 to June 2022



Of the MSP samples submitted from July 2021 through December 2022, 19.7% tested positive for xylazine through DART-MS testing with NIST.[41] This is substantially lower than the xylazine presence seen in CHRS samples (62.7%). It is important to note that CHRS RAD samples are coming directly from people who use drugs seeking resources at SSPs, while MSP samples are being obtained by MSP who might not know if an object had contact with drugs. Out of the total number of xylazine positive MSP samples, 88% were seen in combination with other substances. [41] This is similar to the percent of xylazine samples containing other substances in CHRS samples (85.1%). The combinations seen commonly were with fentanyl (72%), cocaine (38%), mannitol (22%), caffeine (16%), quinine (14%), and other drugs (each below 10% of samples). [41]

Conclusion

The Rapid Analysis of Drugs Project (RAD) allows programs to create and provide tailored harm reduction messaging, education materials, and risk reduction strategies to the people they serve based on local and statewide results. CHRS and local programs can tailor education to current trends in results, and inform participants of their results as well as community trends. SSPs have increased knowledge on

substances causing wounds which has allowed for improved treatment of injection-related wounds. Prior to RAD, many SSPs and harm reduction programs were unaware of xylazine presence in Maryland's drug market. RAD collects data from 7 jurisdictions, and findings from that project should be interpreted to indicate a need for further study rather than as a basis for drawing definitive conclusions about xylazine in Maryland. MSP drug checking data also indicate the presence of xylazine in Maryland's drug supply, which strengthens our conclusion that xylazine is present in the state's drug supply. The CHRS data and MSP data are each representative of specific sample populations. To gain a better understanding of the real time drug market in Maryland, drug checking will need to expand to reach the broader population.

Since the RAD pilot our 8 participating programs have found RAD beneficial to their participants. After our feedback call many of our programs shared their thoughts on the importance of participating. These included benefits for participants, staff, and the community. Participants of RAD were able to learn what was in their drugs, and get tailored services including wound care specifically for xylazine. Staff were able to see the pattern of drugs within their community and region. They also were able to get a more comprehensive look at the drug market, and assist with wound care. Due to the information shared by RAD, programs had chances to teach the community and stakeholders about drugs within the community and even advocate for PWUD. Although there were many facilitators within RAD, there were still a few barriers. Some included the length of time it took for results to be shared with participants. Another barrier included the level of trust from PWUD and the safety of participants and staff.

Chapter 5. Xylazine Testing at the Office of the Chief Medical Examiner & Xylazine Concentration Report

Authors: Rachel Alinsky, Rebecca Phipps, Sharmin Hossain, Renee M. Johnson, Kelly Dunn

Overview

The Maryland Xylazine Workgroup noted a need for more rigorous data quantifying the amount of xylazine in overdose decedents to develop recommendations about COD designations. Responding to this need, OCME implemented the "Xylazine Toxicology Project" in February 2022. The purpose of the project was to quantify xylazine concentrations among recent opioid overdose decedents. This Chapter summarizes the results of the Xylazine Toxicology Project.

Introduction

The emergence of xylazine in recent overdose deaths raises the question of whether and under what circumstances it should be designated by medical examiners (ME) as a cause of death (COD). Xylazine is an alpha-2-adrenergic agonist that has been used since the 1960s in veterinary medicine as a sedative, analgesic, and muscle relaxant.[15,31,32] Xylazine has never been approved for human use because early studies demonstrated it can result in severe hypotension and depression of the central nervous system. However, intentional misuse of xylazine has been reported since 2012, whereupon it acts as an analgesic, hypnotic, and anesthetic.[31–34] Given its acute effects, it is likely that xylazine contributes to overdose deaths independently or synergistically, i.e., works with another drug to cause overdose.

We reviewed the literature to ascertain what constitutes a toxic dose of xylazine. Because human studies on xylazine were terminated due to the adverse effects, the majority of pharmacokinetic evidence regarding xylazine toxicity comes from case reports. The published case reports show a wide range of potentially toxic xylazine concentrations, ranging from 5 to 4,600ng/mL. The Maryland Office of the Chief Medical Examiner (OCME) has limited experience with cases in which xylazine concentration has been quantified. They identified one prior case that involved injected xylazine administration in a non-overdose suicide; the blood xylazine concentration was 2,300 ng/mL in this case, and no other drugs were detected in blood. Toxicity of xylazine is thought to depend on the route of administration (i.e., injected versus smoked). Xylazine is more toxic when co-used with alcohol or other drugs.[35,36] Notably, xylazine appears to be toxic at lower concentrations when in the presence of fentanyl, suggesting a synergistic effect.[36]

The purpose of the Maryland Toxicology Project was to conduct a pilot to quantify xylazine concentrations among recent opioid overdose decedents. Findings will build upon OCME experience and the existing literature, and will provide new information to determine the role of xylazine played in Maryland opioid overdose deaths.

Methods

The established procedures for toxicology testing at OCME enhanced the feasibility of this project. All overdose decedents receive a post-mortem examination and undergo a series of toxicology testing that includes a wide range of therapeutic and recreational drugs. Postmortem toxicology testing consists of blood alcohol concentration assessment, immunoassay screening (morphine, benzodiazepines, and oxymorphone), an alkaline drug screen (antidepressants, antihistamines, benzodiazepines, cardiac drugs, narcotics, and neuroleptics, among others), and, in some cases, an acidic/neutral drug screen (antiepileptics and barbiturates). Confirmation and quantitation testing is performed based on the results of the screening tests. Xylazine has been included in this toxicology panel since 2006.

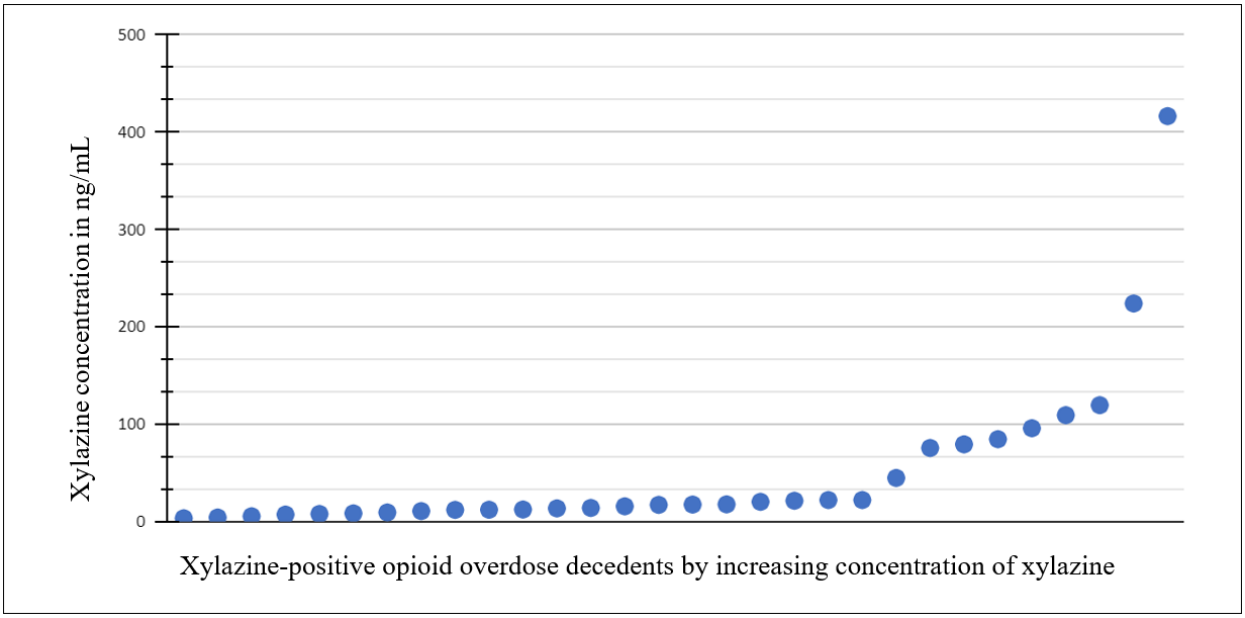
We performed a pilot to quantify xylazine concentrations among recent opioid overdose decedents who tested positive for xylazine as part of the routine toxicology testing performed by OCME. Inclusion criteria were death by opioid overdose, post-mortem examination by OCME, and xylazine positivity in blood serum testing. When xylazine is found to be present in the blood, this is indicative of active drug circulating in the body at the time of death, suggesting recent use. Conversely, if xylazine is found in the urine but not the blood, this suggests use sometime within the past several days, but that it would not have been producing an effect at the time of the death. We received the MDH IRB approval in March 2022 and the testing project was underway in April 2022. Results were received by May 2022.

Thirty consecutive cases were identified that met study criteria, and blood samples were collected and analyzed at a third party laboratory in Pennsylvania to determine the concentration of xylazine as well as all other prescription and illicit drugs that were found on screening toxicology. Variables of interest including decedent demographics (age, sex, race/ethnicity), concentration of xylazine, type and concentration of opioids (including fentanyl, heroin, and prescription opioids), and presence of psychostimulants, alcohol, and other Central Nervous System (CNS) depressants.

Results

Full quantitative toxicology testing was performed on 30 xylazine-positive opioid overdose decedents. The mean age of decedents was 42.8 years, approximately two-thirds were male, and two-thirds were Hispanic/Latino. Xylazine concentrations ranged from 3.3 to 416 ng/mL, with 28 decedents having concentrations below 125 ng/mL (Figure 5.1).

Figure 5.1. Xylazine concentrations (ng/mL) among xylazine-positive opioid overdose decedents (n=30)



We classified opioid overdose decedents into three groups based on concentration of xylazine, i.e., <10 ng/mL, 10-20 ng/mL, and >20 ng/mL. More than one-half (n=17) were in the bottom two categories. There were 7 decedents with concentrations <10 ng/mL, 10 cases with concentrations between 10-20 ng/mL, and 13 cases with xylazine concentrations >20 ng/mL (Table 5.1).

Table 5.1. Classification of decedents (n=30) by concentration of xylazine (ng/mL)

Concentration	*n*	Mean	(SD)
<10 ng/mL	7	6.5	(2.1)
10-20 ng/mL	10	14.2	(2.4)
>20 ng/mL	13	102.6	(105.5)

Xylazine was found to be present with a combination of multiple other substances. As seen in Table 5.2, 100% of cases were positive for IMF and/or fentanyl analogs; fentanyl concentrations ranged from 2.0 ng/mL to >80 ng/mL, and there was no correlation between xylazine concentration and fentanyl concentration. In 23% of the cases, decedents were positive for prescriptions opioids (in addition to fentanyl), including methadone, morphine, and tramadol; several decedents tested positive for two prescription opioids. Stimulants were found in 50% of cases, of which 37% tested positive for cocaine, and 13% were positive for amphetamine or methamphetamine. Benzodiazepines were present in 13% of decedents, and included diazepam, flubromazepam, chlordiazepoxide, and bromazolam. Ethanol was found to be positive in 16% of cases using a cut-off of 0.05% blood alcohol concentration. Miscellaneous other substances included antidepressants (23%), antihistamines (17%), and quinine – a

known fentanyl adulterant (50%).[37,38] There were other combinations of substances also found among decedents: prescription opioid + stimulant (1 case), prescription opioid + stimulant + ethanol (1 case), prescription opioid + ethanol (1 case), prescription opioid + benzodiazepines (1 case), stimulant + ethanol (2 cases), stimulant + benzodiazepines (3 cases). stimulant (1 case), prescription opioid + stimulant + ethanol (1 case), prescription opioid + ethanol (1 case), prescription opioid + benzodiazepines (1 case), stimulant + ethanol (2 cases), and stimulant + benzodiazepines (3 cases).

Table 5.2. Substances found in xylazine-positive opioid overdose decedents (n=30)

SUBSTANCES DETECTED	% of cases positive
Fentanyl and Fentanyl analogs	**100%**
Prescription Opioids[1]	**23%**
Methadone	13%
Morphine	10%
Tramadol	7%
Stimulants	**50%**
Cocaine	37%
Amphetamine, methamphetamine	13%
Benzodiazepines	**13%**
Alcohol (Blood Alcohol Concentration >0.05%)	**17%**
Miscellaneous	
Antidepressants	23%
Antihistamines	17%
Quinine	50%

[1] Sub-categories sum to more than 23% as several decedents were positive for more than one prescription opioid.

Conclusions

This pilot demonstrated the distribution of xylazine concentrations found in 30 overdose decedents in Maryland, all of whom had opioids as a cause of death. Seven decedents had concentrations of xylazine below 10 ng/mL, suggesting its lethality at low doses in combination with IMF. The xylazine concentrations in this pilot study ranged from 3.3 to 416ng/mL, which is similar to prior published case studies that demonstrated xylazine toxicity at concentrations as low as 5ng/mL. All 30 decedents had IMF as a cause of death, highlighting that xylazine is likely an adulterant in IMG. Seventeen percent of the decedents were positive for alcohol and one-half were positive for stimulants.

Chapter 6. Workgroup Findings & Recommendations

Authors: Renee M. Johnson, Marie Stratton, Sharmin Hossain, Taylor Parnham, for the Maryland Xylazine Workgroup

Major Findings

The purpose of this report was to summarize the work of the Maryland Xylazine Workgroup. In Chapter 1 we describe the emerging threat of xylazine, and Chapters 2 and 3 present information about xylazine toxicology among overdose decedents in Maryland. We report that 17% of opioid overdose decedents in 2020 were xylazine positive, that the number of xylazine-positive overdose decedents has grown in recent years, and that most decedents who test positive for xylazine had IMF as a cause of death.

In Chapter 4 we reviewed data from the "Rapid Analysis of Drugs" (RAD) project, which involves testing drug paraphernalia donated from volunteer participants who use drugs. We found that information about xylazine in the drug supply was consistent with what we learned from overdose decedents. Xylazine was identified in 62.7% (n=281) of the samples during the pilot phase of RAD. Xylazine was most prevalent in samples that also included opioids; 82.6% of the xylazine samples also contained opioids (232 out of 281).

In Chapter 5 we briefly summarize a pilot conducted on 30 overdose decedents who tested positive for xylazine in an initial OCME toxicology report; the purpose was to generate new information about quantification of xylazine in post-mortem toxicology overdose decedents. Findings showed that xylazine-positive decedents usually had fentanyl and stimulants as CODs. Xylazine concentrations ranged widely – most decedents had concentrations between 3.3 to 125ng/mL, and two had concentrations above 200 ng/mL. Xylazine would be typically considered to contribute death if it produces a similar effect or acts by the same mechanism as the drugs significantly contributing to death (usually fentanyl). However, not enough is known about the drug to make cause of death determinations.

Recommendations

It is critical that the state of Maryland is prepared to manage xylazine should it become more prominent. Therefore, we present recommendations for practice, surveillance, and policy development.

Recommendation 1 – Build and maintain an infrastructure to respond to the problem.

Maryland's strong infrastructure for overdose response can be leveraged to address the potential threat of xylazine. Carrying out this recommendation will include: [a] continuing to meet as a Workgroup, [b] identifying additional stakeholders to join the group, and [c] seeking funding to expand on the initial work if needed. We discussed reaching out to the following stakeholders to solicit their

participation in the Workgroup: Overdose Fatality Review, Maryland Opioid Operational Command Center, and Maryland Office of Preparedness & Response.

Recommendation 2 – Continue to monitor the issue.

Our Workgroup considers the potential threat of xylazine to be substantial enough to warrant continued monitoring. We committed to continuing to: [a] review the literature on the topic, [b] monitor issuance of public health advisories, law enforcement alerts, and policy initiatives, [c] analyze the data available to generate new information about xylazine in the drug supply and in the toxicology of people who have overdosed. We also discussed identifying additional sources of data that could be used to better understand the issue, such as data on calls to poison control or emergency department visits. We plan to investigate options for assessing capacity of xylazine testing among overdose patients within the healthcare system, as well as capacity for treating xylazine-related skin and soft tissue infections. It is currently very low.

Recommendation 3 – Disseminate information about the problem to stakeholders in Maryland and beyond.

The Workgroup values disseminating information about xylazine to agencies, organizations, and communities across the state with the goal of facilitating an effective and broad response to the problem. This includes sharing findings with local health departments, harm reduction organizations, people who use drugs, law enforcement agencies, and others upon request. We also noted that information should not just flow one way – we are eager to learn from state and local agencies and use their knowledge to inform programs and policy development.

Recommendation 4 – Investigate factors underlying the emergence of xylazine in the drug supply.

Our final recommendation is about understanding the source of xylazine and how it makes its way into the drug supply. Completing this recommendation will involve working with law enforcement in Maryland and neighboring states, as well as reviewing data and reports on drug trafficking, drug seizures, and trends in the drug supply (e.g., from National Forensic Laboratory Information System [NFLIS], the National Drug Early Warning System [NDEWS]).[39,40] Xylazine is approved for veterinary use, and it is not clear whether it is being diverted from the legal to the illicit market. We hope to work with the Department of Agriculture and the Board of Veterinary Examiners and examine the potential for diversion.

Summary

Xylazine is an emerging public health threat that could exacerbate the overdose crisis and complicate overdose prevention. Our findings provide new information about xylazine in Maryland, and underscore the importance of continuing to investigate its role in overdose. Given the potential threats posed by xylazine, we plan to continue meeting as a Workgroup to ensure a strong infrastructure for monitoring the problem, dissemination of information, and mounting a comprehensive and coordinated response.

Chapter 7. Addendums with more recent xylazine data analysis

Chapter 2 Addendum

Xylazine in Post-Mortem Toxicology Screening of Opioid Overdose Decedents in Maryland (2021)

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Introduction

Xylazine is an emerging public health threat that could exacerbate the overdose crisis and complicate prevention of overdose fatalities. Analysis of overdose death data can provide needed information about xylazine in Maryland to guide prevention and policy development. Previously, we summarized 2020 data on xylazine in the post-mortem toxicology of opioid overdose decedents in Maryland. Those findings are presented in *Xylazine in Maryland: An Initial Report of the Maryland Xylazine Workgroup 2022.* The present analysis reviews data from 2021 and summarizes monthly trends from 2020-2021.

Methods

Data are from Maryland's State Unintentional Drug Overdose Reporting System (SUDORS). SUDORS case criteria includes all drug poisoning deaths. We used data from 2021 for descriptive analyses, and data from 2020-2021 for a trend analysis. We restricted analysis to adult decedents who had opioids as a cause of death (COD). Decedents were classified as xylazine-positive or xylazine-negative based on post-mortem toxicology testing.

Descriptive Analysis of Xylazine in Opioid Overdose Deaths (2021)

Drug use and death circumstances variables for the descriptive analysis included: [1] whether illicitly manufactured fentanyl (IMF) was a COD, [2] whether heroin was a COD, [3] whether there was

any evidence of drug injection, and [2] whether naloxone had been administered. Demographic variables included: age category (i.e., <25 years, 25-55 years, >55 years), sex (male, female), and race/ethnicity (i.e., White, non-Hispanic; Black, non-Hispanic; and all other groups combined). We also summarized data on county where the overdose took place. We employed basic analytic measures such as counts and proportions. An omnibus chi-square test was performed to statistically test the distribution of xylazine-positive cases by demographic subgroups and drug use circumstances. For subgroups with more than two categories (i.e., race/ethnicity, location, and age group), we used logistic regression to test for pairwise differences across categories.

Trend Analysis of Xylazine-Positive Opioid Overdose Decedents (Jan. 2020-Dec. 2021)

We estimated the proportion of opioid overdose decedents who were xylazine positive by month, from January 2020 through December 2021. We used a time series regression model to characterize the statistical significance of the average monthly change in the proportion of opioid overdose decedents who were xylazine-positive. We tested for a linear change in trend using month as a predictor variable (i.e., January set as 1, February set as 2, and so on). In a subsequent model, we tested whether there was a change in the direction of the trend by adding a quadratic term into the model (i.e., January set as 1, February set as 4, March set as 9, and so on).

Results

Of the 2,496 opioid overdose decedents in 2021, 27.8% (n=693) were xylazine-positive (Table 1). A smaller proportion of Hispanic/Latino decedents were xylazine-positive compared to non-Hispanic White decedents (16.8% vs. 29.7%, p=0.009). There was no difference in the proportion of non-Hispanic Black and non-Hispanic White decedents who were xylazine-positive (26.6% vs. 29.7%, p=0.096). Differences in the proportion who were xylazine-positive by age category were modest. More than 60% of overdoses in Maryland in which the decedent was xylazine-positive occurred in either Baltimore City (n=316) or Baltimore County (n=106).

Table 2 describes drug use circumstances of opioid overdose decedents by xylazine toxicology. Xylazine-positive decedents were significantly more likely to have IMF or heroin as CODs than xylazine-negative decedents. Among decedents who were xylazine-positive, 99.6% had IMF as a COD and 3.5% had heroin as a COD. Xylazine-positive (vs. negative) decedents were significantly more likely to have had evidence of drug injection (27.3% vs. 16.3%, p<0.001), and were more likely to have been administered naloxone (19.1% vs. 15.6%, p<0.05).

Figure 1 shows the proportion of opioid overdose decedents who were xylazine positive by month, from January 2020 through December 2021. The proportion was lowest at the beginning of the time period (3.8%), peaked in February of 2021 (32.4%), and was at 25.5% at the end of the time period.

For each month from September 2020 forward, the proportion of xylazine-positive decedents exceeded 15%. The test for a linear trend was statistically significant (β=3.28, p<0.001), indicating an average increase in the proportion of xylazine-positive decedents of 3.2 percentage points each month. A subsequent test to assess a change in the direction of the trend was modest, but statistically significant (β=-0.11, p<0.001). That result suggests that there was a change in the direction of the trend, specifically a decrease following an increase.

Conclusion

This analysis of opioid overdose data suggests that xylazine is commonly-detected among decedents in Maryland, especially in Baltimore City and Baltimore County. More than one-fourth (27.8%) of Maryland decedents in 2021 were xylazine-positive, an increase from the 2020 estimate of 17.1%. Nearly all of the xylazine-positive decedents in Maryland had IMF as a cause of death, which strongly suggests that xylazine is being used with IMF.

An analysis of the proportion of opioid overdose decedents who were xylazine positive by month (from January 2020 through December 2021) indicates that the proportion was lowest in early 2020, peaked early 2021, and may have leveled off thereafter. To further investigate this trend, staff at the the Center for Environmental, Occupational, & Injury Epidemiology (Georgette Lavetsky, MHS; Chief) within the Environmental Health Bureau (Clifford S. Mitchell, MD, MS, MPH; Director) conducted a preliminary analysis of SUDORS data from January through June of 2022. Their analysis showed that the monthly average of xylazine-positive decedents for that time period was 18.5%. (It is worth noting that their analysis included decedents of all ages and was not restricted to those with opioids as a COD, so that estimate is not entirely comparable to what is reported above.) Taken along with findings from the RAD study and from Maryland Vital Statistics Administration data, the trend analysis provides early evidence that the proportion of overdose decedents who are xylazine-positive is no longer increasing. Although this is promising news, there were >20 xylazine-related deaths per month throughout all of 2021 and Maryland is a long way from the January 2020 estimate of <5% of opioid overdose decedents being xylazine-positive. Additionally, drug markets change quickly and it may not be not unusual for there to be variation in specific drugs that contribute to overdose, even in 6-month periods. It remains critical to continue monitoring the proportion of opioid overdose decedents who are xylazine positive to assess the severity of xylazine as a threat to the health of Marylanders.

Based on the findings presented here and from other Maryland agencies, we provide three recommendations for consideration. First, we need to better understand xylazine-related morbidity; this information would complement the data on mortality and provide a more complete picture of the problem of xylazine in Maryland. It is critical to determine the proportion of people with non-fatal

overdose who are xylazine-positive, and also to identify the prevalence of other xylazine-related health problems, such as skin infections. Second, it will be critical to monitor the demography and geography of overdose involving xylazine to develop targeted prevention strategies and ensure that prevention strategies reach vulnerable populations. Data from 2021 highlight notable disparities. Most xylazine-involved overdose deaths occurred in the greater Baltimore area, and 41% of xylazine-positive overdose decedents are Black, despite that Black people comprise 30% of the state's population. Third, qualitative assessment with people who sell and use IMF could generate critical knowledge to inform prevention and policy development. A qualitative assessment could address some of the many unknowns about xylazine – such as motivations for and awareness of using it, perceptions about its effects (i.e., how it makes people feel), knowledge about and experience of its health risks, risk reduction behaviors and communication, willingness to adopt strategies to avoid it (e.g., use of test strips), service utilization, and how and why it is added to IMF.

Table 1. Demographic and geographic characteristics of xylazine-positive opioid overdose decedents; Maryland, 2021

	Total	Xylazine positive		*p*
		%	*n*	
All Decedents	2,496	27.8%	693	---
Sex				
Male	1,808	28.7%	518	Ref.
Female	688	25.4%	175	0.109
Race/Ethnicity				
White, Non-Hispanic	1,278	29.7%	379	Ref
Black, Non-Hispanic	1,066	26.6%	283	0.096
Hispanic/Latino	95	16.8%	16	0.009
All other/unknown	57	26.3%	15	0.589
Age Category				
<25	118	27.1%	32	0.613
25-55	1,687	29.0%	489	0.045
>55	690	24.9%	172	Ref.
County of Overdose				
Baltimore City	1,001	31.6%	316	<0.001
Baltimore County	347	30.6%	106	0.009

All Other/Unknown	1,148	23.6%	271	Ref.

Note. Analyses represent pairwise comparisons and all the categories were compared with the reference category. Numbers may not sum to total due to missing data.

Table 2. Death and drug use circumstances by post-mortem xylazine toxicology; Maryland, 2021 (n=2,496)

	Xylazine Positive ***n*** **= 693**	**Xylazine Negative** ***n*** **= 1,803**	***p***
IMF was a cause of death	99.6%	90.9%	<0.001
Heroin was a cause of death	3.5%	1.9%	<0.019
Evidence of injection	27.3%	16.3%	<0.001
Administered naloxone	19.1%	15.6%	0.040

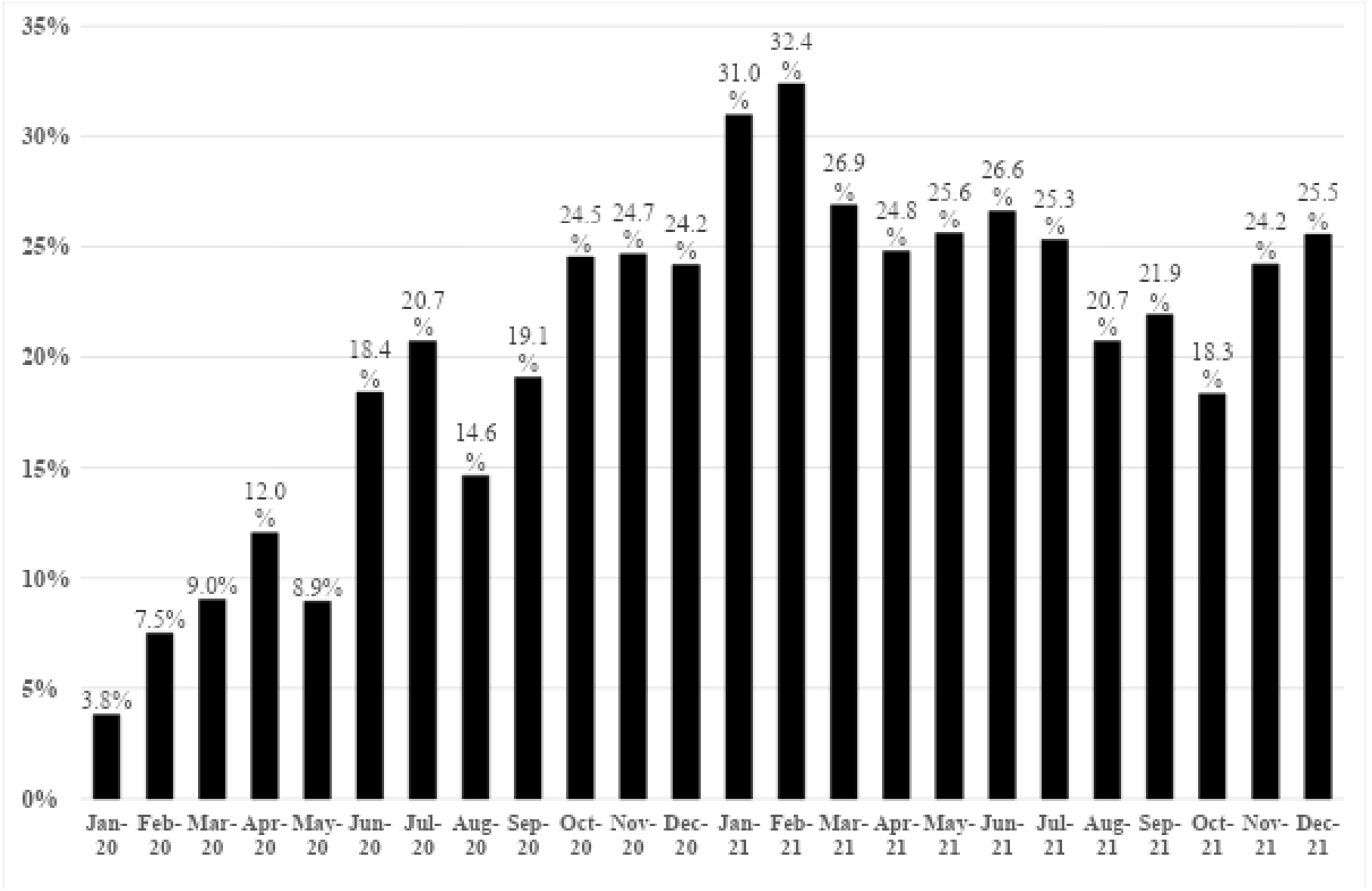


Figure 1. Proportion of opioid overdose decedents who were xylazine positive, by month; Maryland. 2020-2021

Chapter 4 Addendum

Updated Findings from the Center for Harm Reduction Services' Rapid Analysis of Drugs Project (RAD)

Authors: Margaret Rybak and Jasmine Lopes

Overview

Maryland's Center for Harm Reduction Services (CHRS), Rapid Analysis of Drugs (RAD) program completed a pilot year at 8 syringe service programs (SSP) from October 2021 to September 2022. In September 2022, the RAD program expanded in two ways: 1) to be an available service for all SSPs in Maryland and 2) to test syringes. As of June 2023, 15 of the 22 SSPs in Maryland participate in RAD. Staff capacity has been the biggest barrier for SSPs who have not begun drug checking efforts at their program. SSP staff had conveyed strong feedback that syringe testing would allow them to broaden their testing efforts. This testing was initially excluded from the pilot study in order to finalize a syringe testing safety protocol with the National Institute of Standards and Technology (NIST). The Maryland State Police (MSP) and High Intensity Drug Trafficking Area (HIDTA) have continued to test seizure samples through their partnership with NIST separately from CHRS. Those aggregate results are included below for comparison.

Results

Since May 2023, 1417 samples have been collected and analyzed - 545 samples were collected during the pilot study (October 2021 - September 2022) and 956 have been collected since the expansion of RAD (October 2022 - May 2023). The results below will divide out the pilot and post pilot samples, in order to better understand the impact of additional operational RAD programs and larger sample size.

Xylazine was identified in 40.2% (n=569) of samples. Of those only 3.3% (n=19) contained only xylazine (Table A4.1). Additionally, over 80% of those samples contained xylazine and one other substance compound, e.g., heroin and semi-synthetic opiates, fentanyl and related compounds, cocaine and related compounds, cutting agents and diluents, pharmaceutical, and miscellaneous compounds. Xylazine was commonly seen in combination

with fentanyl and related compounds (85.3%, n=486). RAD rarely tested samples that contained only xylazine (3.3%).

Table A4.1: Combinations of substances present with xylazine in samples of drug paraphernalia; Rapid Analysis of Drugs Project, MD, Oct. 2021 - May 2023							
Xylazine & Related Compounds	**Heroin & Semi-synthetic opiates**	**Fentanyl & Related Compounds**	**Cocaine & Related Compounds**	**Cutting Agents & Diluents (Non-Pharmaceutical)**	**Pharmaceuticals (except Xylazine & Related Compounds)**	**Miscellaneous Compounds**	**Combination of Substances, %, (*n*)**
x							3.3 (19)
x		x					35.1 (200)
x				x			2.3 (13)
x	x	x					1.1 (6)
x		x		x			34.4 (196)
x		x			x		2.6 (15)
x			x	x			1.1 (6)
x		x	x	x			5.6 (32)
x		x		x	x		3.5 (20)
x		x		x		x	1.9 (11)
x		x	x	x	x		1.1 (6)
Note. Polysubstance samples <5 five were suppressed for privacy.							

Xylazine was identified in drug samples collected from each jurisdiction participating in RAD including Allegany County, Baltimore City, Baltimore County, Calvert County, Cecil County, Frederick County, Harford County, Howard County, St. Marys County, Washington County, and Wicomico County. Figure A4.1 shows that Cecil and Calvert County have the largest number of

samples containing xylazine. Eighty-five percent of samples in Cecil County contained xylazine (n=265), as did 75.5% of samples from Calvert county (n=139).

Figure A4.1: Number of total samples and samples with xylazine in seven counties; Rapid Analysis of Drugs Project, MD, Oct. 2021 - May 2023

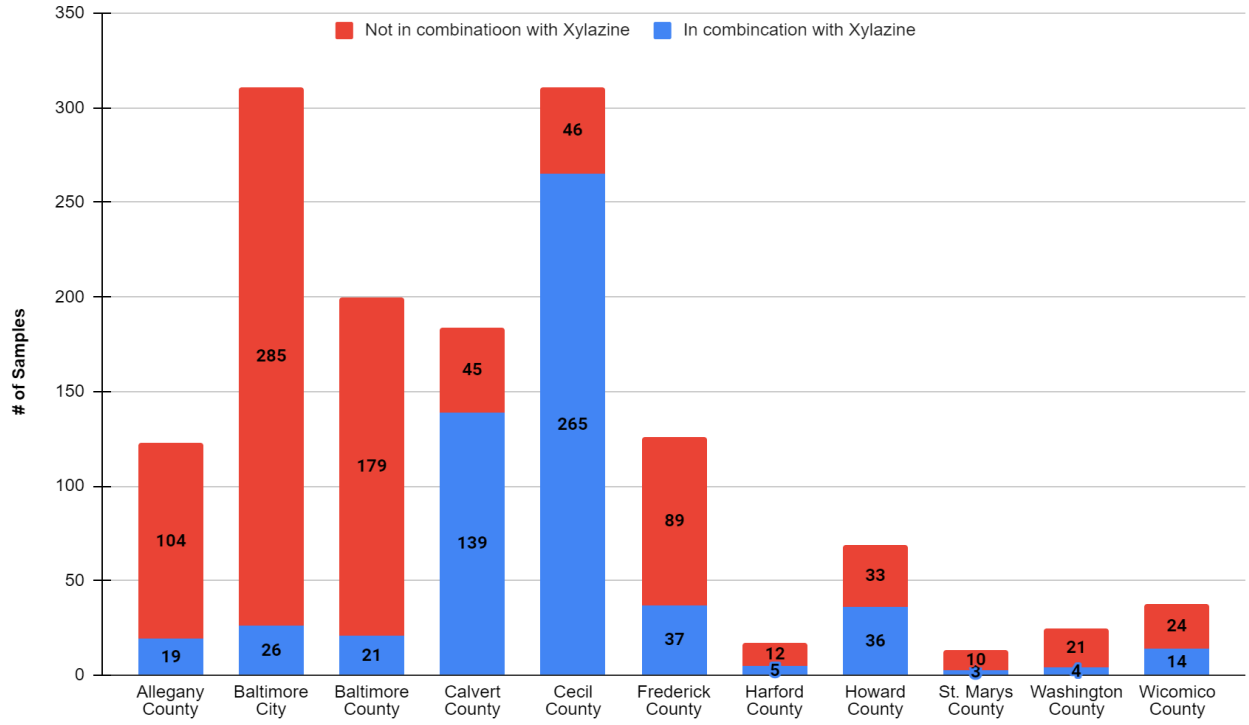
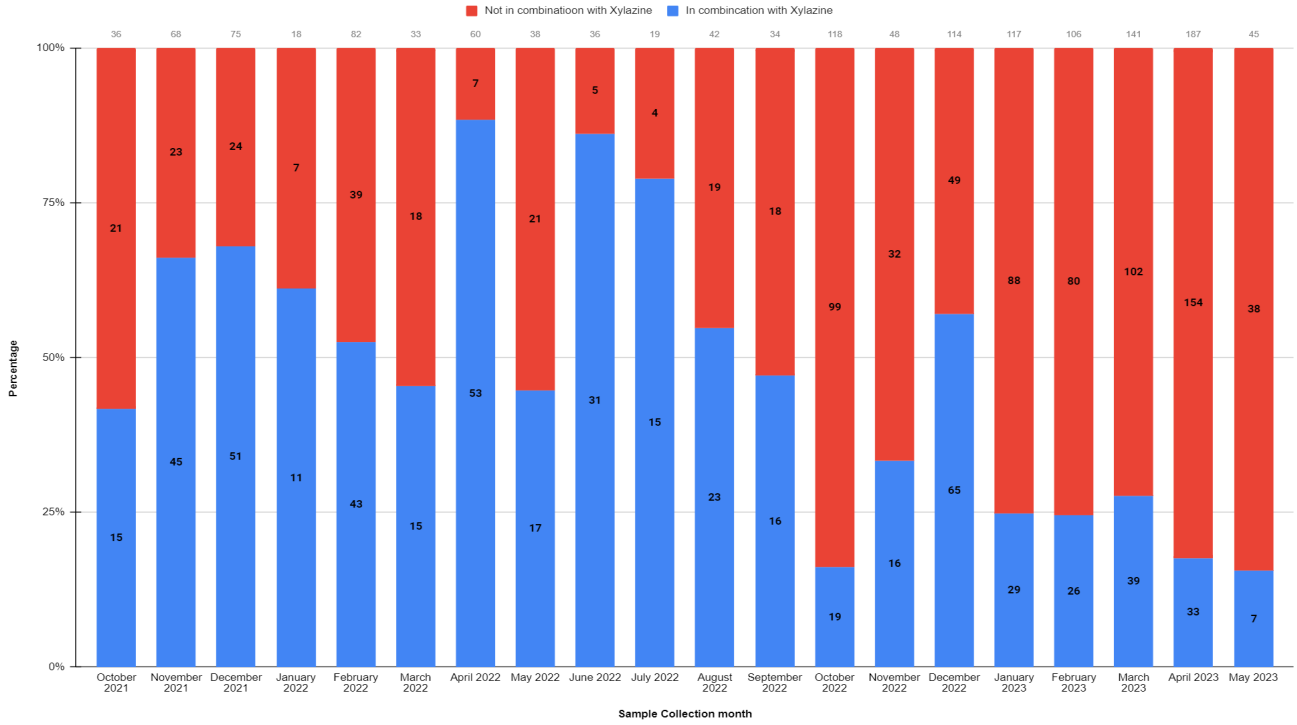


Figure 4.2 shows the number of samples per month, as well as the number that were positive for xylazine. The percentage of samples containing xylazine increased from October 2021 (41.7%, n=15) to December 2021 (68%, n=51). Later in the pilot, the percentage of samples with xylazine increased, to 88.3% (n=53) in April 2022 and 86.1% (n=31) in June 2022. In July 2022 (80%, n=15) the number of samples containing xylazine began to decrease. There was a slight increase in November 2022 (33.3%, n=16) and December 2022 (57%, n=65). Since the expansion of RAD (October 2022 - May 2023) only 26.7% of samples contained Xylazine.

Figure A4.2: Percentage of Samples in Combination with Xylazine in Maryland from October 2021 to May 2023



The aggregate MSP/ HIDTA data shows a slight decrease in the number of xylazine-positive seizure samples from May 2022 to April 2023 (Figure A4.3). This data is not inclusive of the entire state, as some agency labs do not submit their data to HIDTA. Additionally, since Xylazine and Medetomidine are not scheduled, some labs do not test for them. The highest reported month was July 2022 with 313 samples containing xylazine (Figure A4.3). The lowest reported month was December 2022 with 157 samples containing xylazine (Figure A4.3).

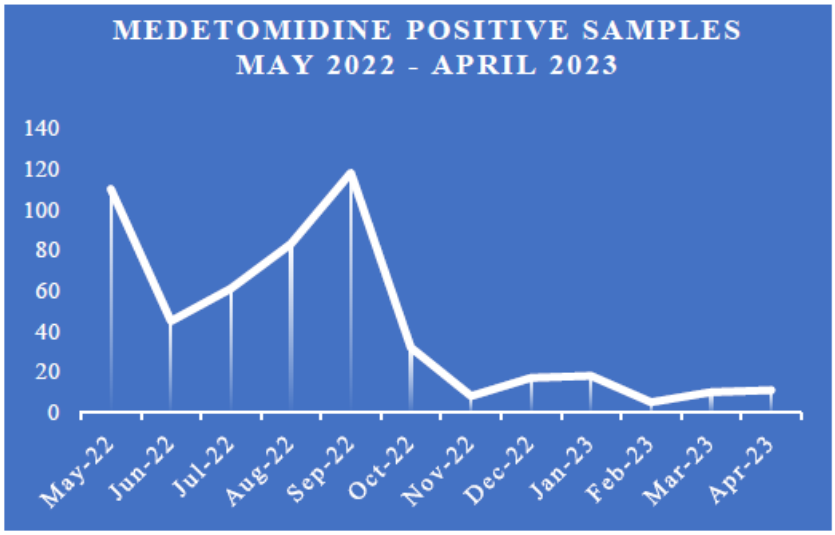
Figure A4.3: Number of samples positive for xylazine within MSP/ HIDTA secure drug checking data in Maryland from May 2022 to April 2023

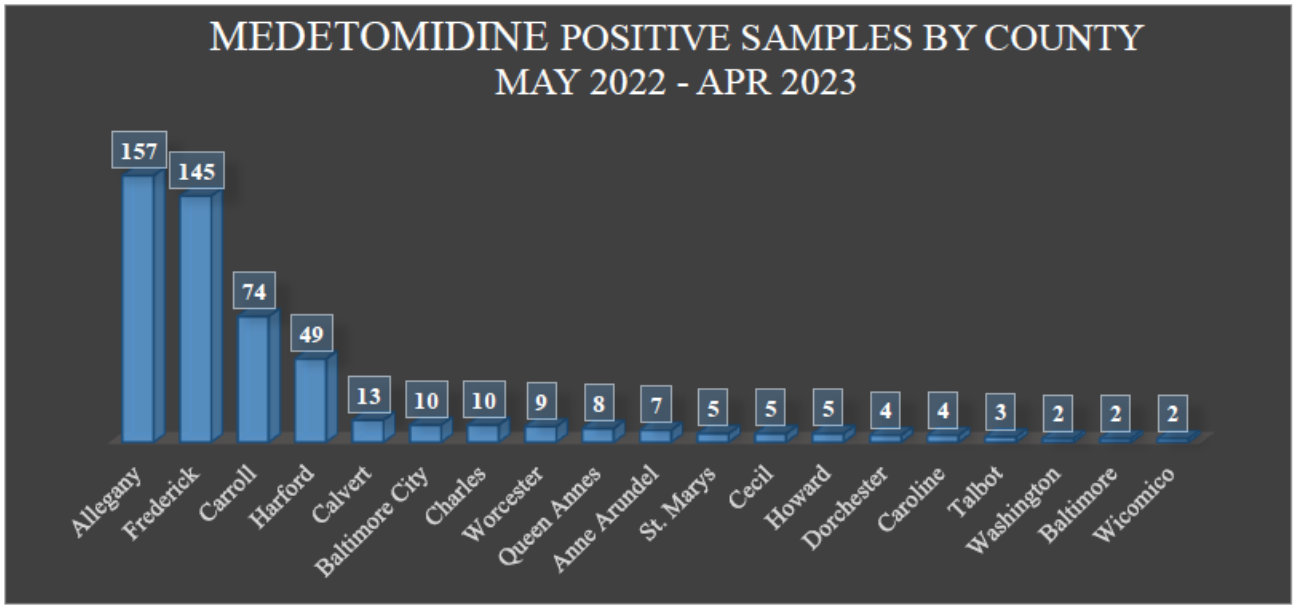
DATE	XYLAZINE
May-22	318
Jun-22	213
Jul-22	313
Aug-22	242
Sep-22	206
Oct-22	225
Nov-22	190
Dec-22	157
Jan-23	250
Feb-23	207
Mar-23	198
Apr-23	166

There was concern that medetomidine, another veterinary substance, might become more prevalent as slightly lower rates of xylazine continue to be the trend. Based on MSP/HIDTA data, this does not appear to be the case (Figure A4.4). Medetomidine has been seen in combination with fentanyl, cocaine, and xylazine. The presence of medetomidine has decreased throughout Maryland within the past 6 months (Figure A4.4).

Figure A4.4: Number of samples positive for medetomidine within MSP/ HIDTA secure drug checking data in Maryland from May 2022 to April 2023

DATE	MEDETOMIDINE
May-22	110
Jun-22	45
Jul-22	61
Aug-22	83
Sep-22	118
Oct-22	32
Nov-22	8
Dec-22	17
Jan-23	18
Feb-23	5
Mar-23	10
Apr-23	11





Conclusion

The Rapid Analysis of Drugs (RAD) program has allowed CHRS and SSPs to monitor changes in the Maryland drug supply as they are occuring. The expansion of RAD added 7

additional programs for a total of 15 testing SSPs. The increased volume of samples and diversity of sample location allows for a more holistic understanding of xylazine's presence in Maryland. Geographically xylazine-positive RAD samples have been most prevalent in Calvert, Cecil, Frederick, Howard, and Wicomico counties.

The overall trend in both CHRS RAD data and MSP/HIDTA seizure data shows a slight decrease in the presence of xylazine throughout the state of Maryland. Xylazine has largely been seen in combination with fentanyl and other opioids. For the RAD samples, a portion of the variation seen in xylazine prevalence is the result of adding additional programs who may serve a population who primarily use substances other than opioids. MSP seizure data has shown that medetomidine is also trending down within Maryland, as opposed to taking xylazine's place.

RAD continues to be a beneficial resource to participants. Overtime, RAD has facilitated a deeper level of trust between programs and their participants. This drug checking data has been used to further wound care efforts in the state around xylazine, through wound care training, xylazine informational flyers for the general public, people who use drugs, and providers, and linkage to care efforts. SSP programs and jurisdictional leaders continue to use RAD as a resource to teach stakeholders about the drug landscape in Maryland and advocate for the needs of people who use drugs.

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Xylazine in Maryland:
An Initial Report of the Maryland Xylazine Workgroup, 2022

Prepared by the Maryland Xylazine Workgroup and Maryland Overdose Data to Action Team

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