Mitigating Risks from Human Xylazine Exposure

The meeting will begin shortly

REAGAN-UDALL FOUNDATION FOR THE FDA

REAGAN-UDALL FOUNDATION FOR THE FDA

Welcome

Susan C. Winckler, RPh, Esq.
Chief Executive Officer
Reagan-Udall Foundation for the FDA

Thank you for joining

REAGAN-UDALL FOUNDATION FOR THE FDA

Due to the meeting size, your microphone and video will remain off during the meeting.

This public meeting is being recorded. The slides, transcript, and video recording will be available on the FDA Foundation website after the meeting.

While we won't have time to directly address audience questions during today's meeting, you may use the Zoom chat function for comments.

Today's Agenda (Eastern Time)

REAGAN-UDALL FOUNDATION FOR THE FDA

9:15 a.m.	Welcome & Introduction
9:25 a.m.	Opening Remarks
9:55 a.m.	Session 1: Current Landscape and Epidemiological Trends
11:05 a.m.	Session 2: Pharmacological and Clinical Research Needs
12:05 p.m.	Lunch
1:10 p.m.	Session 3: Exploring Product Development Research Needs
2:20 p.m.	Session 4: On the Ground Response to Xylazine
3:35 p.m.	Session 5: Future Directions
4:45 p.m.	Closing Remarks & Adjourn

REAGAN-UDALL FOUNDATION FOR THE FDA

Opening Remarks

David Holtgrave, PhD
Assistant Director
White House Office of National Drug Control Policy

REAGAN-UDALL FOUNDATION FOR THE FDA

Opening Remarks

Marta Sokolowska, PhD
Deputy Center Director for Substance Use and Behavioral Health
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

REAGAN-UDALL FOUNDATION FOR THE FDA

Session 1: Current Landscape and Epidemiological Trends

- **CDR Jean Ko, PhD**, Centers for Disease Control and Prevention
- **Amanda DiStefano**, Liberty Mid-Atlantic High Intensity Drug Trafficking Area
- **Van Jackson**, Liberty Mid-Atlantic High Intensity Drug Trafficking Area
- **Traci Green, PhD, MSc**, Brandeis University
- **Erin Russell, MPH**, Health Management Associates

Xylazine detection in drug overdose deaths

Jean Ko, PhD
Deputy Director of Scientific Programs
Division of Overdose Prevention
National Center for Injury Prevention and Control
Centers for Disease Control and Prevention

October 4, 2023

General Disclaimer

The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Background: Xylazine

- Non-opioid sedative that is not approved for use in humans
- No clinically proven effective antidote
- Alternative names:
  - Tranq
  - “Anestesia de caballo”
  - Zombie
  - Rompun
- Identified in Puerto Rico in early 2000s

What is an adulterant?

- A pharmacologically active substance that is added to a product

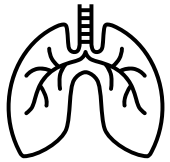
Why are adulterants used?

- Adulterants are intentionally added to drugs to increase bulk, enhance or mimic a pharmacological effect, or to facilitate drug delivery

Clinical presentation: Xylazine

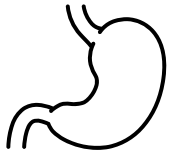
miosis, blurry vision

Central nervous system depression, dizziness, ataxia



apnea or shallow breathing

transient hypertension followed by hypotension, bradycardia, tachycardia, premature ventricular contractions



hyperglycemia

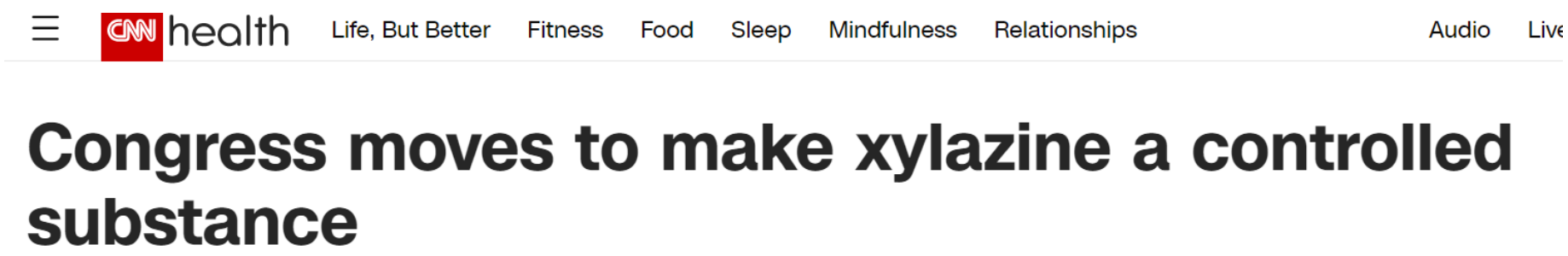
- Ruiz-Colón K, Chavez-Arias C, Díaz-Alcalá JE, Martínez MA. Xylazine intoxication in humans and its importance as an emerging adulterant in abused drugs: A comprehensive review of the literature. Forensic Sci Int. 2014 Jul;240:1-8. doi: 10.1016/j.forsciint.2014.03.015. Epub 2014 Mar 26. PMID: 24769343.

Xylazine in the news

U.S. Department of Justice · Drug Enforcement Administration

PUBLIC SAFETY ALERT

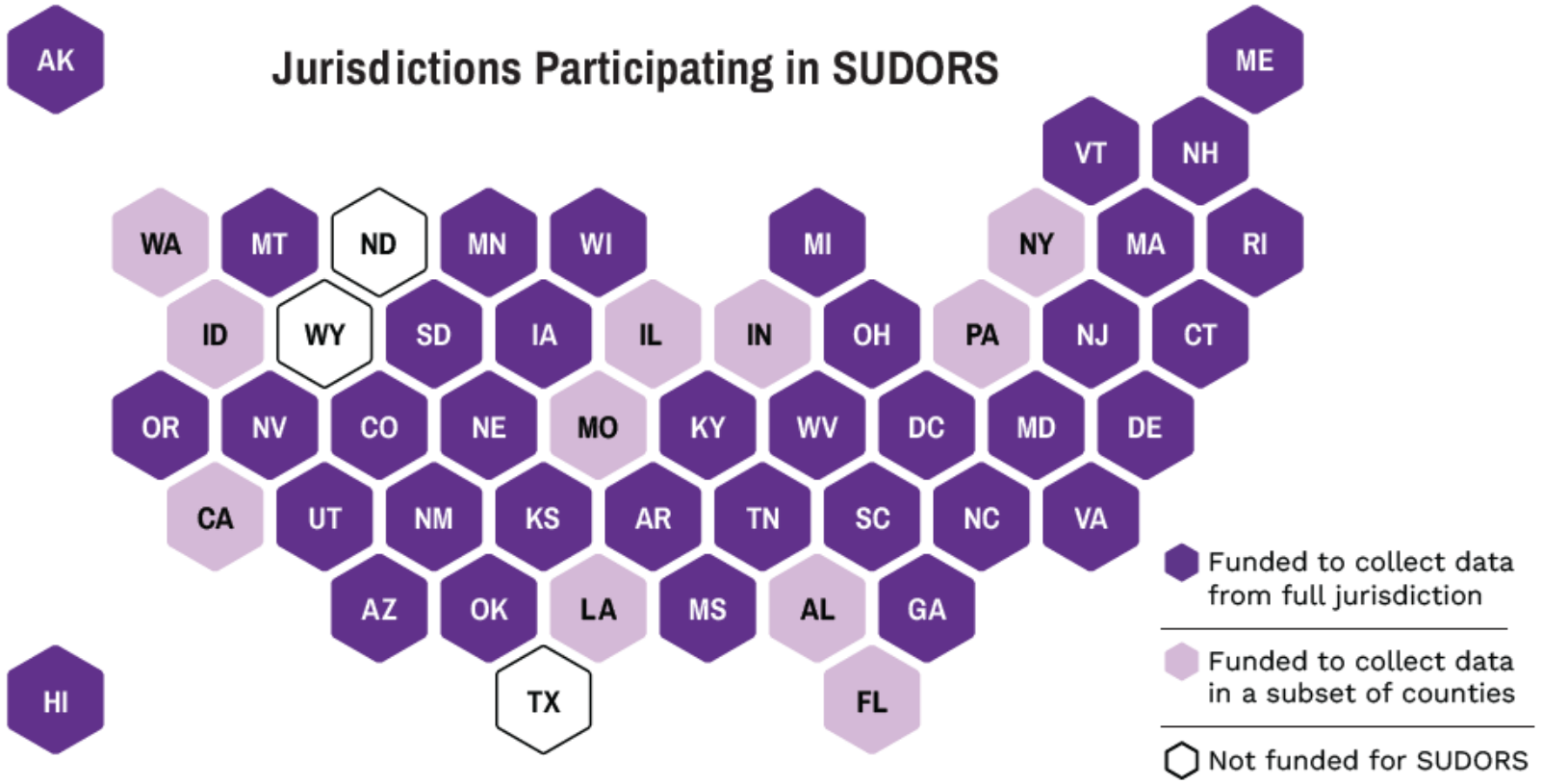
DEA Reports Widespread Threat of Fentanyl Mixed with Xylazine



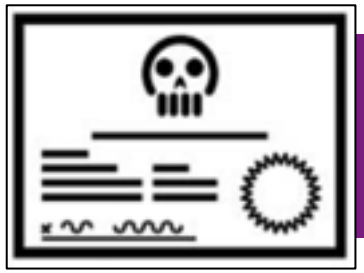
Illicitly Manufactured Fentanyl (IMF)–Involved Overdose Deaths with Detected Xylazine — United States, January 2019–June 2022

Kariisa M, O'Donnell J, Kumar S, Mattson CL, Goldberger BA. Illicitly Manufactured Fentanyl–Involved Overdose Deaths with Detected Xylazine — United States, January 2019–June 2022. MMWR Morb Mortal Wkly Rep 2023;72:721–727. DOI: http://dx.doi.org/10.15585/mmwr.mm7226a4

State Unintentional Drug Overdose Reporting System (SUDORS)

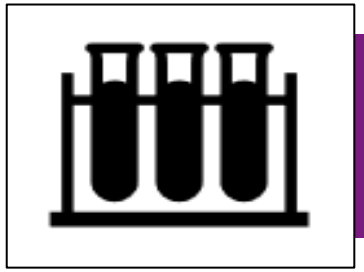


SUDORS data used for analysis

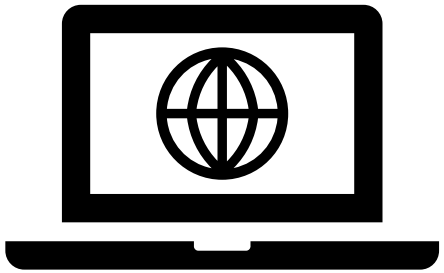


Death Certificates

Medical Examiner/ Coroner Reports



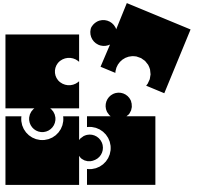
Post-mortem toxicology results



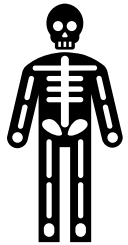
>600 data elements

Demographics

OD risk factors



Circumstances



Comorbidities

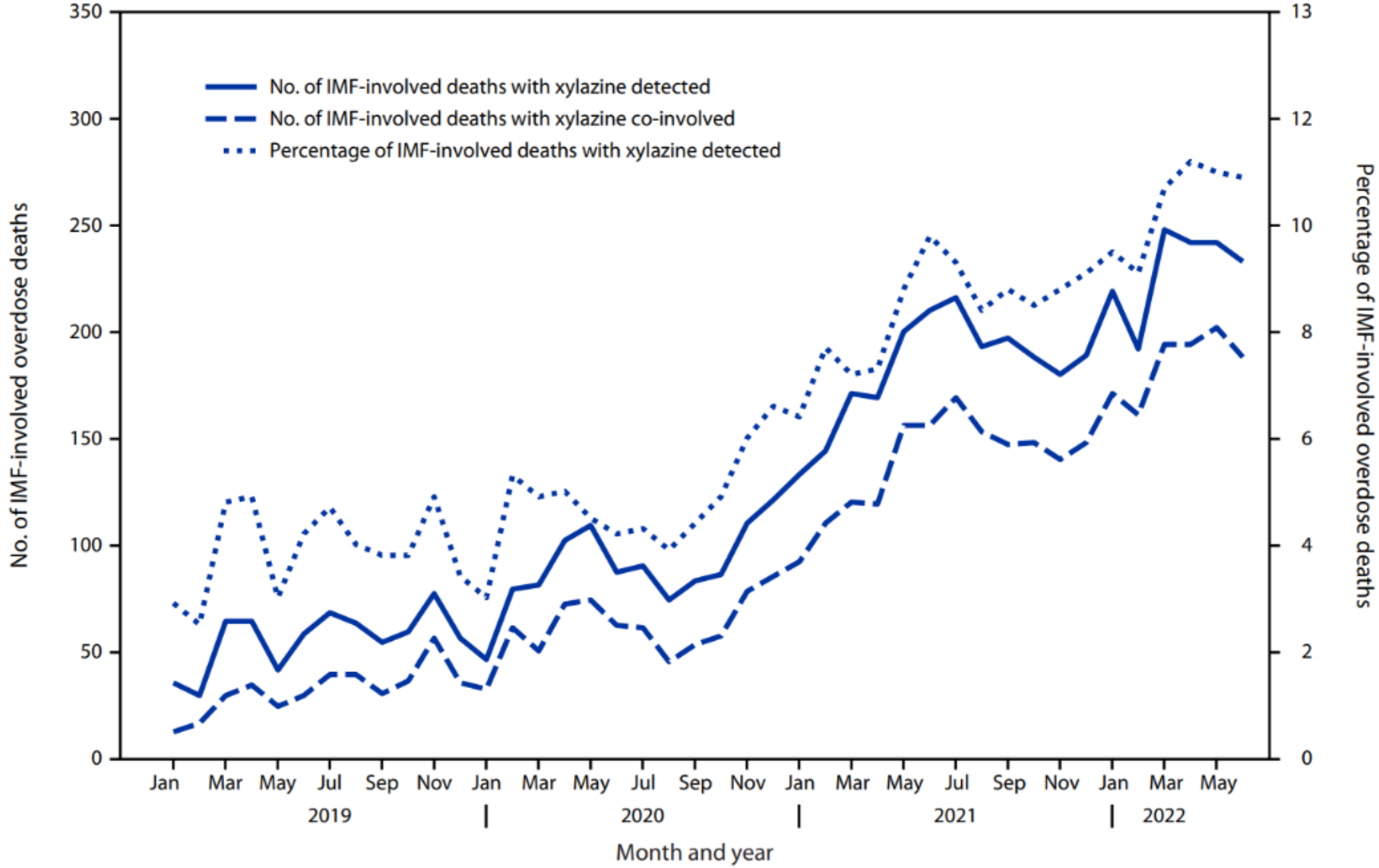
Contributing drugs

Our analytic approach

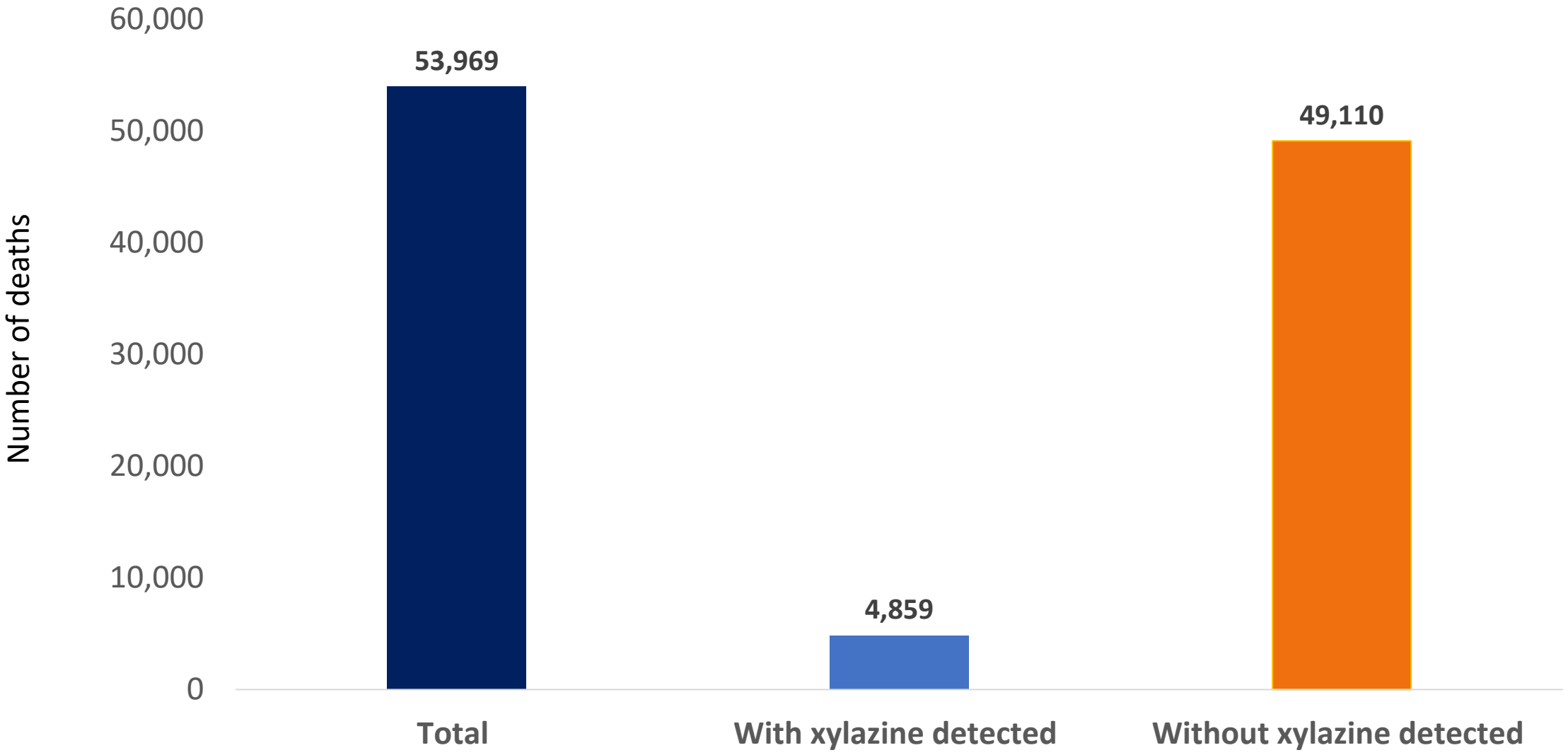
- Examined trends of IMF-involved deaths among 21 jurisdictions (20 states and DC) with complete January 2019–June 2022 SUDORS data

- Among 32 jurisdictions (31 states and DC) with complete January 2021-June 2022 SUDORS data:
  - Compared characteristics of IMF-involved deaths with and without xylazine detected
  - Mapped IMF-involved deaths by xylazine detection or co-involvement

Xylazine detection and co-involvement among IMF-involved deaths increased from January 2019 to June 2022 in 21 jurisdictions

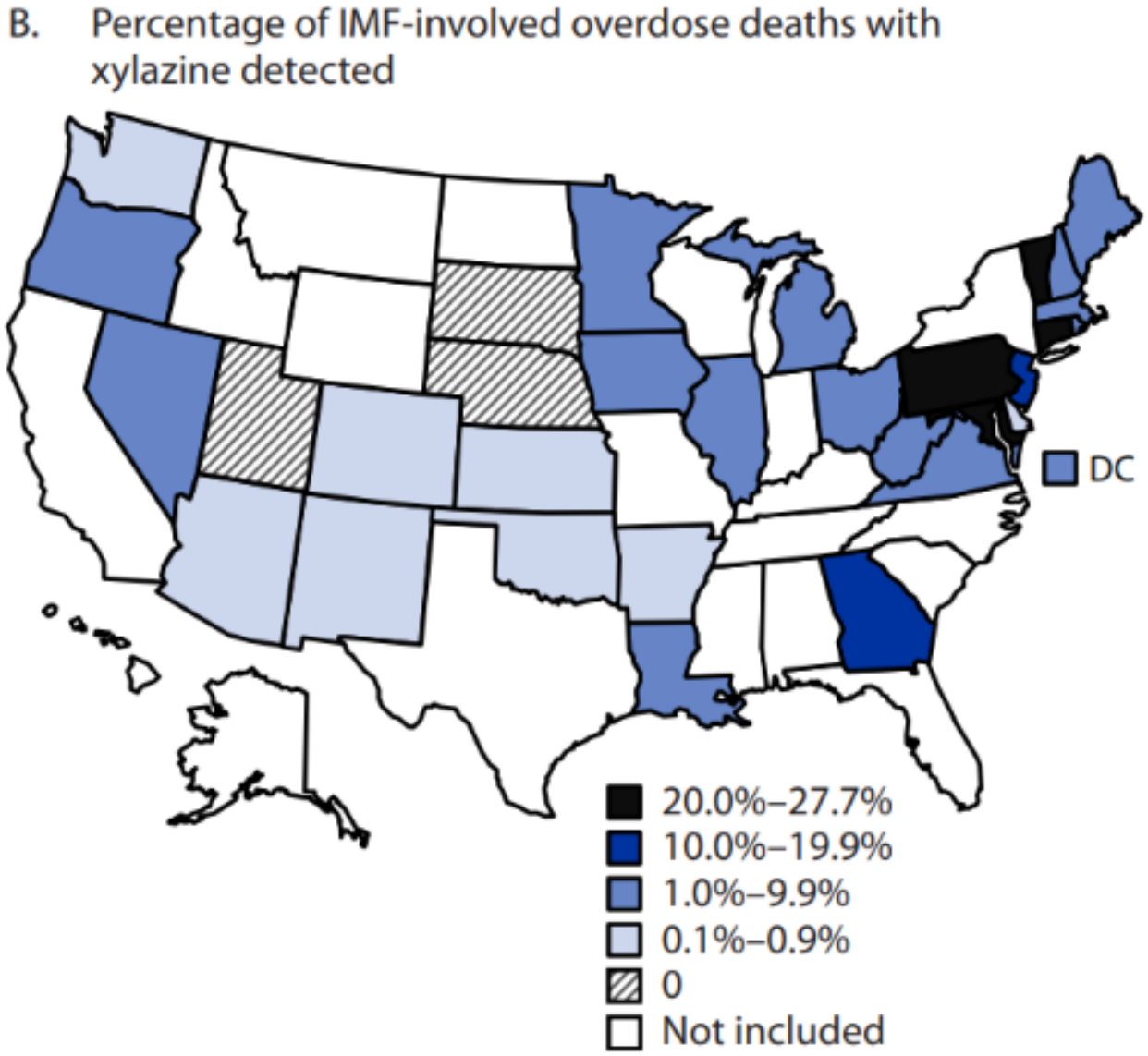


Xylazine detection among IMF-involved deaths in 32 jurisdictions during January 2021-June 2022



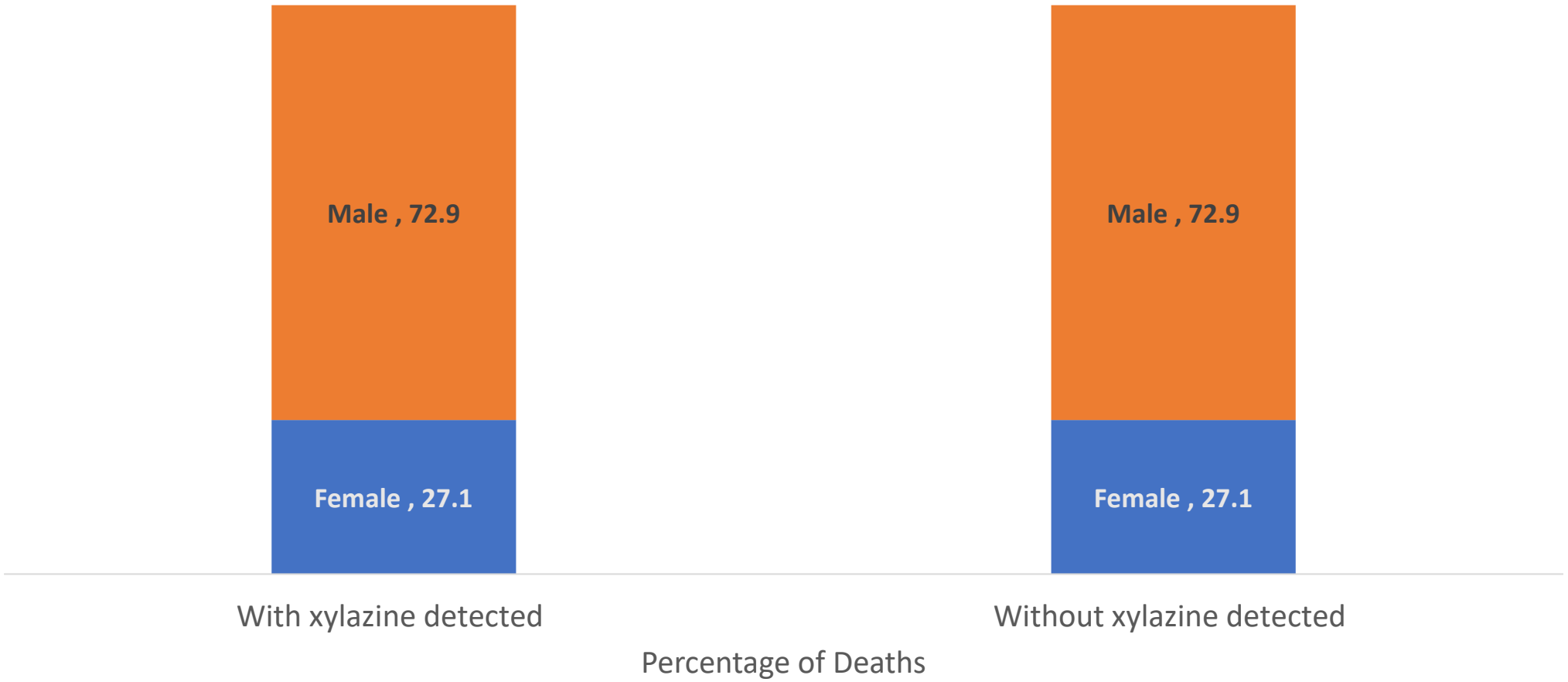
*SUDORS, 31 states and D.C., January 2021-June 2022

Xylazine detection among IMF-involved deaths was highest in the Northeast



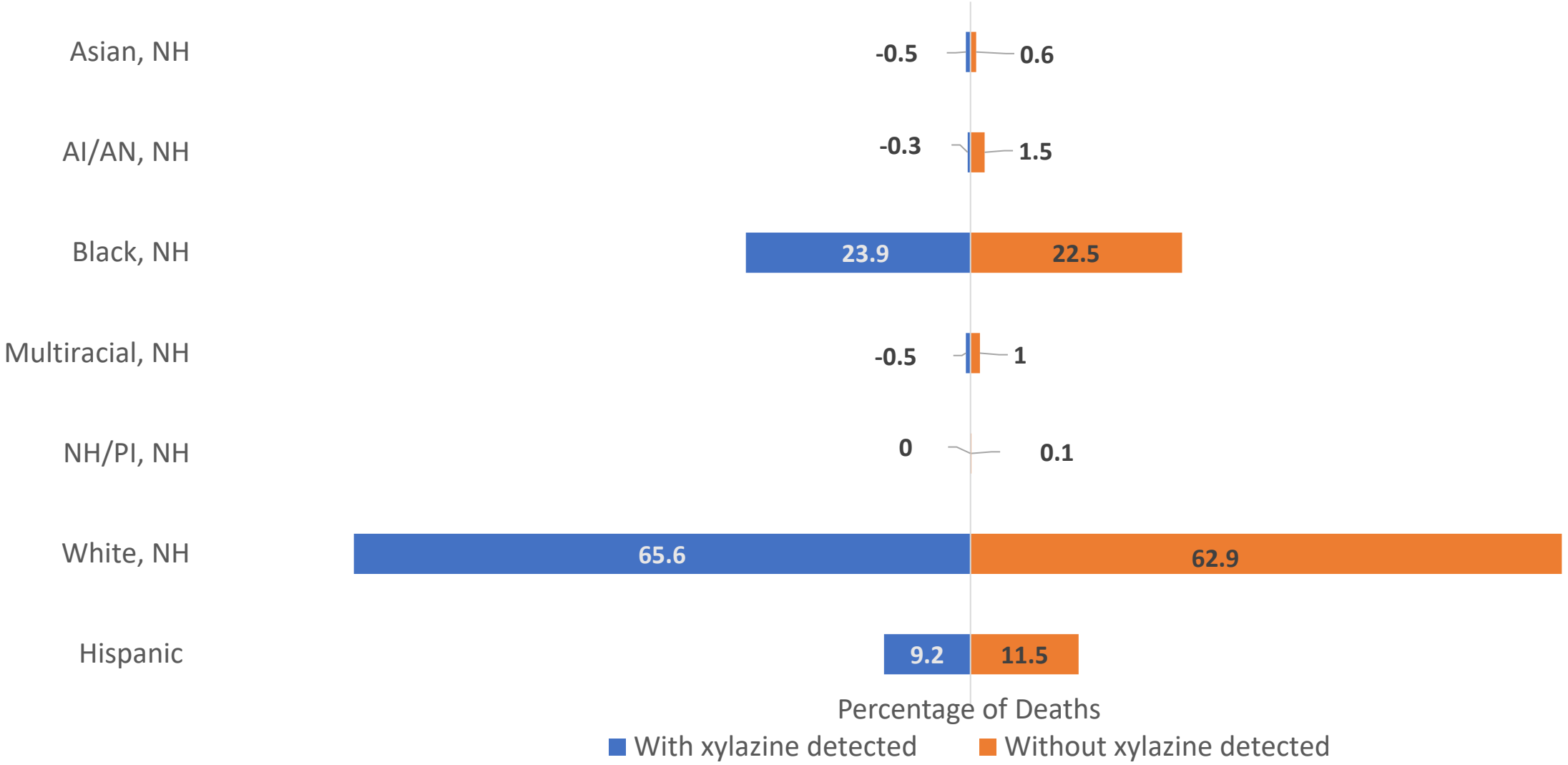
*SUDORS, 31 states and D.C., January 2021-June 2022

Demographic characteristics among IMF-involved deaths with and without xylazine detected were similar



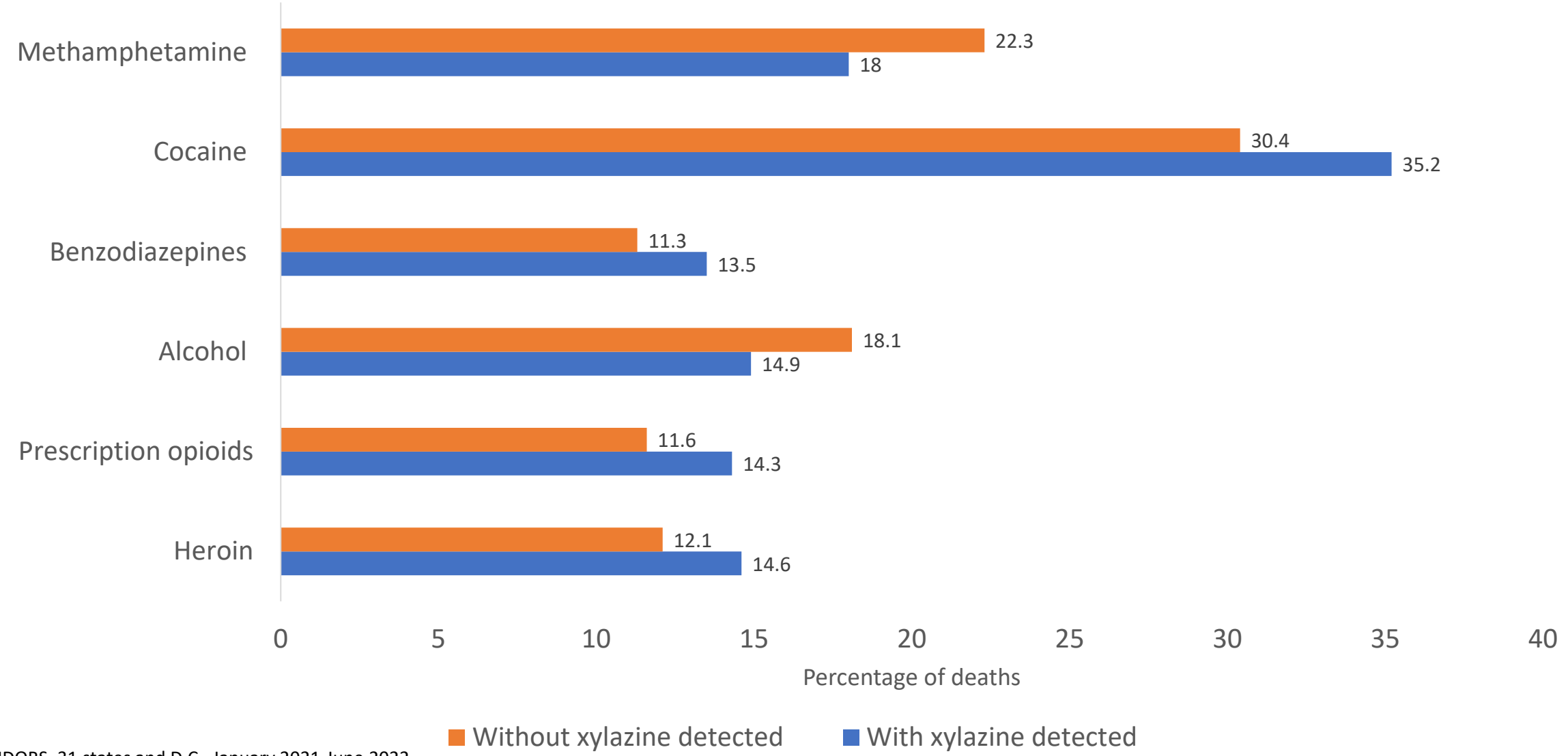
*SUDORS, 31 states and D.C., January 2021-June 2022

Demographic characteristics among IMF-involved deaths with and without xylazine detected were similar



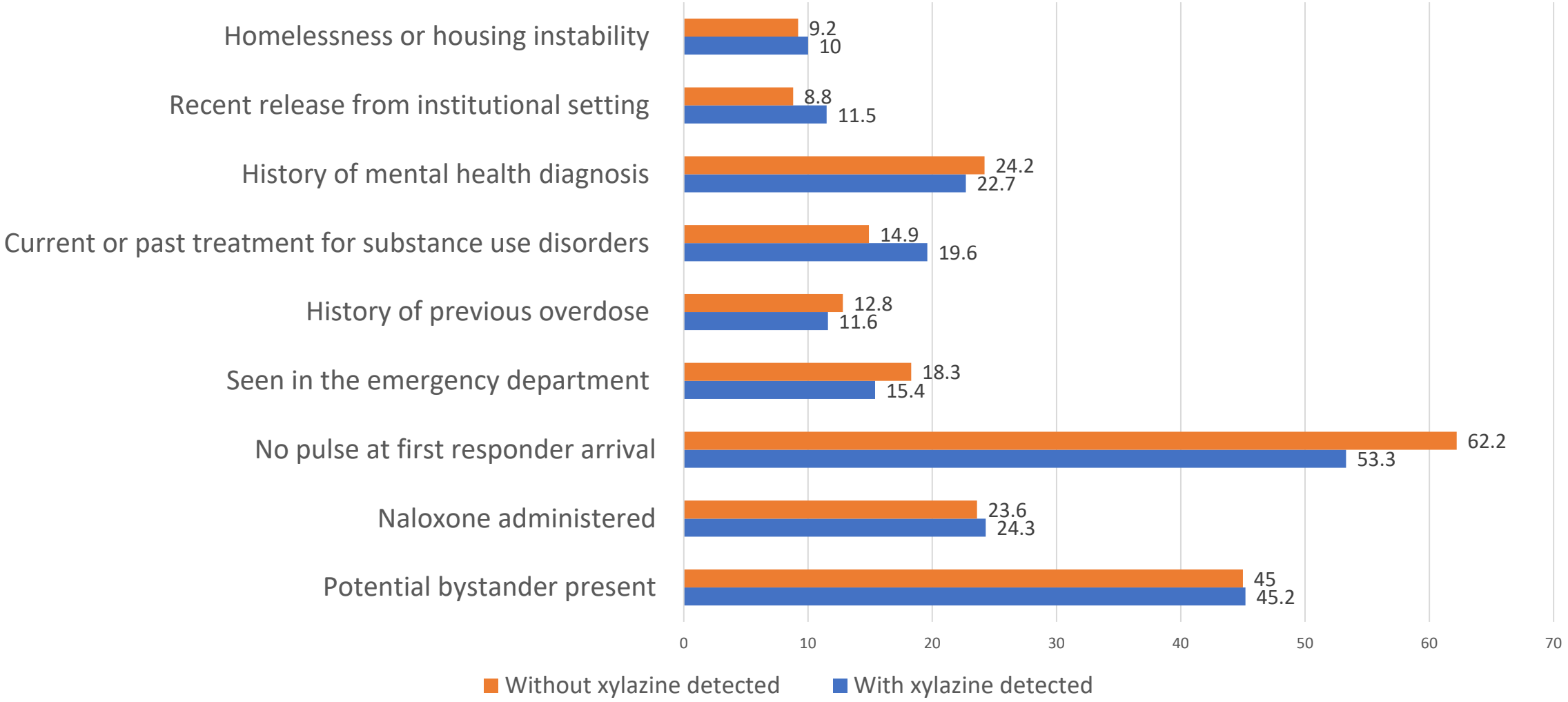
*SUDORS, 31 states and D.C., January 2021-June 2022

Proportion of co-occurring drugs listed as a cause of death among IMF-involved deaths with and without xylazine detected



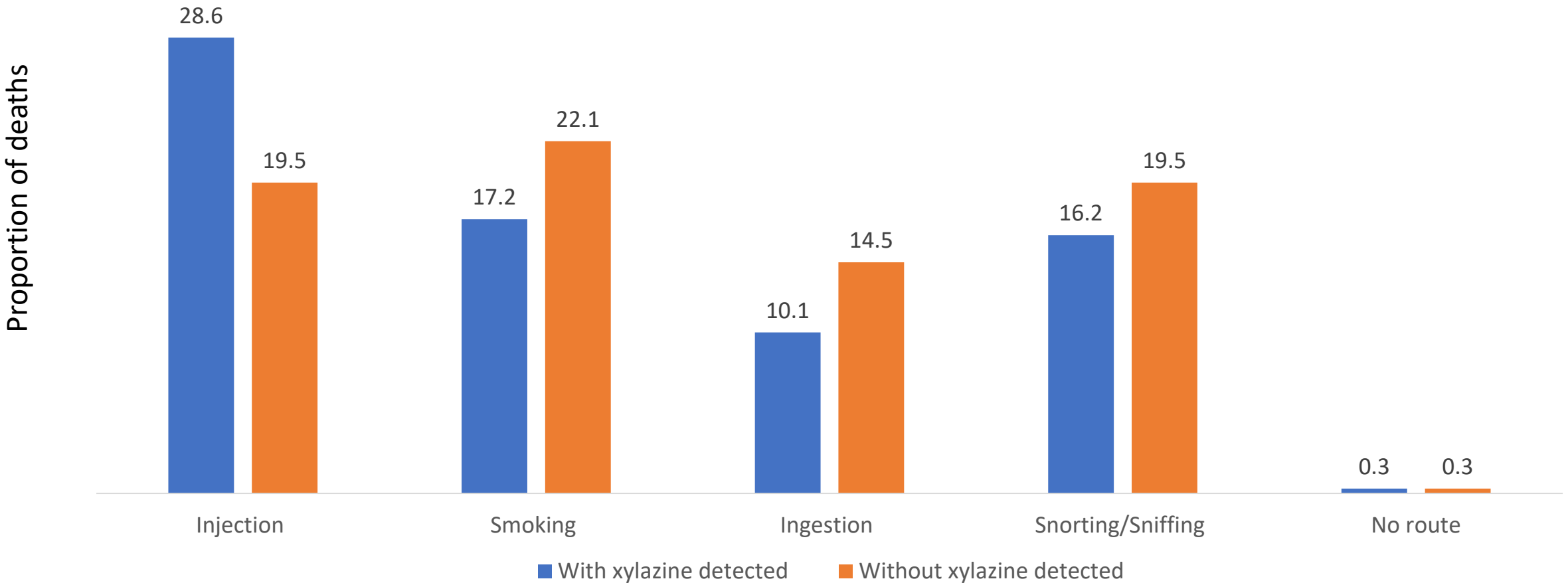
*SUDORS, 31 states and D.C., January 2021-June 2022

Overdose circumstances among IMF-involved deaths with and without xylazine detected



*SUDORS, 31 states and D.C., January 2021-June 2022

Injection was more prevalent for IMF-involved overdoses with xylazine detected



*SUDORS, 31 states and D.C., January 2021-June 2022

Limitations

- Analyses are not nationally representative, and results might not be generalizable
- Toxicological testing of xylazine was not uniform across jurisdictions or over time
  - Likely underestimating the true prevalence of xylazine in overdose deaths
  - Potentially overestimating the true increase during the analysis period

Public health implications

- Naloxone should be administered to reverse effects of opioids even if xylazine is suspected to be present because xylazine is mainly found in IMF products
- Supportive care is critical in event of overdose involving xylazine
- Xylazine testing strips could potentially aid in intervention efforts

Improving surveillance of xylazine in overdose deaths is warranted

- Xylazine prevalence may be underestimated due to variability in testing frequency across the US
- Implementation of routine standardized toxicology testing for xylazine is needed to better understand role of xylazine in overdose mortality and morbidity risk
- Further investigation into motivations for adding xylazine to IMF products is warranted

How can communities reduce harms of xylazine and opioids/fentanyl mixed with xylazine?

- Call 911 immediately after recognizing an overdose or resuscitating a patient and administer naloxone
  - Consider xylazine as a potential contributor to overdose when naloxone administration is ineffective
  - Provide rescue breaths
- Link people who are at risk for overdose with care
- Provide test strips for people who use drugs as part of community drug checking programs
- Educate the public about the increasing presence of xylazine in the drug supply and how to respond to suspected xylazine-involved injuries and overdoses

Acknowledgments

CDC Division of Overdose Prevention staff

+ Mortality Team, Epidemiology and Surveillance Branch
+ Data Management Team, Epidemiology and Surveillance Branch

State, local, and territorial health departments

Jurisdictions and partners participating in OD2A

+ State, local, and territorial health departments
+ Medical examiner and coroner offices
+ Vital registrar offices

Thank you!

Questions?

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Mitigating Risks from Human Xylazine Exposure – The Law Enforcement Perspective

Amanda DiStefano, Intelligence Analyst II, Liberty Mid-Atlantic HIDTA

Van Jackson, Drug Intelligence Officer, Liberty Mid-Atlantic HIDTA

Liberty Mid-Atlantic HIDTA Overview

- HIDTA: High-Intensity Drug Trafficking Area
- Funded through the Office of National Drug Control Policy (ONDCP)
- A “Program”, not an “Agency” but a collaboration of participating Federal, state, local & tribal agencies
- Purpose: Reduce drug trafficking and production in the U.S.
- Overdose Response Strategy (ORS)

Designated in 1995 as two counties: Philadelphia, PA & Camden, NJ

Present Day: 11 counties (5 in Pennsylvania, 5 in New Jersey, 1 in Delaware)

Xylazine in Philadelphia

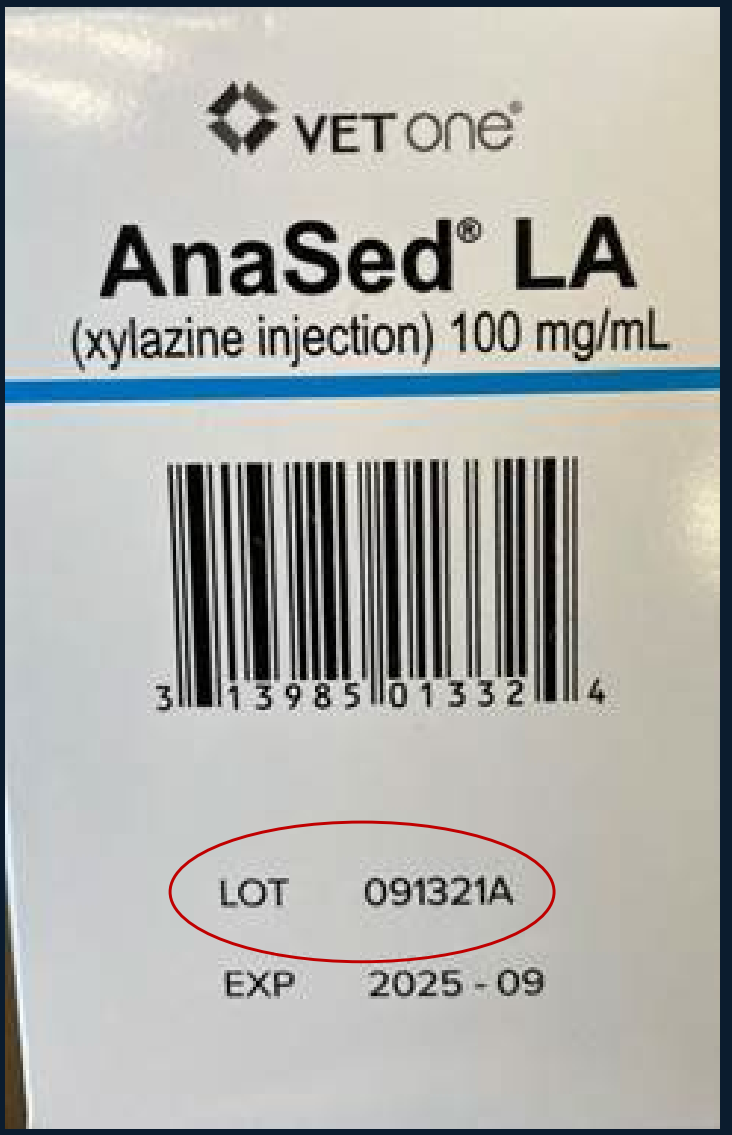
- Early 2000s: First detection in Puerto Rico
- 2006: First detection in Philadelphia
- Philadelphia street opioid scene has strong ties to Puerto Rico influencing the introduction of xylazine
- 2018-2019: 73% increase in xylazine detections in drug overdose deaths
- Xylazine is present in over 90 percent of street opioid samples
- Fiscal Year 2023: CBP seized 12.24 kilograms destined for Philadelphia from China
  - Additional 53 bottles (~ 1 kilogram) destined for Philadelphia from Dominican Republic

Year >	2019	2020	2021	2022	2023*
Total Samples >	47	46	199	306	156
Samples Containing Heroin (N)	12	4	26	27	20
Samples Containing Heroin (%)	26%	9%	13%	9%	13%
Avg. Purity of Heroin (%)	-	-	-	6.0%	1.8%
Samples Containing Fentanyl (N)	46	46	196	305	154
Samples Containing Fentanyl (%)	98%	100%	98%	100%	99%
Avg. Purity of Fentanyl (%)	-	-	-	12.6%	15.2%
Samples Containing Xylazine (N)	31	36	187	279	154
Samples Containing Xylazine (%)	66%	78%	94%	91%	99%
Avg. Purity of Xylazine (%)	-	-	-	34.8%	39.0%

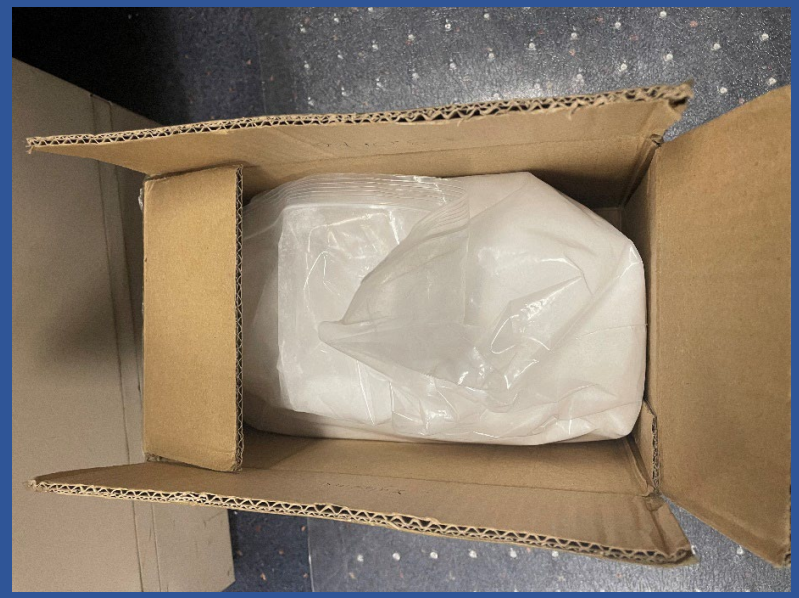
Source: NMS Labs

*Philadelphia Department of Public Health surrendered samples as of August 2023

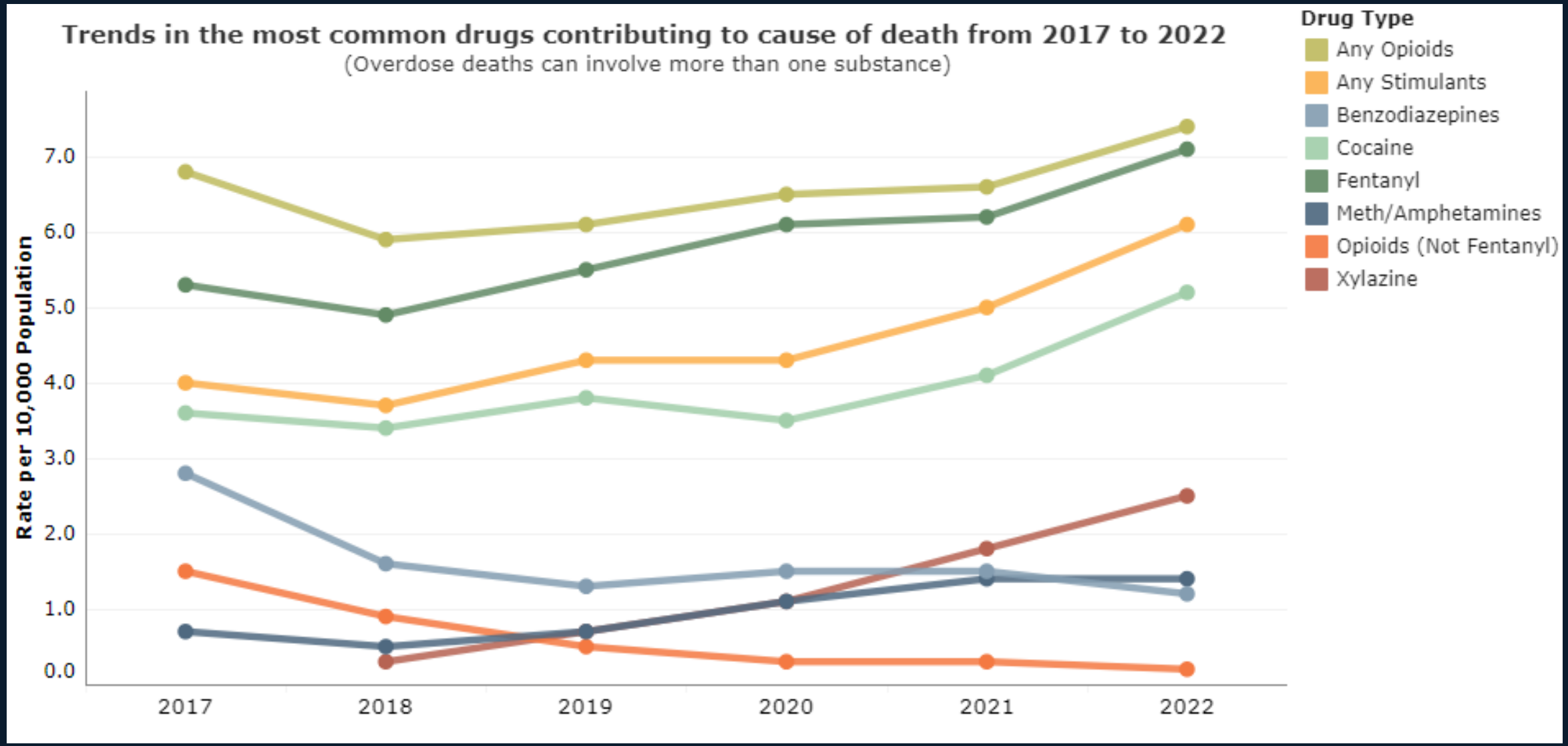

VETone
AnaSed® LA
(xylazine injection) 100 mg/mL


VETone
AnaSed® LA
(xylazine injection) 100 mg/mL
3 13985 01332 4
LOT 091321A
EXP 2025 - 09

January 2023: 20-year prison sentence was given for a 2020 case that involved a controlled delivery of xylazine (via FedEx) leading to a seizure of 2.7 kilograms of fentanyl, cash and various weapons



September 2023: 3 kilograms of xylazine shipped via UPS from Illinois to Philadelphia



Source: Pennsylvania Office of Drug Surveillance and Misuse Prevention

Outlook

- Detections of xylazine in drug exhibits and overdose-related post-mortem toxicology will likely continue to rise as more forensic laboratories implement testing
- As states continue to add xylazine to the list of scheduled drugs, alternatives to xylazine will likely appear (Medetomidine, Dexmedetomidine)
- Xylazine is being used as an adulterant - important to keep the focus on what is really driving the opioid epidemic
- Continue to administer naloxone, use proper personal protective equipment, and reinforce response measures when identifying those experiencing an overdose

MITIGATING RISKS FROM HUMAN XYLAZINE EXPOSURE

Current Landscape and Epidemiological Trends

Traci Green, PhD, MSc

Professor and Director
Opioid Policy Research Collaborative, Brandeis University
Deputy Director
COBRE on Opioids and Overdose, Rhode Island Hospital

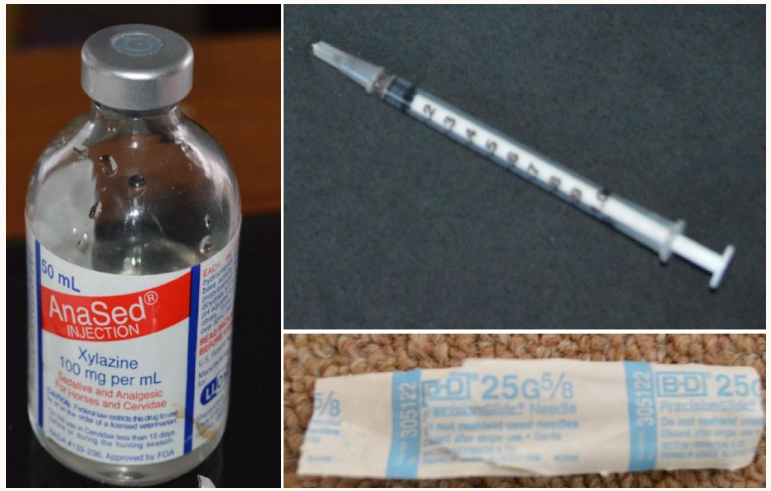
Brandeis UNIVERSITY

DRUG SUPPLY-NATIONAL DATA

Despite no human consumption, xylazine is increasingly found in the drug supply across the U.S.

- Long seen in Puerto Rico, evidence from death records & drug seizure data from RI, CT, NJ place xylazine there from 2000s onwards but uncommon.
- *Recent shifts:* Philadelphia heroin/fentanyl overdose study detected <2% between 2010-2015 but 31% in 2019. Current data show > 90% of heroin samples also contain xylazine in Philadelphia
- Millenium Health Signals Report (UDS based) released Sept 2023 detected xylazine use from samples in all US Census regions, highest rates in Mid-Atlantic and East North Central areas

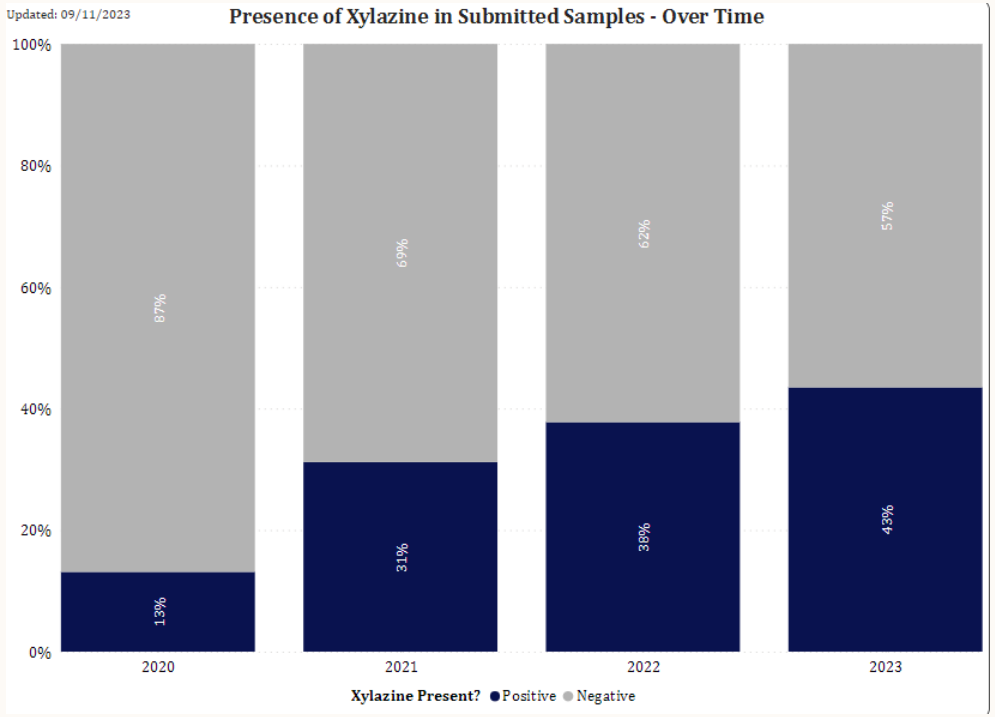
www.youtube.com/watch?v=2JymE2v_mBY



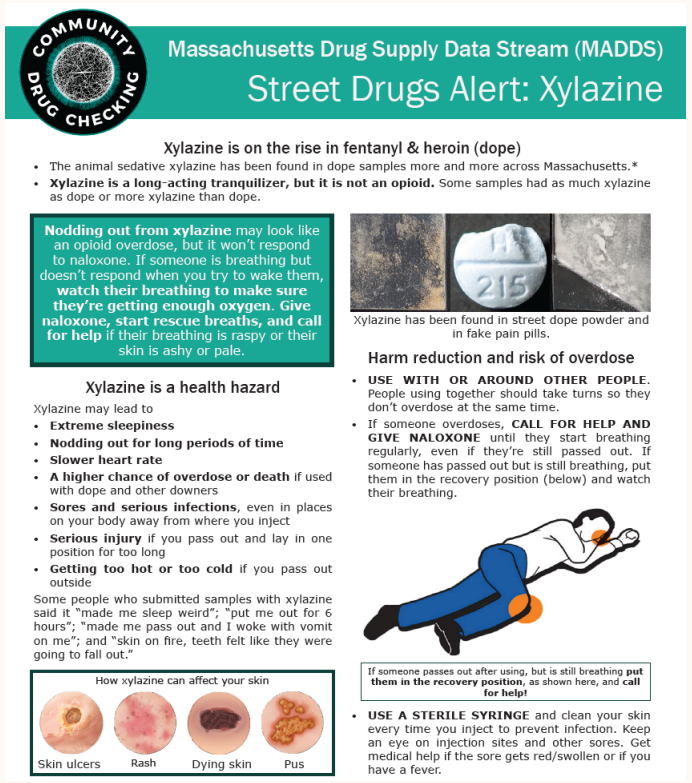
Source: Dr. Banerjee 4/13/16 RI Gov Task Force presentation of 2015 decedent case

DRUG SUPPLY MASSACHUSETTS DATA

- Community drug checking work coordinated through our team in Massachusetts (MADDS) has detected xylazine in progressively higher proportions since 2020, with over 1/3rd of opioid samples in 2022 and 2023 containing xylazine.
- Since the **initial public health bulletin** reporting xylazine by MADDS in **March 2021**, the veterinary sedative xylazine continues to be detected in a substantial number of **samples sold as and also containing fentanyl and heroin** throughout Massachusetts as well as in pressed pills (fake M30/ “Percocet”).

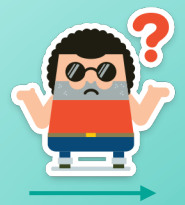


Xylazine in heroin and fentanyl samples over time, MADDS, data from 9/11/2023



Source: streetcheck.org

MADDS: Massachusetts Drug Supply Data Stream



Mobile van

Peer ambassadors

Mail-based submissions

Dropbox spot

Harm Reduction Partner site

Syringe Service Program

Community Health Center

Overdose Education and Naloxone Distro program

Low-barrier treatment program

Outreach

Police department or
District Attorney Collaborator

Samples | No samples

Fourier Transform Infrared Spectrometer (FTIR)

Fentanyl, Benzodiazepine, Xylazine Test Strips

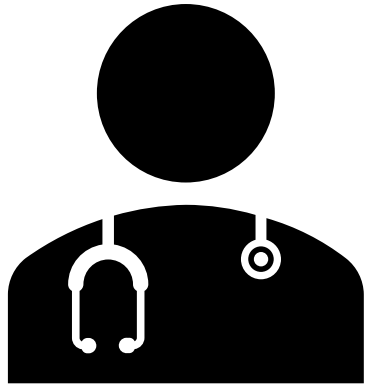
GCMS/LC-QToF by

off-site lab

Drugsdata.org

Rhode Island Hospital

University of North Carolina



Medical Toxicology Consultation

cfsre The Center for Forensic Science Research & Education

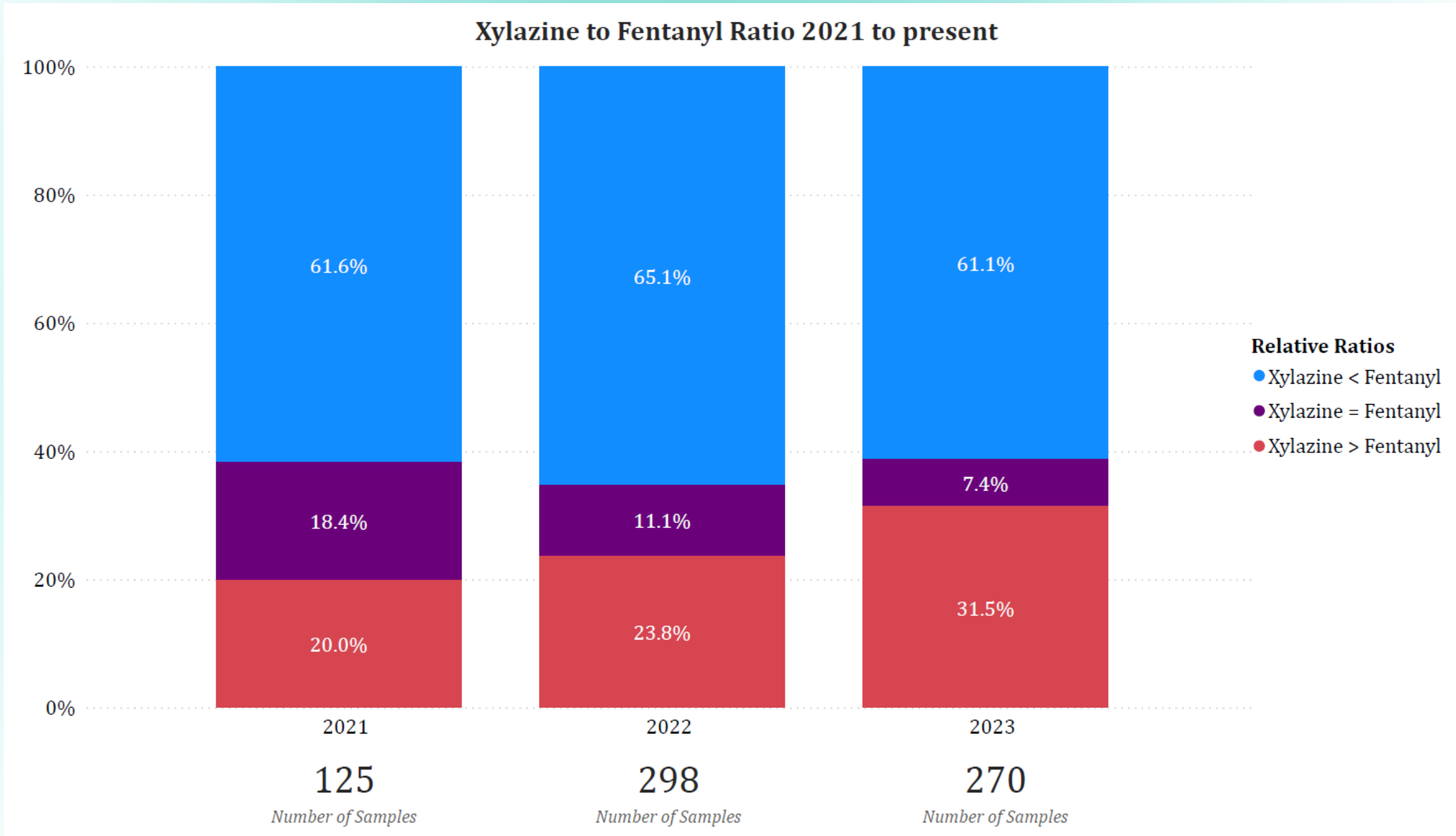
COMMUNITY DRUG CHECKING


StreetCheck
Community Drug Checking

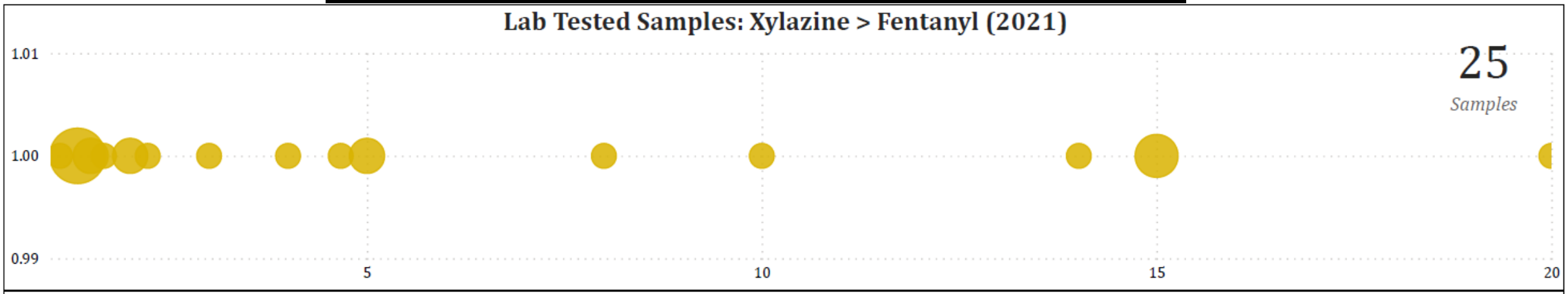
Community Drug Checking Refines Response Capacity

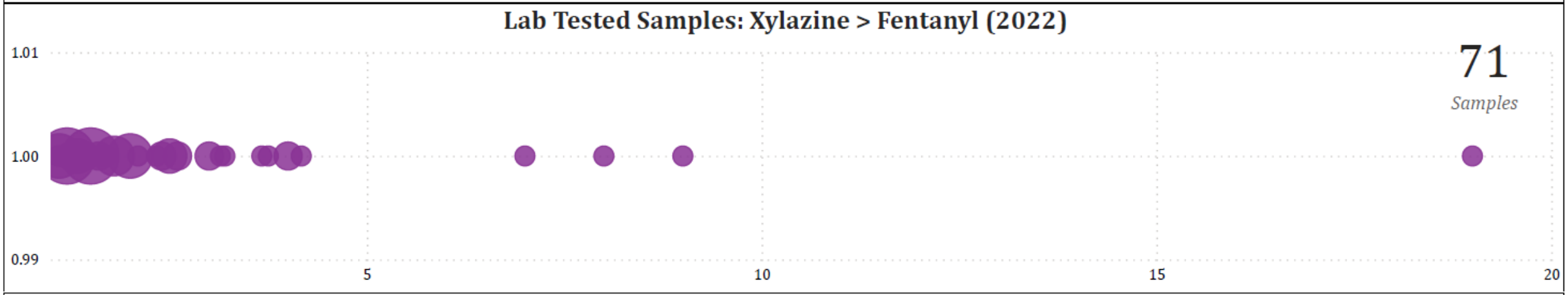
	Qualitative	Semi-quantitative	Quantitative
Devices	Test strips, FTIR, lab testing	FTIR, lab testing	Lab testing, requires weighable sample (5-10mg)
What is reported?	absence/presence	Ratios, major/minor/trace	% component breakdown
What can be measured?	Relative prevalence	Relative exposure	Measured exposure
Question	How common is xylazine in the drug supply?	Relative to ___, is there more xylazine in the drug supply?	What percent of a drug sample does xylazine compose? How much xylazine is in a given drug sample?

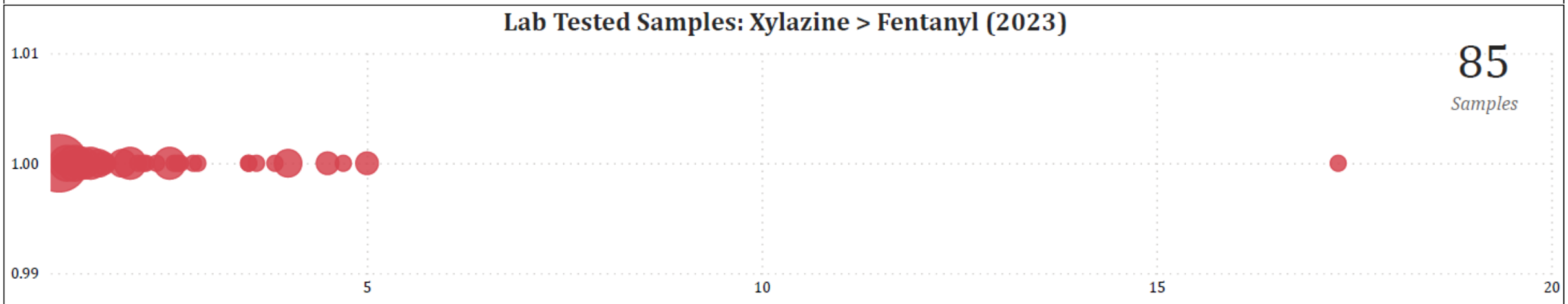
Xylazine to Fentanyl Ratio is Shifting: More Xylazine Exposure

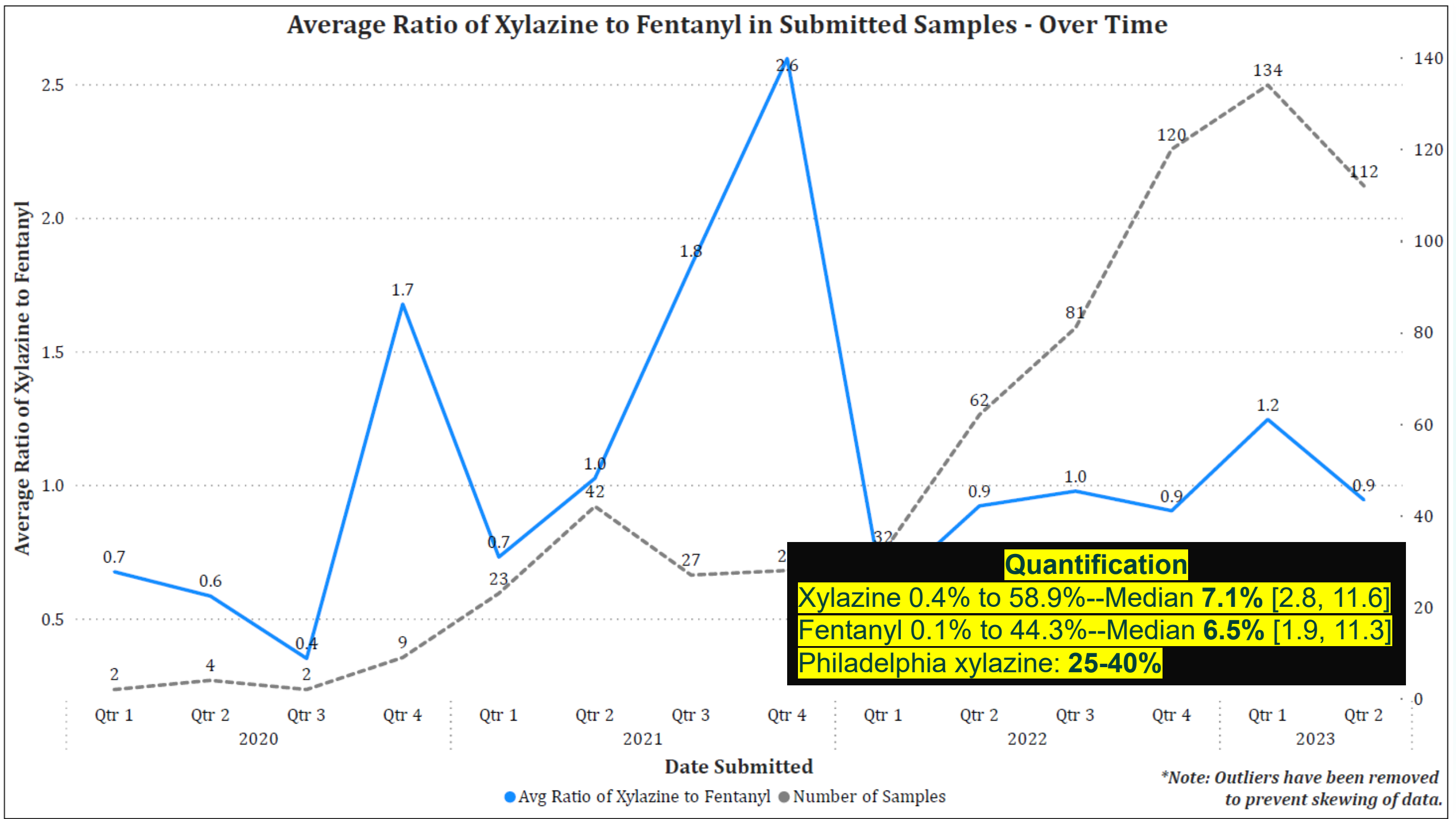


What is Happening When Xylazine> Fentanyl








Average Ratio of Xylazine to Fentanyl in Submitted Samples - Over Time
Average Ratio of Xylazine to Fentanyl
2.5
2.0
1.5
1.0
0.5
140
120
100
80
60
40
20
0
0.7
0.6
0.4
1.7
0.7
1.0
1.8
2.6
0.9
1.0
0.9
1.2
0.9
2
4
2
9
23
42
27
32
62
81
120
134
112
Qtr 1
Qtr 2
Qtr 3
Qtr 4
2020
2021
2022
2023
Date Submitted
Quantification
Xylazine 0.4% to 58.9%--Median 7.1% [2.8, 11.6]
Fentanyl 0.1% to 44.3%--Median 6.5% [1.9, 11.3]
Philadelphia xylazine: 25-40%
Avg Ratio of Xylazine to Fentanyl
Number of Samples
*Note: Outliers have been removed to prevent skewing of data.

Xylazine Trajectory

March 2023

Wk 1:
Not yet used

Wk 2:
Used, stronger than usual, developed abscesses

Active Component	Ratio
Xylazine	200
Fentanyl	100
4-ANPP	50
Heroin	1

FTIR Results

Substance	Component
Xylazine	Major
Fentanyl	Major
Mannitol	Minor

Active Component	Result
Xylazine	5
Fentanyl	2
4-ANPP	1

FTIR Results

Substance	Component
Xylazine	Major
Fentanyl	Major
Mannitol	Minor

April 2023

Wk 5:
Multiple overdoses (nonfatal, fatal)

Active Component (Relative Ratio)	Result
Xylazine	8
Fentanyl	2
4-ANPP	1

FTIR Results

Substance	Component
Xylazine	Major
Fentanyl	Major
Mannitol	Unknown

- Injected: stronger than usual, tasted and smelled like CHEMICALS.
- No “dope rush”, just went out. Only used 3 bags vs. usual 5-10. On second use, felt foggy, hard time walking.

HST_0712 (Complete)

Location
Massachusetts [redacted]

Suspected as
Heroin

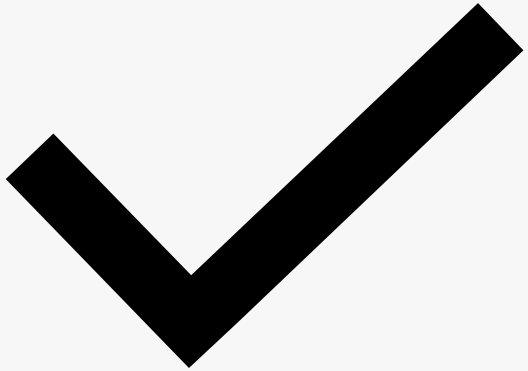
Completed Analysis ***This sample was confirmed by the laboratory to contain Xylazine (8), Fentanyl (2), 4-ANPP (1)***

Key Findings

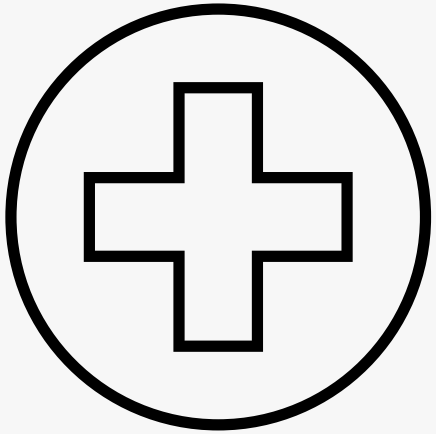
!! Note that this stamp is associated with several severe overdoses in the local area. Please take care and keep plenty of naloxone with you!!

Xylazine is a strong sedative and high amounts of a strong sedative can be harmful. Learn more **here.**

Xylazine-Related Effects



USE EXPERIENCE, UTILITY



COMPLICATED OVERDOSE MANAGEMENT

ATYPICAL SKIN LESIONS: ULCERS, INFECTION

OVERSEDATION & TREATMENT

REPORTED USE EXPERIENCES

Sensations

- No rush but did go into a nod [smoke]
- Good quality, noticed little white chunks-thought to be pressed fentanyl pill [snorts]
- Really strong, strongest substance used in 6 months [smokes, snorts; similar among injection use]
- Weird high after initial push [snorts]; Very good high [snorts]

Numbing and burning, painful use

- Made participant's arm numb [commenting on injection]
- Burning and swelling at injection site [injects]; Burns nose, leaves abscesses [snorts, injects]
- Cooked down fine but injection was painful and swollen right away [injects]

Sedation and consciousness

- Feels more sedated [injects], Instantly sleepy [injects]; No control of muscles [injects]; Extreme almost immediate tiredness and then blacked out [injects]; Felt like cut with benzo [injects]

Wounds

- Wounds appeared on ankle [snorts], back [smokes]; Got abscess at injection site [injects]; Has been using the same (pressed) pills for 2 weeks, now doing wound care and referral with VA [injects]

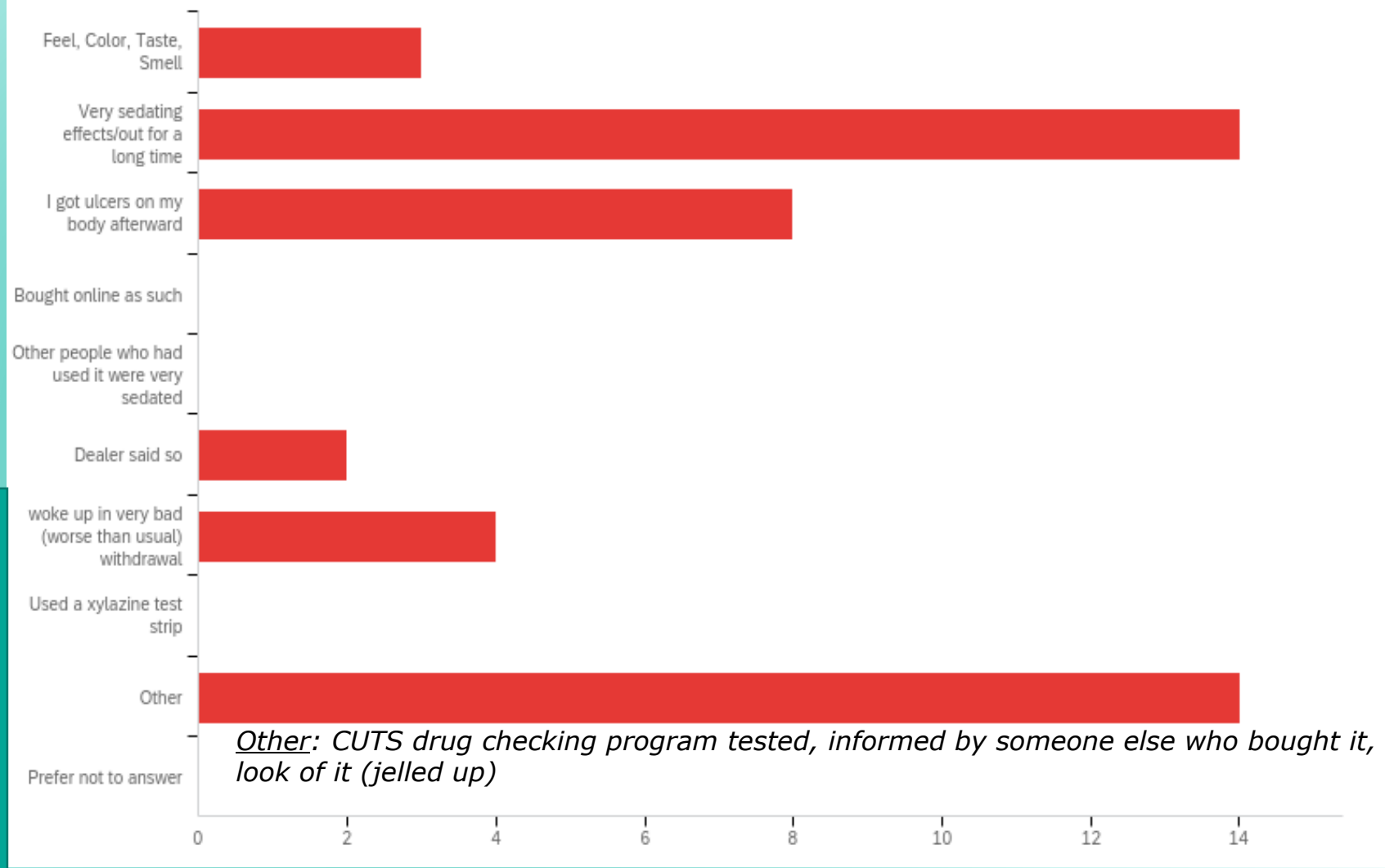
Withdrawal and other symptoms

- Rash and paranoia [unclear ROA]
- Woke up feeling sick the next day—vomited [injects]

Cohort Study, Rhode Island

What makes you think it was xylazine that you used?

Only 26% report **having used xylazine or drugs they thought or knew to have xylazine in them** in the past 6 months



Other: CUTS drug checking program tested, informed by someone else who bought it, look of it (jelled up)

Implies need for information for **consumer safety**

Community drug checking
Test strips
Public sharing of drug seizure data

Data collection Feb-August 2023, **NIDA: UG3/UH3 DA056881 (PI: Green)**

REPORTED USE EXPERIENCES

Sensation

- No rush but did go into a nod [smoke]
- Good quality, noticed little white chunks-thought to be pressed fentanyl pill[snorts]
- Really strong, strongest substance used in 6 months [smokes, snorts]
- Weird high after initial push [snorts]; Very good high [snorts]

Numbing and burning, painful use

- Made participant's arm numb [commenting on injection]
- Burning and swelling at injection site [injects]; Burns nose, leaves abscesses [snorts, injects]
- Cooked down fine but injection was painful and swollen right away [injects]

Sedation and consciousness

- Feels more sedated [injects], Instantly sleepy [injects]; No control of muscles [injects]; Extreme almost immediate tiredness and then blacked out [injects]; Felt like cut with benzo [injects]

Wounds

- Wounds appeared on ankle [snorts], back [smokes]; Got abscess at injection site [injects]; Has been using the same (pressed) pills for 2 weeks, now doing wound care and referral with VA [injects]

Withdrawal and other symptoms

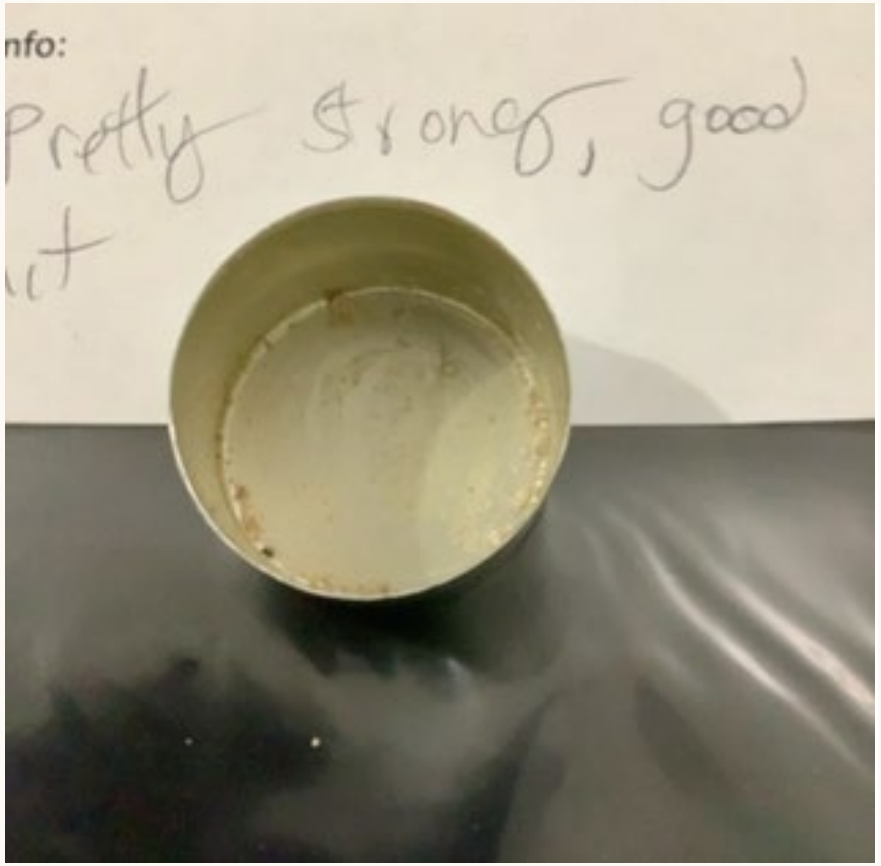
- Rash and paranoia [unclear ROA]
- Woke up feeling sick the next day—vomited [injects]

YOU KNOW, I DON'T LIKE FALLING ASLEEP AND WAKING UP AND HAVING NO IDEA HOW I ENDED UP ON THE FLOOR OR WHY MY ARM IS SORE FROM, YOU KNOW, BEING IN AN AWKWARD POSITION OR WHY I HAVE CUTS AND BRUISES AND I DON'T KNOW HOW I GOT THEM.

("SHOOK", 38, MALE, LATINO, PHILADELPHIA).

Source: Reed et al., 2022

CONSIDERATIONS BASED ON USE EXPERIENCES IN EMERGING AREAS



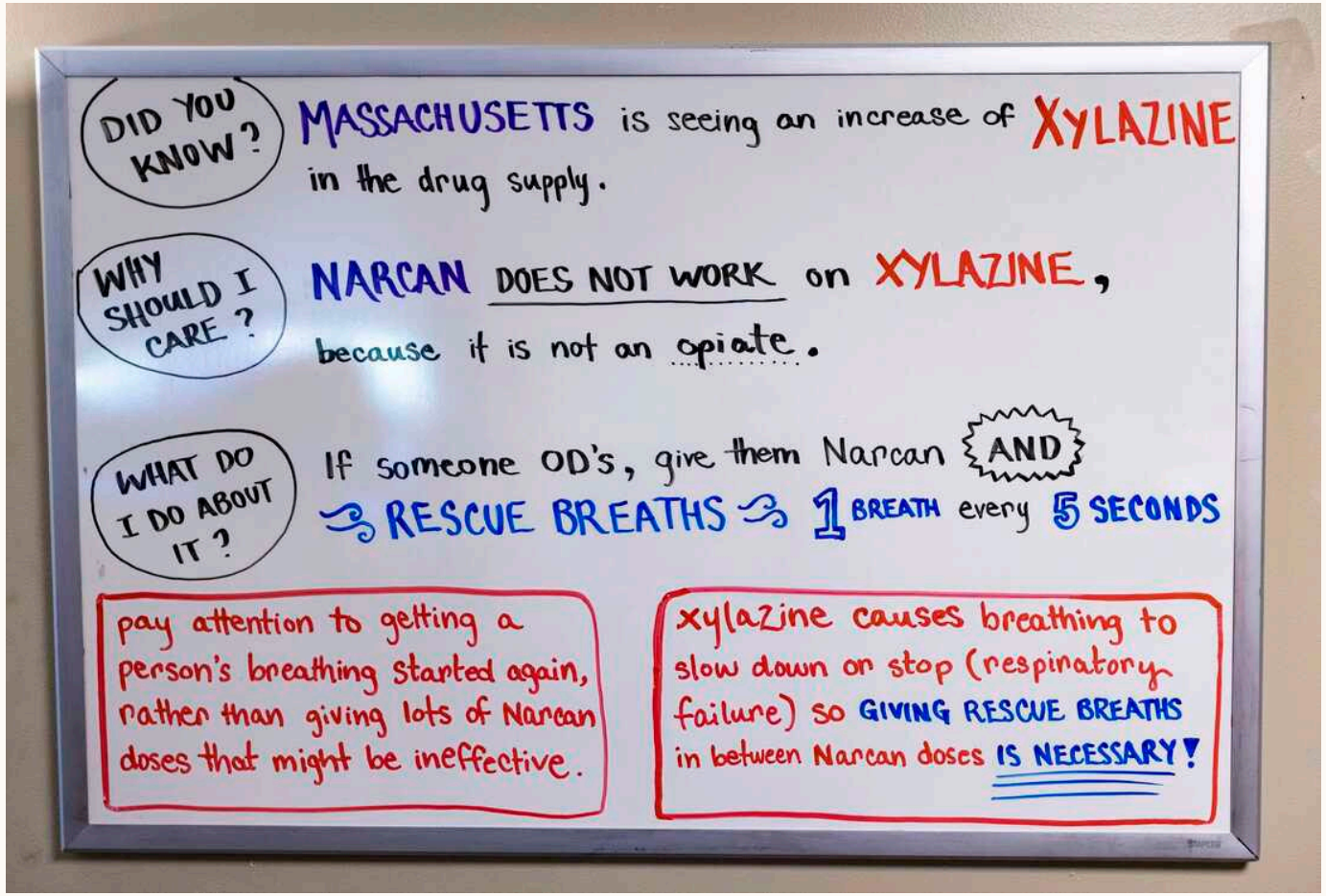
Source: CUTS Study, Streetcheck.org
>900 use experience reports

- Using alone: amplifies xylazine risk's
  - Overdose complications; lack of movement: circulation, compartment syndrome, amputation
- Using in public:
  - Oversedation, victimization, physical/sexual violence, harm
  - Environmental exposure harms (heat, cold)

Implies need to increase ***witnessing*** of use, response to oversedation, ***monitoring***

Overdose prevention sites
Monitoring Hotlines, Apps: NeverUseAlone, MA Overdose Prevention Hotline
SPOT/supervised place for observation and treatment
Safe, trusted partnered use or monitoring

BACK TO BASICS: NALOXONE FIRST, *RESCUE BREATHING*



REPORTED USE EXPERIENCES

Sensation

- No rush but did go into a nod [smoke]
- Good quality, noticed little white chunks-thought to be pressed fentanyl pill[snorts]
- Really strong, strongest substance used in 6 months [smokes, snorts]
- Weird high after initial push [snorts]; Very good high [snorts]

Numbing and burning, painful use

- Made participant's arm numb [commenting on injection]
- Burning and swelling at injection site [injects]; Burns nose, leaves abscesses [snorts, injects]
- Cooked down fine but injection was painful and swollen right away [injects]

Sedation and consciousness

- Feels more sedated [injects], Instantly sleepy [injects]; No control of muscles [injects]; Extreme almost immediate tiredness and then blacked out [injects]; Felt like cut with benzo [injects]

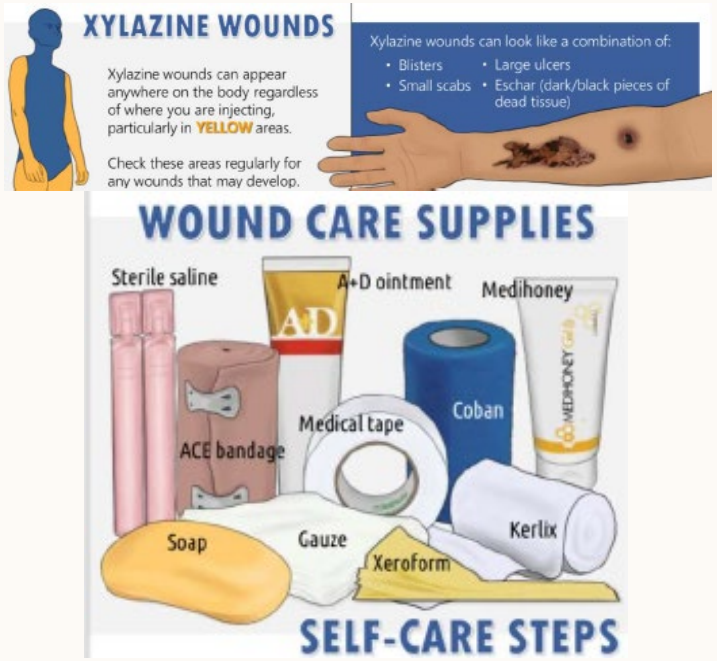
Wounds

- **Wounds appeared on ankle [snorts], back [smokes]; Got abscess at injection site [injects]; Has been using the same (pressed) pills for 2 weeks, now doing wound care and referral with VA [injects]**

Withdrawal and other symptoms

- Rash and paranoia [unclear ROA]
- Woke up feeling sick the next day—vomited [injects]

CONSIDERATIONS FOR WOUNDS BASED ON USE EXPERIENCES IN EMERGING AREAS



Source: Boston Medical Center

- *Xylazine wound prevention*: Unclear why they appear, what helps to prevent them, what exacerbates their appearance or progression
- *Wound care*: clearer from practice/info exchange
- *Scaling up care*: very unclear for treatment programs, EDs/hospitals, CHCs, criminal justice

Implies need for **systems change**

Task shift to peer-based, mobile, non-institutionalized care, especially harm reduction groups

Makeshift to self-manage

I FIGURED I'LL DRAIN IT MYSELF WITH MY NEEDLES YOU KNOW? AND I PUT IT IN AND I DRAINED IT MYSELF A LITTLE BIT AND THEN THE BLOOD WOULD START TRICKLING OUT WITH LIKE A LITTLE BIT OF PUS AND SHIT AND IT WOULD SMELL AND I WAS LIKE 'OH, ALL RIGHT THAT'S CLEAN', YOU KNOW? NEXT TIME I DRAIN OUT MAYBE I'LL BE BETTER. BEFORE LONG ALL THE SPOTS I STABBED TO DRAIN IT TURNED INTO A BIG PURPLE NIPPLE.

Source: Benrubi et al., 2023

REPORTED USE EXPERIENCES

Sensation

- No rush but did go into a nod [smoke]
- Good quality, noticed little white chunks-thought to be pressed fentanyl pill[snorts]
- Really strong, strongest substance used in 6 months [smokes, snorts]
- Weird high after initial push [snorts]; Very good high [snorts]

Numbing and burning, painful use

- Made participant's arm numb [commenting on injection]
- Burning and swelling at injection site [injects]; Burns nose, leaves abscesses [snorts, injects]
- Cooked down fine but injection was painful and swollen right away [injects]

Sedation and consciousness

- Feels more sedated [injects], Instantly sleepy [injects]; No control of muscles [injects]; Extreme almost immediate tiredness and then blacked out [injects]; Felt like cut with benzo [injects]

Wounds

- **Xylazine wounds appeared on the skin [injects]; Got abscess at injection site [injects]; Has been using the same (pressed) pills for 2 weeks, now doing wound care and referral with VA [injects]**

Withdrawal symptoms

- **Rash and paranoia; Anxiety, panic attacks [injects]**
- **Woke up feeling sick the next day—vomited [injects]; very uncomfortable coming out; felt sick, didn't take dope sick away [injects]; Makes you withdrawal quicker [injects]**

CONSIDERATIONS FOR WITHDRAWAL BASED ON USE EXPERIENCES IN EMERGING AREAS

- *Self manage:* seek available benzodiazepines, stimulants
- *Re-administer: xylazine, fentanyl*
- *Accessible alternatives are few*
- *Current withdrawal care options hard to scale*

Implies need for **safer withdrawal care alternatives and easier start to medication treatment**

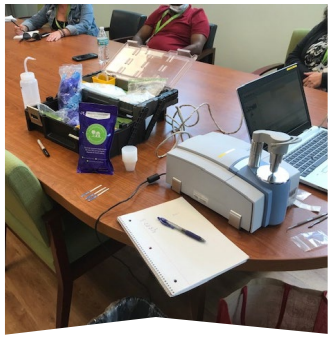
Single dose buprenorphine from pharmacies for withdrawal
ED-based opioid withdrawal support

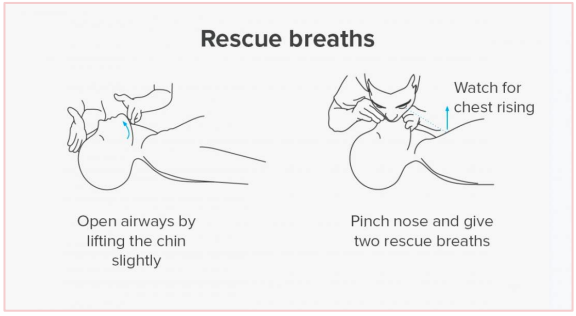
Rapid methadone start from hospitals/EDs/mobile teams,
Quick start buprenorphine (Martin et al, 2022)

Xylazine withdrawal support case study

Until we have research to answer our many questions, strategies should:

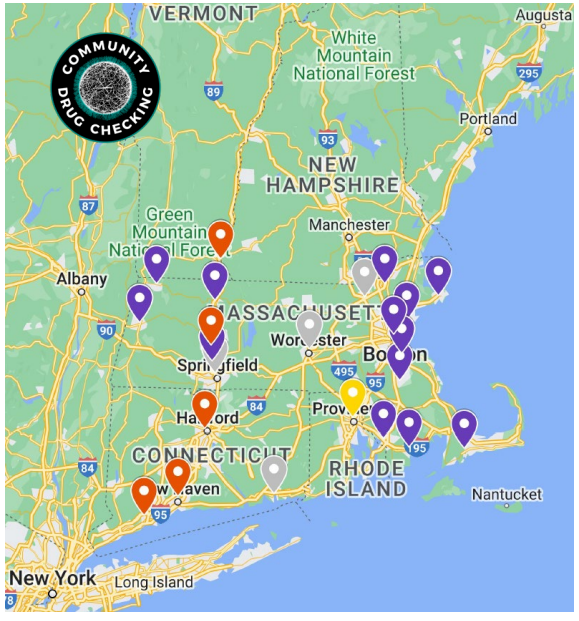
Minimize Dose & Exposure to Xylazine	Mitigate Harm	Invest in Innovative Interventions, Task Shifts, & Make Shifts
Information for consumer, supplier, distributor: Drug Checking, test strips	Overdose prevention sites, Hotlines, supervised observation & treatment sites	Mobile teams (people, vans)
Lower barrier, additional medication treatment (e.g., methadone, buprenorphine, HAT?)	"Back to basics" overdose response trainings, Rescue breathing	Wound care in more low-barrier spaces
Withdrawal supports & broadscale strategy (e.g., standing order/ protocol for buprenorphine)	Measurable stigma reduction @ institutional level (e.g., quality indicator, metrics)	Self-management of wounds





And Invest in Data

- Community drug checking holds a mirror up to supply in local community
- Services provide lifesaving information, prevention intervention, are data-generating for monitoring
- Would benefit from clear direction, legality, support
- Capacity is growing but need investments in practice, science, staffing
  - *Laboratory guidance: Permit laboratories to test publicly submitted samples for community drug checking purposes*
- Testing arrangements and tools need to be realistic and applicable in community settings
- **Cannot be a critical component of a strategy AND exist in indecision**



WWW.STREETCHECK.ORG

tracigreen@brandeis.edu

RESOURCES/REFERENCES

Resources

Dr. Joseph D'Orazio, Temple University, Philadelphia, Presentation for COBRE on Opioids and Overdose https://www.youtube.com/watch?v=Rqpf0jIuyCo

The Guardian: www.youtube.com/watch?v=2JymE2v_mBY

Xylazine Resources on MADDS: https://heller.brandeis.edu/opioid-policy/community-resources/madds/xylazine-resources.html

Streetcheck.org

References

Bowles JM, McDonald K, Maghsoudi N, et al. Xylazine detected in unregulated opioids and drug administration equipment in Toronto, Canada: clinical and social implications. *Harm Reduct J*. 2021;18(1):1-6. doi:10.1186/S12954-021-00546-9/TABLES/2

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

Tobias S, Shapiro AM, Wu H, Ti L. Xylazine Identified in the Unregulated Drug Supply in British Columbia, Canada. *Can J Addict*. 2020;11(3):28-32. doi:10.1097/CXA.0000000000000089

Torruella RA. Xylazine (veterinary sedative) use in Puerto Rico. *Subst Abus Treat Prev Policy*. 2011;6(1):1-4. doi:10.1186/1747-597X-6-7/METRICS

Wong SC, Curtis JA, Wingert WE. Concurrent detection of heroin, fentanyl, and xylazine in seven drug-related deaths reported from the Philadelphia Medical Examiner's Office. *J Forensic Sci*. 2008;53(2):495-498. doi:10.1111/J.1556-4029.2007.00648.X

Mohr A, Browne T, Martin D, Logan B. *Xylazine: A Toxic Adulterant Found in Illicit Street Drugs*. 2020.

Shi XX, Yin BS, Yang P, et al. Xylazine Activates Adenosine Monophosphate-Activated Protein Kinase Pathway in the Central Nervous System of Rats. *PLoS One*. 2016;11(4). doi:10.1371/JOURNAL.PONE.0153169

Andresen-Streichert H, Iwersen-Bergmann S, Mueller A, Anders S. Attempted Drug-facilitated Sexual Assault-Xylazine Intoxication in a Child. *J Forensic Sci*. 2017;62(1):270-273. doi:10.1111/1556-4029.13270

REFERENCES CONT'D

Johnson J, Pizzicato L, Johnson C, Viner K. Increasing presence of xylazine in heroin and/or fentanyl deaths, Philadelphia, Pennsylvania, 2010-2019. *Inj Prev*. 2021;27(4):395-398. doi:10.1136/injuryprev-2020-043968

Alexander RS, Canver BR, Sue KL, Morford KL. Xylazine and Overdoses: Trends, Concerns, and Recommendations. *Am J Public Health*. 2022;112(8):1212-1216. doi:10.2105/AJPH.2022.306881

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

Thangada S, Clinton HA, Ali S, et al. Notes from the Field: Xylazine, a Veterinary Tranquilizer, Identified as an Emerging Novel Substance in Drug Overdose Deaths — Connecticut, 2019–2020. *MMWR Morb Mortal Wkly Rep*. 2021;70(37):1303-1304. doi:10.15585/MMWR.MM7037A5

Philadelphia Department of Public Health. Health Department Releases Update on 2021 Overdose Death Counts. Published December 2, 2021.

Korn WR, Stone MD, Haviland KL, Toohey JM, Stickle DF. High prevalence of xylazine among fentanyl screen-positive urines from hospitalized patients, Philadelphia, 2021. *Clin Chim Acta*. 2021;521:151-154. doi:10.1016/J.CCA.2021.07.010

Reed MK, Imperato NS, Bowles JM, Salcedo VJ, Guth A, Rising KL. Perspectives of people in Philadelphia who use fentanyl/heroin adulterated with the animal tranquilizer xylazine; Making a case for xylazine test strips. *Drug Alcohol Depend Reports*. 2022;4:100074. doi:10.1016/J.DADR.2022.100074

McNinch J, Maguire M, Wallace L. A case of skin necrosis caused by intravenous xylazine abuse. In: *Society of Hospital Medicine*. 2021.

Reyes JC, Negrón JL, Colón HM, et al. The Emerging of Xylazine as a New Drug of Abuse and its Health Consequences among Drug Users in Puerto Rico. *J Urban Health*. 2012;89(3):519. doi:10.1007/S11524-011-9662-6

Zhu D. Public health impact and harm reduction implications of xylazine-involved overdoses: a narrative review. Harm Reduction Journal. 2023; 20:131.

HMA

Tracking Xylazine in Maryland: program and policy implications

Presented by:
Erin Russell

GOALS

- Describe how Maryland established a statewide drug checking program in response to xylazine
- Present results from the Rapid Analysis of Drugs program
- Identify policy changes that would support translation of Maryland's program to other states

MARYLAND'S RAPID ANALYSIS OF DRUGS PROGRAM

OVERVIEW OF MARYLAND'S RAPID ANALYSIS OF DRUGS (RAD) PROGRAM

- Paraphernalia is collected voluntarily from syringe service program participants and tested with Direct Analysis in Real Time-Mass Spectrometry (DART-MS)
- Key Considerations:
  - Existing programmatic infrastructure (SSPs are approved and monitored by the Maryland Department of Health, currently 23 operate in 14 counties)
  - Trusting relationships between programs and participants
  - Legal coverage through Maryland's Syringe Service Program law that allows for covered activities to exempt volunteers, staff, and participants from arrest, charge, and prosecution for possession of paraphernalia

SYRINGE SERVICE PROGRAMS

- **Offer sterile drug administration equipment to people who use them**
- **Grounded in harm reduction**: *a low barrier, person-centered approach to meeting individual needs without contingency*

Dave Purchase by New York Times, 2013

SYRINGE SERVICE PROGRAMS CONTINUED

- May provide comprehensive care
- Drug checking was a new service among many
- Mobile van, fixed-site, backpack/street-based outreach

Harm Reduction Program, Washington County Department of Health, Maryland

Dr. Ed Sisco, NIST, 2022

STATEWIDE DRUG CHECKING PROGRAM

- Maryland Department of Health recruited syringe service programs across the state, provided training and technical assistance
- National Institute of Standards and Technology (NIST) conducted testing and reporting back to programs
- Demonstrated effectiveness of field-collected sample testing and published findings in Morbidity and Mortality Weekly Report

PROCESS

Drug Paraphernalia Sampling Instructions

Smoking Device

- Wipe entire exterior of device
- Wipe all openings of the device

Smoking Pipe

- Wipe entire exterior of pipe
- Wipe openings of the device
- *Optional:* Tap pipe on top of wipe to dislodge possible residue

Straw

- Wipe entire exterior of straw
- Wipe openings of the straw
- *Optional:* Tap straw on top of wipe to dislodge possible residue

Scale

- Wipe area of scale where material is weighed

Spoon

- Wipe large portion of the spoon
  - Focus on areas with visible residue if present

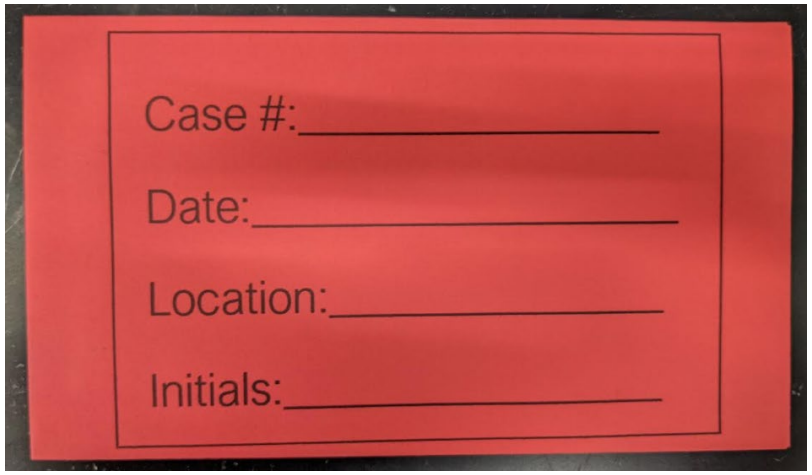
Cautions

- ALWAYS wear nitrile gloves when sampling
  - Change gloves between samples if possible
- Do NOT attempt to open packaging
  - This is especially true if there is visible powder
- Do NOT lick wipe envelope closed

Contact Info:
Ed Sisco – edward.sisco@nist.gov
Amber Burns – amber.burns@maryland.gov
Liz Robinson – elizabeth.l.robinson@nist.gov

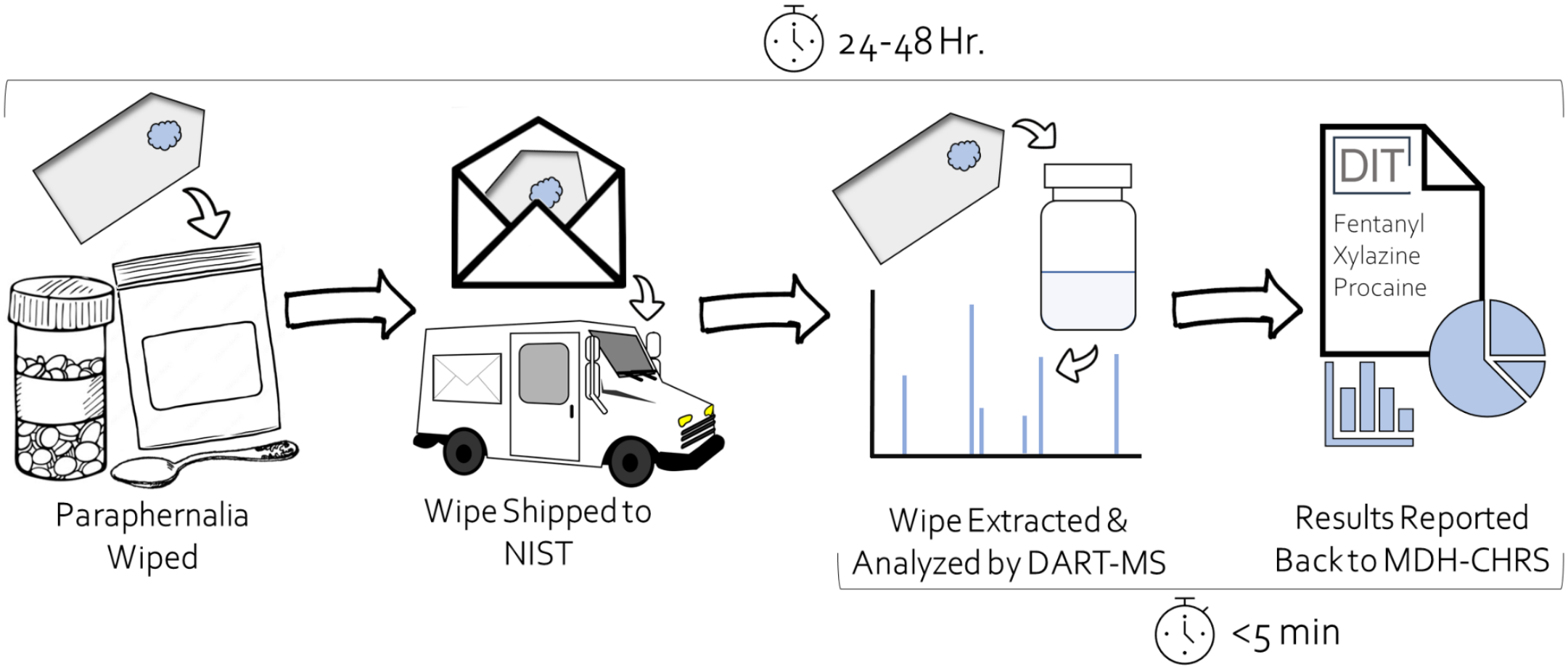
PROCESS CONTINUED

- Swab/wipe placed in small red envelope labeled with: Program name, date of collection, sample serial number



- Additional optional data:
  - Where sample received
  - Type of sample swabbed/sample medium
  - What was the drug sold as?
  - Do you believe you received what you intended to buy?
  - How did the drugs make you feel?
  - Limited location information

PROCESS CONTINUED



RESULTS

Forensic Chemistry 34 (2023) 100489

Contents lists available at ScienceDirect

Forensic Chemistry

journal homepage: www.sciencedirect.com/journal/forensic-chemistry

An analytical platform for near real-time drug landscape monitoring using paraphernalia residues

Meghan G. Appley [a,*,1], Elizabeth L. Robinson [a,2], Allison Thomson [b], Erin Russell [b], Edward Sisco [a,3]

[a] National Institute of Standards and Technology, 100 Bureau Drive, Gaithersburg, MD 20899, United States
[b] Center for Harm Reduction Services, Maryland Department of Health, 1223 W Pratt Street, Baltimore, MD 21223, United States

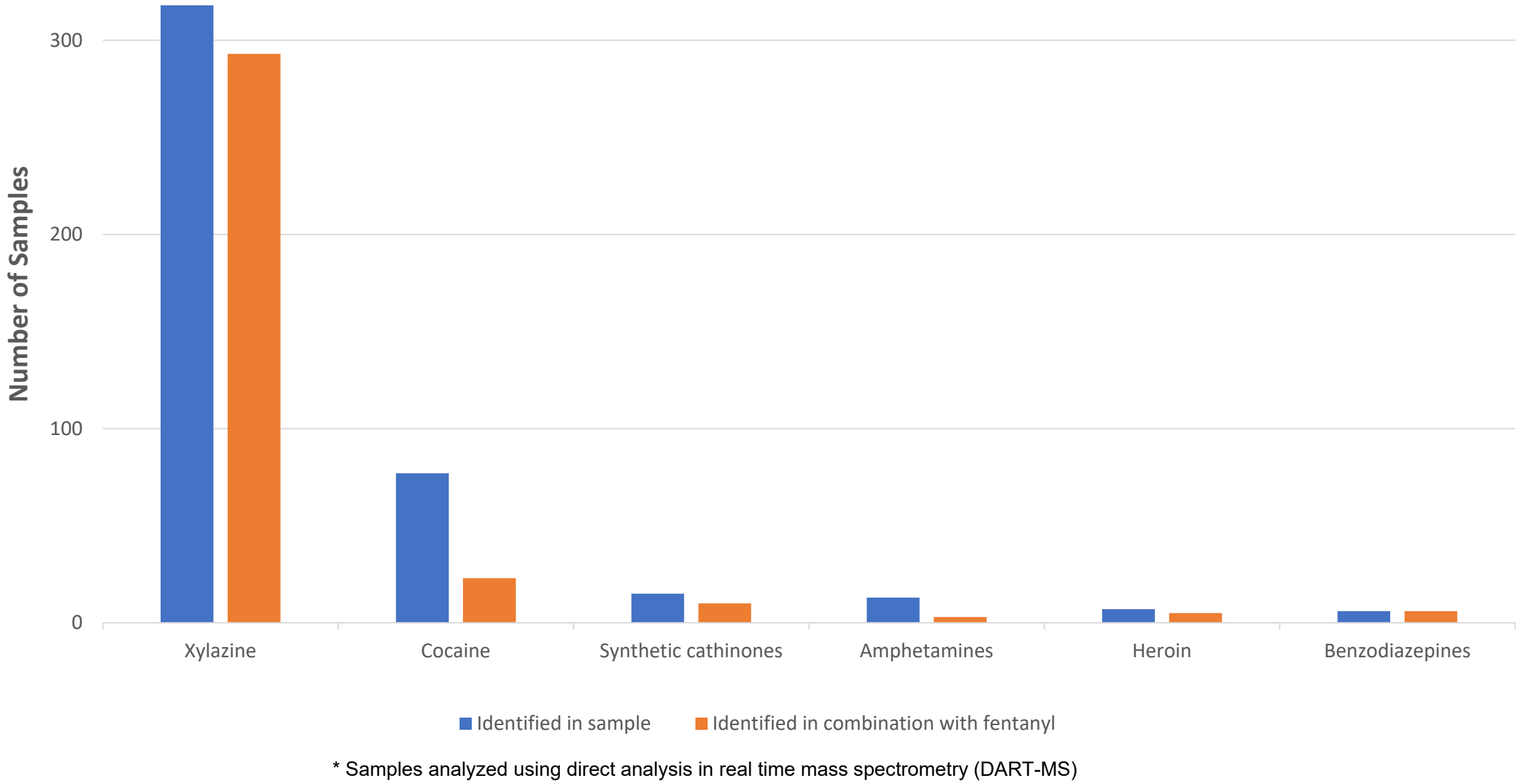
ARTICLE INFO

Keywords:
DART-MS
Illicit drugs
Drug residues
Public health

ABSTRACT

Deaths attributed to drug overdoses are constantly on the rise, but drug trends are frequently changing and often differ across geographical regions. Current analytical techniques are limited in their abilities to rapidly identify drugs that would inform both public health and law enforcement officials about the evolving drug landscape. The work presented here outlines an analytical platform that utilizes ambient ionization mass spectrometry and additional techniques (*e.g.,* tandem mass spectrometry) to qualitatively analyze trace residues from drug paraphernalia to quickly detect both drugs and cutting agents. To demonstrate proof-of-concept, samples collected from syringe service programs throughout the state of Maryland were analyzed by direct analysis in real time – mass spectrometry (DART-MS) to provide rapid, near complete chemical profiles (drugs, cutting agents, and other compounds of interest). To obtain a more complete chemical profile, it was found that a small subset of samples (7.5 %) benefited from additional analysis by either direct analysis in real time – tandem mass spectrometry (DART-MS/MS) or liquid chromatography – tandem mass spectrometry (LC-MS/MS). This additional analysis enabled confirmation of the presence or absence of questioned compounds, assisted in identification of new compounds, and provided isomer differentiation without hindering the rapid reporting of results. This analytical platform utilizing DART-MS and, where necessary, tandem mass spectrometry techniques, was found to detect a wide range of drugs and cutting agents in a manner that can better inform public health and public safety personnel about the drug landscape in "near real-time".

Figure 2. Samples tested (n=496) and found to contain selected substances* (blue) and number of instances the selected substance was found in combination with fentanyl (orange) — Eight syringe services programs, Maryland, November 2021 – August 2022.

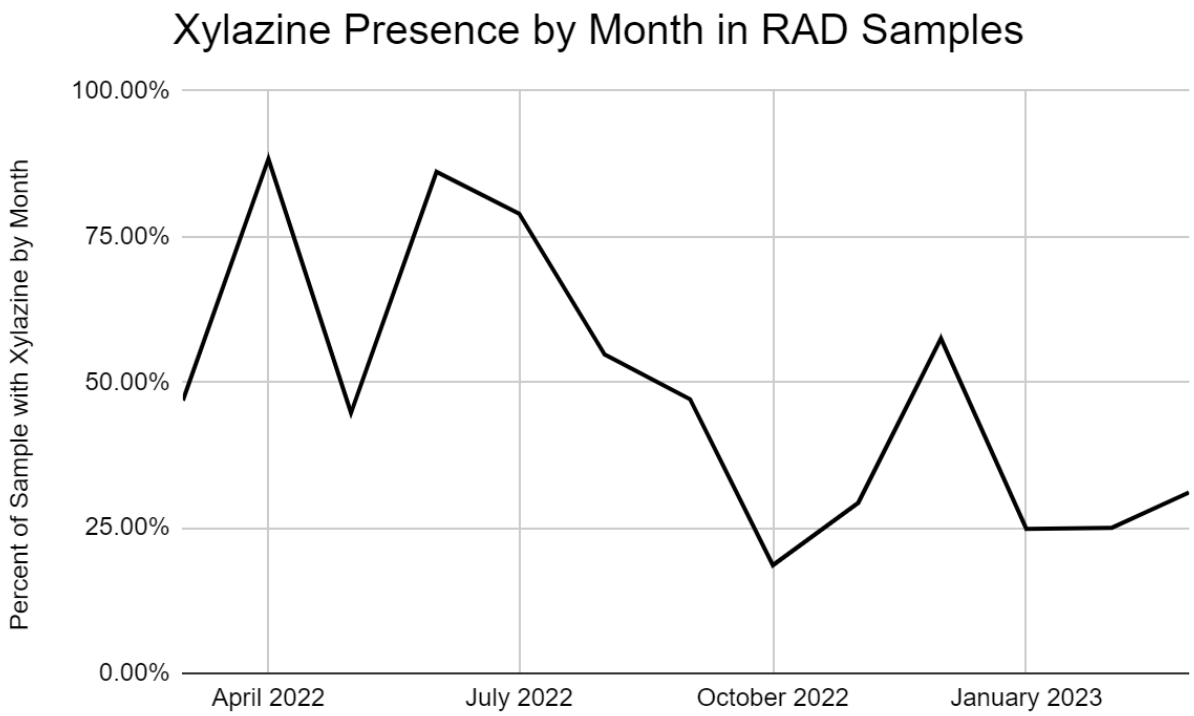


* Samples analyzed using direct analysis in real time mass spectrometry (DART-MS)

CONCORDANCE

- Questionnaires were submitted for 248 (50.0%) samples
  - 50.9% intended to purchase both heroin and fentanyl, or “fentanyl and/or heroin
  - 46.7% sought fentanyl alone
  - 2.4% sought heroin alone
  - Eighty-one percent of samples matched the participant’s intentions but **contained one or more additional substances**,
- When the participant reported intent to buy heroin, no sample tested positive for heroin
- For xylazine positive samples, participants intended to buy “fentanyl” or “fentanyl and/or heroin”

PROPORTION WITH XYLAZINE OVER TIME



- Percentage of samples positive for xylazine peaked in December 2022

IMPACT

PUBLIC AWARENESS

Pilot testing program in Maryland could save life and limb as new illegal drug danger emerges

Meredith Cohn

2, 2022 at 3:06 pm

THE BALTIMORE BANNER
Nonprofit. Local news.

Newsletters iMPACT MARYLAND Food and drink Alerts Cannabis coverage Health Sports Podcast Real estate Donate

Health

A dangerous animal sedative in street drugs is spreading beyond Maryland. It's not the only new threat.

Meredith Cohn

Published 4/24/2023 6:06 a.m. EDT, Updated 4/26/2023 2:31 p.m. EDT

npr WAMU 88.5 AMERICAN UNIVERSITY RADIO

NEWS CULTURE MUSIC PODCASTS & SHOWS SEARCH NEWSLETTERS SIGN IN NPR SHOP DONATE

HEALTH

Caring for people with fentanyl addiction often means treating terrible wounds

August 13, 2023 · 6:00 AM ET

By Scott Maucione

FROM WYPR

PROGRAM IMPACT

- The Department of Health directed **funding to wound care prevention and treatment** at syringe service programs

PROGRAM IMPACT

- **Increased engagement with SSP participants**
  - Programs sharing results directly back to participant and more broadly with all individuals they serve
  - People expressed surprise and concern
  - Providing education on rare or unknown substances and potential side effects and risks
- **Increased interest in various services/linkages**
- **Participants sharing information/results with others**

RECOMMENDATIONS

XYLAZINE RESPONSE RECOMMENDATIONS

1. Technologies for quantitative and qualitative surveillance
   - **Drug checking is offered on-site** at every harm reduction organization
   - Ongoing **qualitative data collection with people who use drugs** to identify risk reduction strategies early on
   - **Comprehensive lab-based drug checking** to provide surveillance for public health intervention, including quantitative testing
2. State and/or county-level coordination of partners
   - **Incorporate the tracking of emerging substances** into **overdose prevention coalition activities** and medical examiner/coroner processes
   - **Prioritize funding for harm reduction programs**

POLICY IMPLICATIONS

1. Legalize drug paraphernalia (U. S. Code Title 21 Section 863) for public health purposes – infectious disease prevention and implementation of drug checking
2. Fund not only technologies that identify novel psychoactive substances for on-site use but technical assistance for programs
3. Establish standards for lab-based drug checking methods, data management, and reporting
   - Integrate findings into a national database

PROGRAM IMPLICATIONS

- New technologies will be **most effective** if integrated into a robust harm reduction network of care for people who are using drugs
  - Nonjudgmental access to all levels of care
  - Low to no barrier services
  - ⬆ Trust ⬇ Stigma

SAFE SUPPLY

- The drug supply is volatile and deadly, “safe supply” programs are a logical answer to what we will find with increased surveillance.
- **Safe supply** provides prescription opioid agonists to support an individual’s dependence, reduce addiction-related behaviors, and prevent their death
- Xylazine is one of many novel psychoactive substances that can disrupt people’s experience with the drug market and put them at increased risk of overdose. **Drug checking technologies and surveillance of the market is not enough.**

CLOSING

- A statewide, regional or national **drug checking** program to track novel psychoactive substances **is feasible.**
- Increased knowledge of xylazine and other substances is only useful if applied in a **robust harm reduction network**
- Federal and state **policy reform is necessary to expand drug checking and harm reduction programs nationally** to have an impact on overdose morbidity and mortality including the decriminalization of paraphernalia and safe supply.

THANK YOU

Erin Russell

Principal, Health Management Associates

erussell@healthmanagement.com

REAGAN-UDALL FOUNDATION FOR THE FDA

Session 2: Pharmacological and Clinical Research Needs

- **Keith K. Burkhart, MD**, Center for Drug Evaluation and Research, FDA
- **Zoë McElligott, PhD**, University of North Carolina
- **Gonçalo Gamboa da Costa, PhD,** National Center for Toxicology Research, FDA
- **Alex Krotulski, PhD,** Center for Forensic Science and Research and Education

October 4, 2023

XYLAZINE: PHARMACOLOGY RESEARCH NEEDS

Keith Burkhart, M.D. Senior Advisor for Medical Toxicology
Acknowledging
Rebecca Racz Pharm.D, Lidiya Stavitskaya, Ph.D and Donna Volpe, Ph.D

CDER Division of Applied Regulatory Science/Office of Clinical Pharmacology/Office of Translational Sciences

Objectives

- Discuss known pharmacology of xylazine
- Discuss potential secondary pharmacology activity that may warrant further investigation
- Disclaimer: This presentation reflects the views of the presenter and should not be construed to represent the views or policies of the U.S. Food and Drug Administration

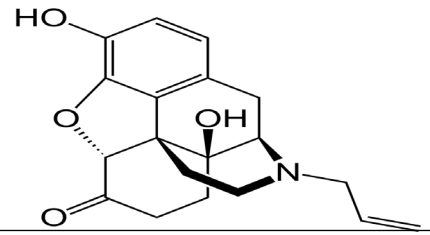
Xylazine Pharmacology

- Alpha-2 adrenergic agonist
- Similar to clonidine, tizanidine, dexmedetomidine
- Reduces release of norepinephrine and dopamine in CNS:

  sedation, miosis, hypotension (initial hypertension from peripheral agonist activity), bradycardia, bradypnea, and decreased perception of painful stimuli (analgesia)

Xylazine Pharmacology

- Dealkylated, oxidized, and hydroxylated metabolites in an overdose victim like those found in rat studies (Meyer, 2013)
- Sedation reversed by antagonists (yohimbine and antipamezole)
- The sedative effects of xylazine in chicks were reduced by pretreatment with high naloxone doses suggesting that xylazine may cause release of endogenous opioids (Ruskoaho, 1984)
- 50% of pediatric clonidine (similar actions as xylazine) overdoses given high dose of naloxone (0.1 mg/kg) had a positive clinical response (improved mental status) (Toce, 2021)
- Xylazine and naloxone (McElligott)



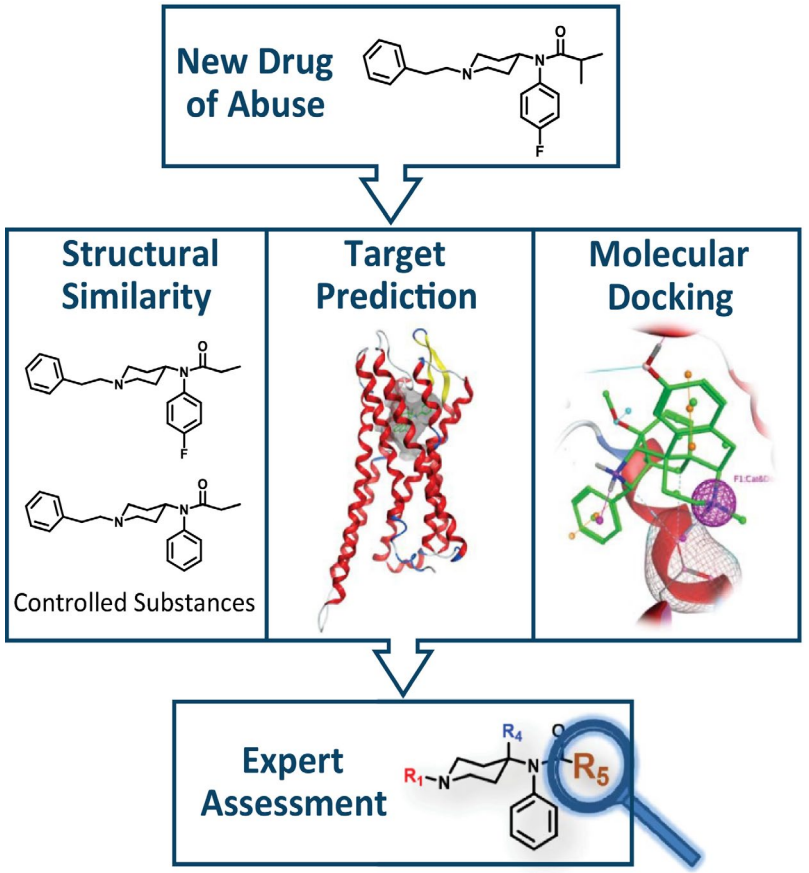
Xylazine: Clinical studies oral, IM and IV preparations

Hrubesh, 1966 Medical Doctor Dissertation at University of Dusseldorf: Anxiolytic and sedative in the preanesthetic and postoperative setting, and as an analgesic post-op “N=107” patients in operative and clinic settings.

- Oral xylazine (up to 40 mg) produced sedation and induced sleep, with no major effects on blood pressure. Recovered in 5 hours
- IV or IM xylazine (20-40 mg): sedation but BP dropped 20-50 mmHg in some patients with bradycardia and bradypnea
- No euphoria reported
- Periods of apnea and shallow breathing followed by normal breathing but maintain minute ventilation at 7 L/min.
- No PK measures of clearance or metabolites

Information Gaps Regarding Xylazine Pharmacology

- Limited data available to understand in vivo xylazine targets
  - Understanding targets influences clinical management and reversal strategies
- In silico tools allow for rapid assessment of misuse liabilities with emerging drug threats
  - Public Health Assessment via Structural Evaluation (PHASE)
  - Successfully used to characterize fentanyl analogs and kratom alkaloids (e.g., mitragynine)



Clin Pharma and Therapeutics, Volume: 106, Issue: 1, Pages: 116-122, First published: 08 April 2019, DOI: (10.1002/cpt.1418)

Kratom Predicted Binding in Addition to Opioid Receptors: Analyzed for over 2000 receptors

		Adrenergic Receptors						Serotonin Receptors			
		Alpha-2A		Alpha-2B		Alpha-2C		5-HT1A		5-HT2A	
ID	Name	Clarity	SEAware	Clarity	SEAware	Clarity	SEAware	Clarity	SEAware	Clarity	SEAware
1–4	Mitragynine, Speciogynine, Speciociliatine, Mitraciliatine	0.92	4.0e-15	0.85	8.4e-9	-	5.1e-13	-	-	0.54	-
5	Paynantheine	0.73	1.2e-14	0.73	8.4e-9	0.85	7.1e-13	-	-	0.79	-
6	Corynantheidine	0.92	2.8e-20	0.92	1.1e-11	-	2.7e-17	0.56	-	0.76	-
7	7-Hydroxymitragynine	0.31	-	0.31	-	0.32	-	-	-	-	-

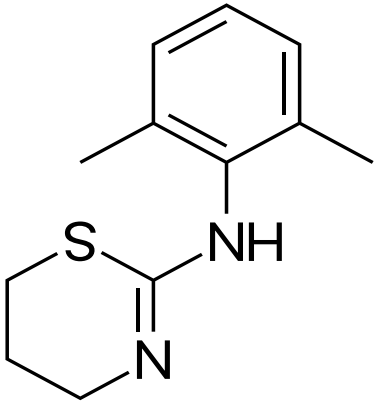
https://doi.org/10.1371/journal.pone.0229646.t003

Clarity: Scores greater 0.4 are considered high confidence, while 0.3-0.4 are lower confidence.
SEAware scores less than 1.0 e-5 are considered positive.

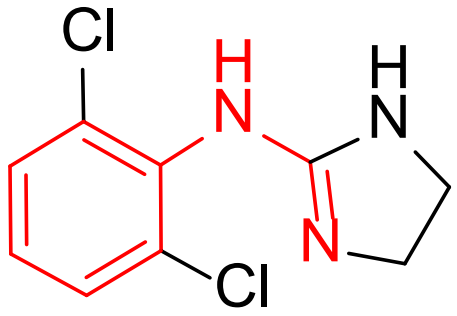
Bryan Roth: National Institute of Mental Health's funded Psychoactive Drug Screening Program confirmed the binding at these predicted receptors for mitragynine.

Structural Similarity Assessment

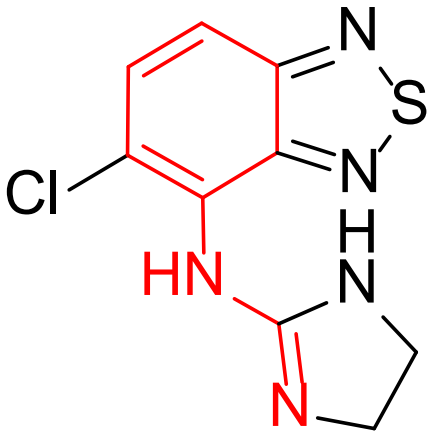
- Xylazine was found to be structurally most similar to clonidine, tizanidine, and levamisole.
- Similar moieties are highlighted in red



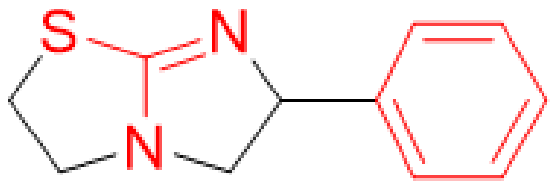
Xylazine



Clonidine



Tizanidine



Tetramisole/ Levamisole

Secondary Pharmacology Assessment

Known (K) and Predicted activity (P), Lower confidence (LC)

Drug	Alpha-2A, B and C adrenergic receptors	Cholinergic receptors	Muscarinic receptor	Nischarin: Mouse Imidazoline-1	Nitric oxide synthase e-,i-,n-	Serotonin 1, 1E receptor:	Trace amine-associated receptor 1
Xylazine	K	LC	LC	P	P	LC	P
Levamisole	LC	LC	LC			LC	
Clonidine	K	LC		K		LC	P
Tizanidine	K			K			

Metabolites 3- and 4-hydroxyxylazine: similar predictions as xylazine

Xylazine (Rompun®) Labeled Veterinary Adverse Events Likely Target

- Alpha-2 adrenergic agonism and Imidazoline-1: Sedation and bradypnea
- Nicotinic Receptor Agonism: Muscle tremors, sweating, salivation
- Serotonin Agonism: Temperature elevation, teeth grinding, and protruding tongue

Hrubesh Dissertation: Reported on the hypercapnic ventilatory response after doses up to 50 mg IV xylazine

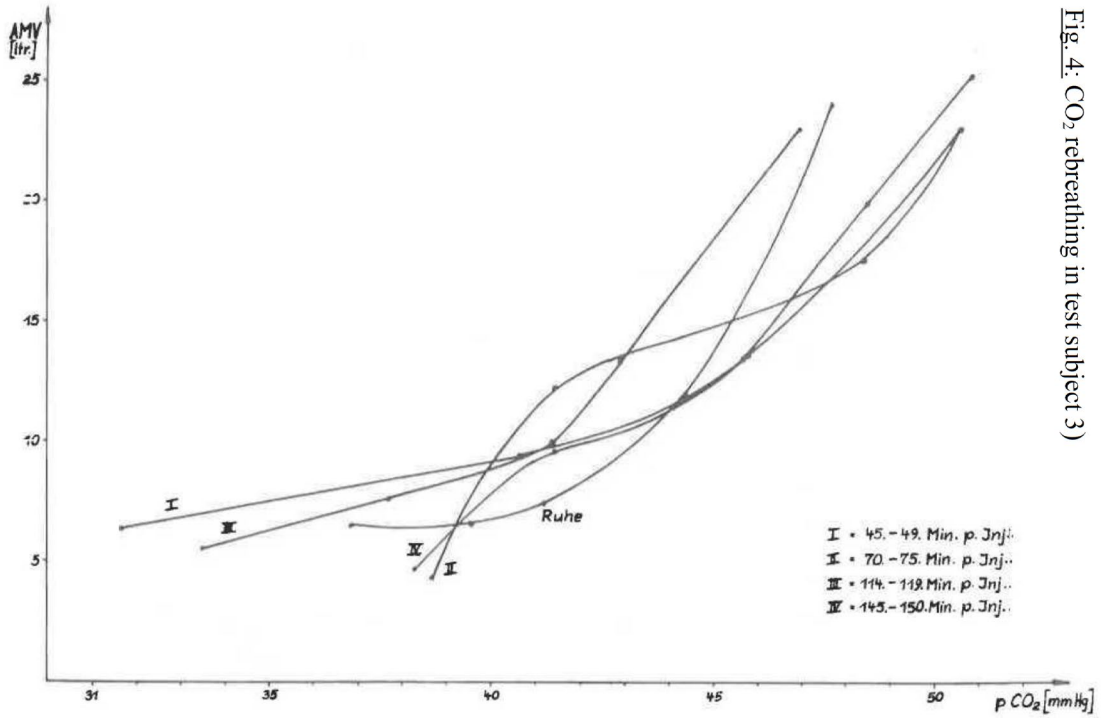


Fig. 4: CO_2 rebreathing in test subject 3)

- 3 of 4 patients maintained the hypercapnic response significantly increasing minute ventilation
- Sato et al in a rat model using dexmedetomidine with adrenergic and imidazoline blockers reports that imidazoline-1 activation preserved the respiratory drive

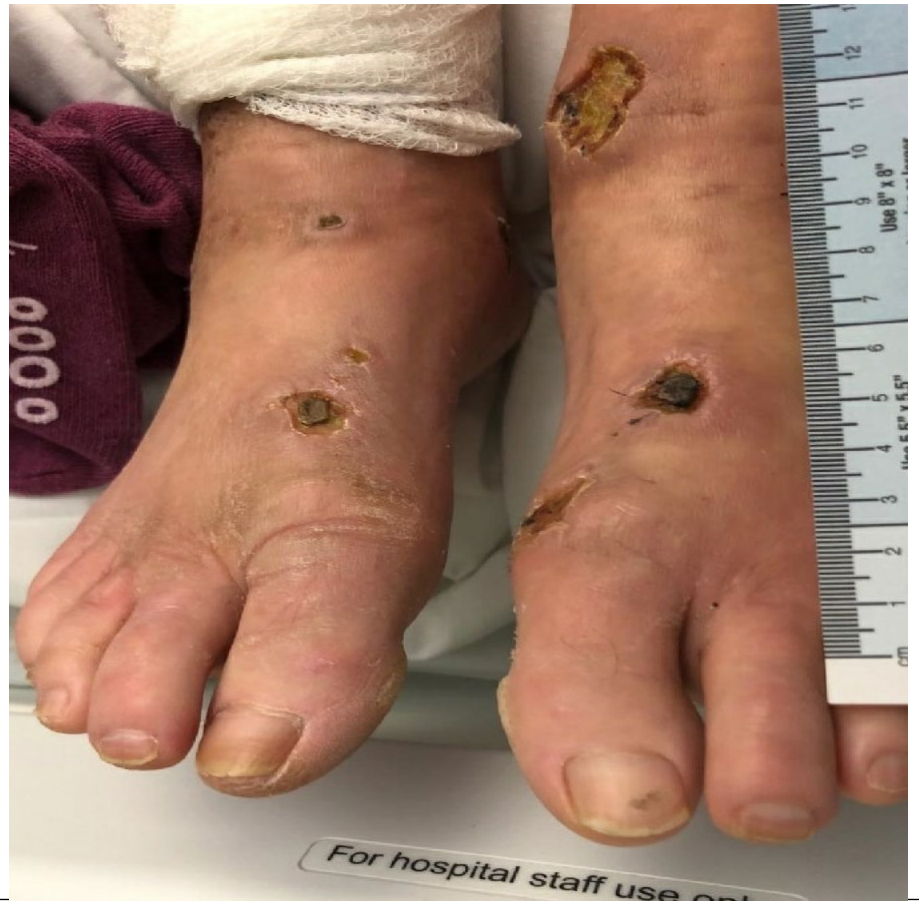
Imidazoline 1 receptor activation preserves respiratory drive in spontaneously breathing newborn rats during dexmedetomidine administration DOI: 10.1111/pan.13107

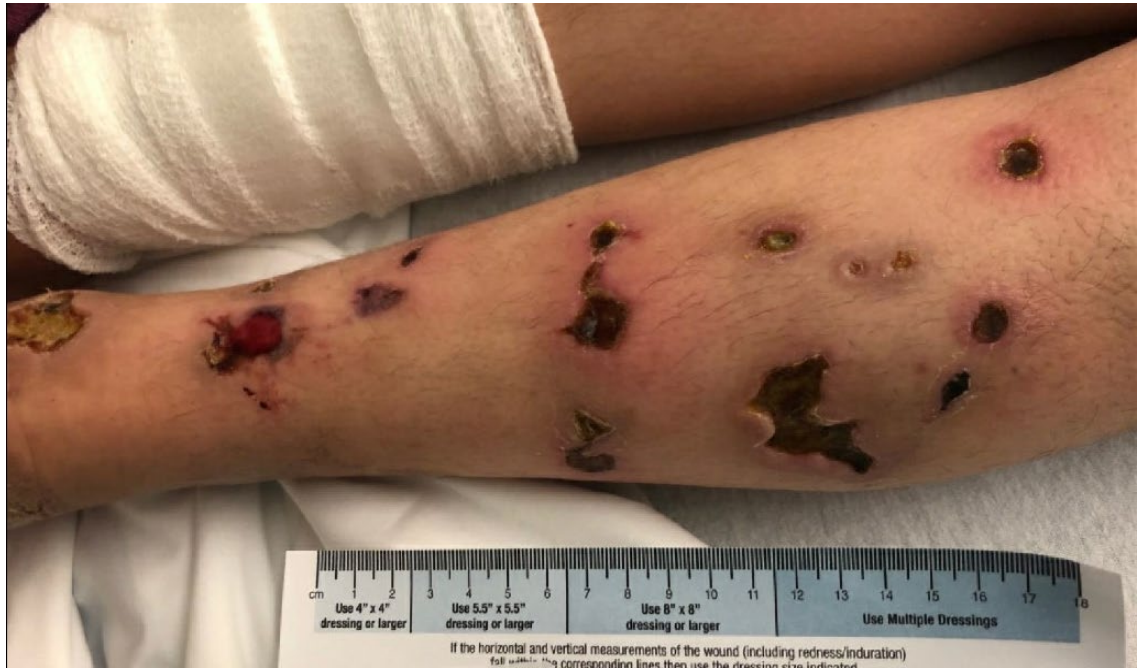
What is xylazine's impact on respiration considering possible serotonin receptor activity?

- Investigations have shown that paroxetine, a selective serotonin reuptake inhibitor, reduces hypercapnic ventilation on its own and had additive effects when combined with oxycodone *
- Other nonclinical and clinical studies in the literature have shown serotonin neurotransmission may depress the hypercapnic ventilatory response
- Quetiapine although more sedating with anticholinergic properties did not depress hypercapnic ventilation *
- Xylazine in overdose is usually found with opioids that have pro-serotonergic effects

* Effect of Paroxetine or Quetiapine Combined With Oxycodone vs Oxycodone Alone on Ventilation During Hypercapnia. doi: 10.1001/jama.2022.17735

Xylazine Wounds:
Courtesy: The Christiana Care Addiction Medicine Service





Xylazine wounds: Does predicted Nitric Oxide Synthase (NOS) activity have a role?

- Nitric oxide (NO) important to wound healing (Man, 2022) including angiogenesis (Cooke, 2003)
- In a rat splenocyte model xylazine shows dose dependent immunomodulation, low stimulatory, but high doses were inhibitory and may have effects independent of NO signaling. Clonidine did not show similar effects (Cupic, 2001)
- Levamisole: Autoimmune reactions (vasculitis, agranulocytosis)
- Bishnoi et al (2023) call for research into immune mediated vasculopathy by xylazine

Conclusions: Pharmacology Research Needs

- Pharmacokinetics:
  - Low dose and overdose
  - Metabolites
- Pharmacodynamics:
  - Secondary pharmacology activity
  - DDI studies (impact on respiration)
  - Wound infections
- Antidotes:
  - Naloxone
  - Other antagonists

References

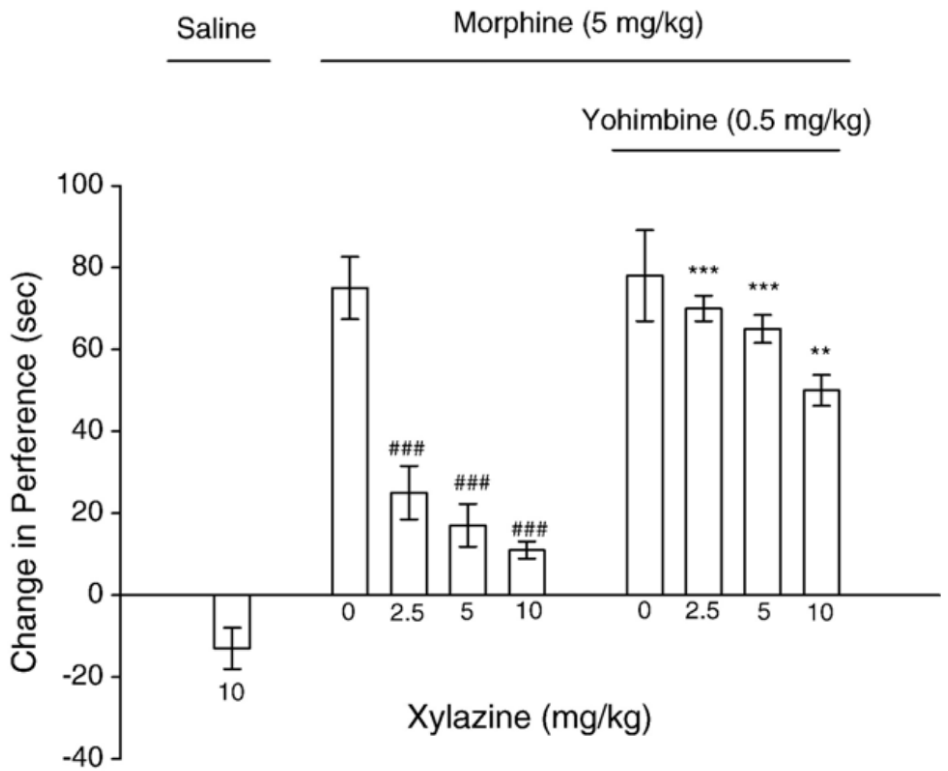
- Bishnoi A, Singh V, Khanna U, Vinay K. Skin ulcerations caused by xylazine: A lesser-known entity. J Am Acad Dermatol. 2023 Aug;89(2):e99-e102
- Cooke, JP. NO and angiogenesis. Atherosclerosis. 2003;4(4):53-60
- Cupic V, Colic M, Pavicic L, Vucevic D, Varagic VM. Immunomodulatory effect of xylazine, an alpha-2 adrenergic agonist, on rat 2 spleen cells in culture. Journal of Neuroimmunology 2001;113:19–29
- Ellis CR, Racz R, Kruhlak NL, Kim MT, Zakharov AV, Southall N, et al. (2020) Evaluating kratom alkaloids using PHASE. PLoS ONE 15(3): e0229646. https://doi.org/10.1371/journal.pone.0229646
- Ellis CR, Racz R, Kruhlak NL, Kim MT, Hawkins EG, Strauss DG, et al. Assessing the Structural and Pharmacological Similarity of Newly Identified Drugs of Abuse to Controlled Substances using PHASE. Clin Pharmacol Ther. 2019; 106(1):116–22. https://doi.org/10.1002/cpt.1418 PMID: 30957872
- Man M-Q, Wakefield JS, Mauro TM, Elias PM. Regulatory role of nitric oxide in cutaneous inflammation. Inflammation 2022 Jun;45(3):949-964
- Meyer GM, Maurer HH. Qualitative metabolism assessment and toxicological detection of xylazine, a veterinary tranquilizer and drug of abuse, in rat and human urine using GC-MS, LC-MS^n, and LC-HR-MS^n. Anal Bioanal Chem. 2013; 405(30):9779-9789
- Ruskoaho H, Karppanen H. Xylazine-induced sedation in chicks is inhibited by opiate receptor antagonists. Eur J Pharmacol. 1984; 100(1):91-96
- 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
- Sato N, Saiki C, Tamiya J, Imai T, Sunada K. Imidazoline 1 receptor activation preserves respiratory drive in spontaneously breathing newborn rats during dexmedetomidine administration. Pediatr Anesth. 2017 May;27(5):506-515
- Schotland P, Racz R, Jackson DB, Soldatos TG, Levin R, Strauss D, Burkhart K. Target adverse event profiles for predictive safety in the post-market setting. Clin Pharmacol Ther. 2020. doi: 10.1002/cpt.2074.S
- Toce MS, Freiman E, O'Donnell, Burns MM. Clinical effects of pediatric clonidine exposure: A retrospective cohort study at a single tertiary care center. J Emerg Med. 2021;60(1):58-66

UNC
SCHOOL OF MEDICINE

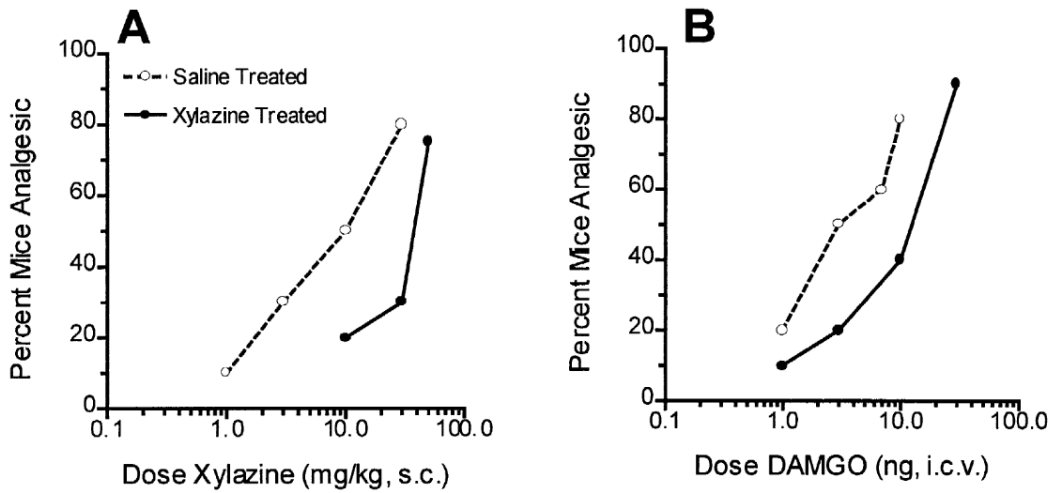
Xylazine is a κOR agonist and exhibits sex-specific behaviors

Zoé McElligott, Ph.D.
Bowles Center for Alcohol Studies
Department of Psychiatry
Department of Pharmacology
UNC Chapel Hill

Xylazine is poorly understood



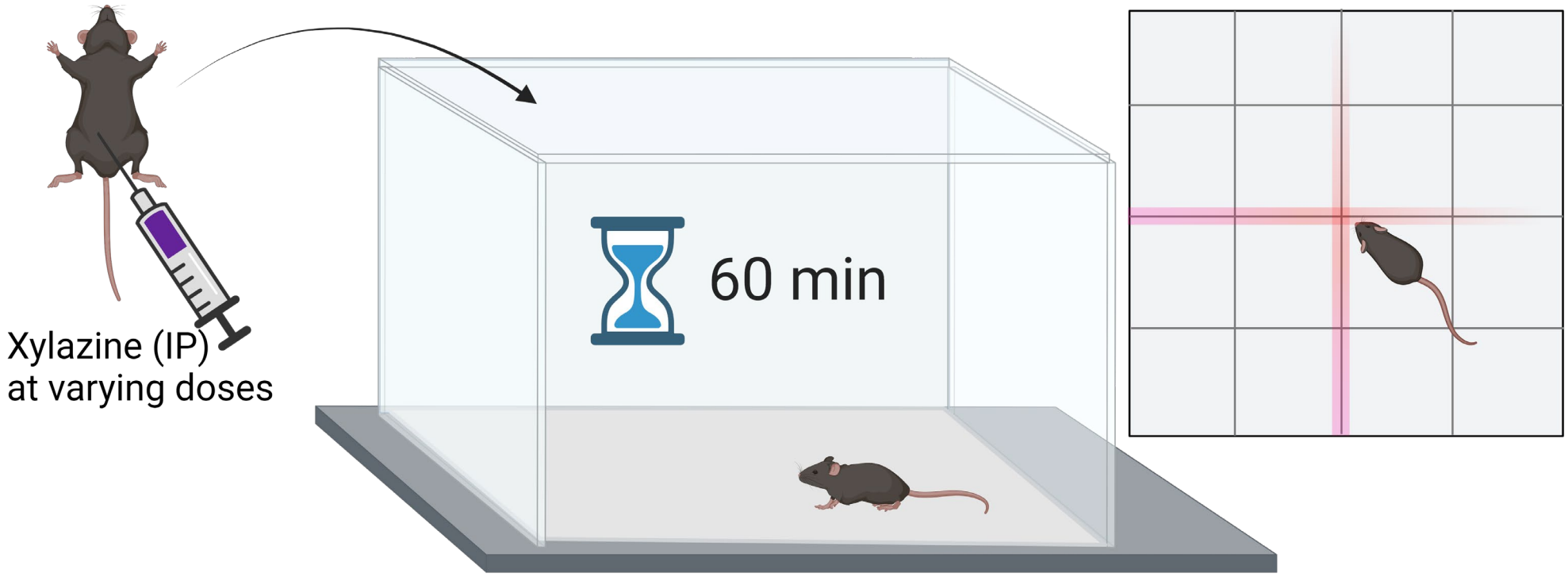
A2A-agonists decreased morphine CPP
Samini et al. (2008)



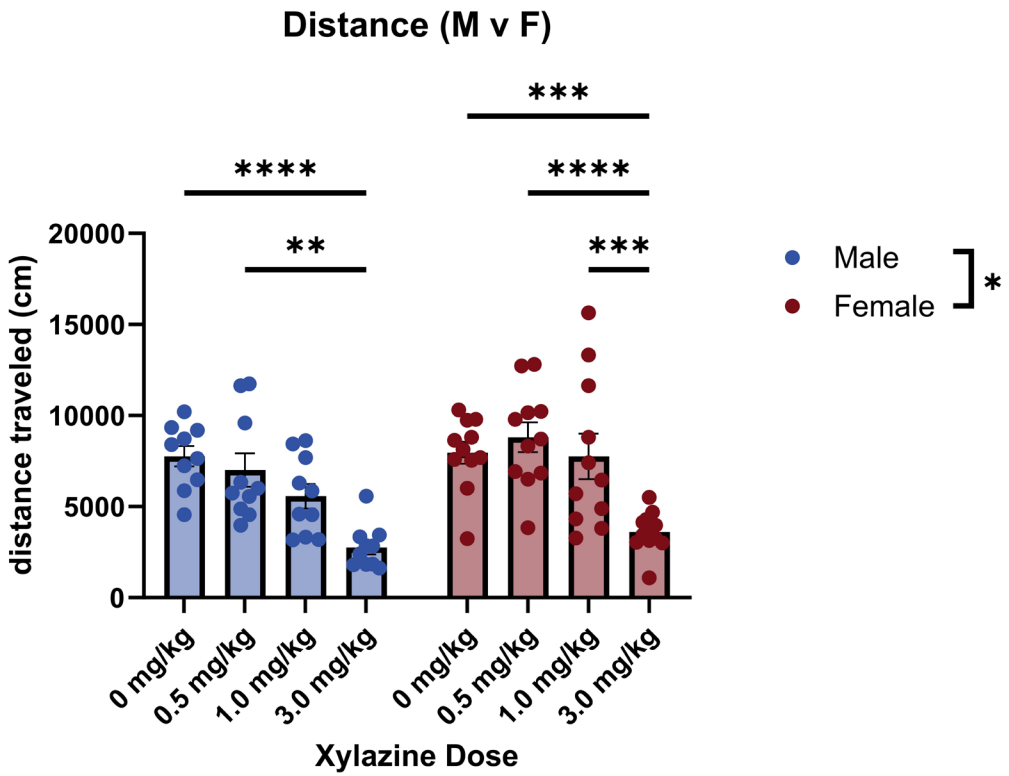
Xylazine tolerant mice required 4.57-fold more xylazine to elicit the same response as saline treated animals and showed a 2.55-fold shift in i.c.v. DAMGO

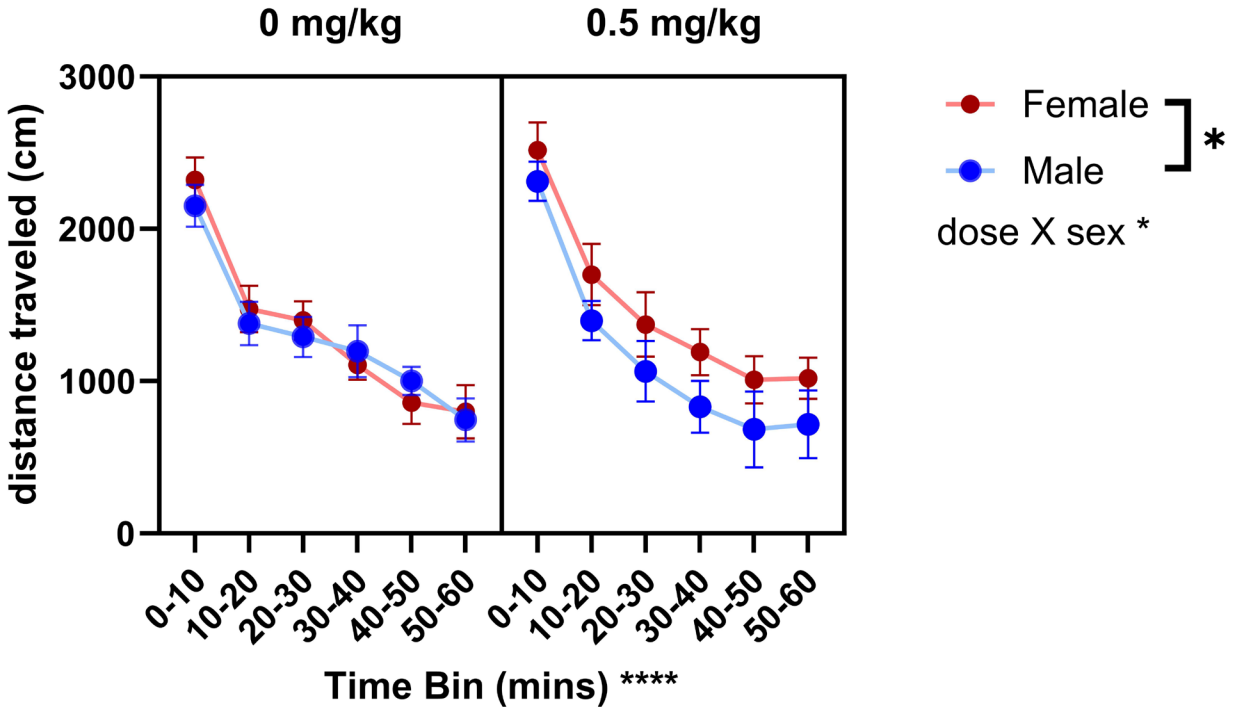
Ware and Paul (2008)

Open-Field Locomotion



0.5 mg/kg xylazine does not impair locomotion





Alexandra Nowlan and Caroline Clodfelter

Bedard et al. (2023, biorxiv)

How does xylazine alter the OWS landscape?

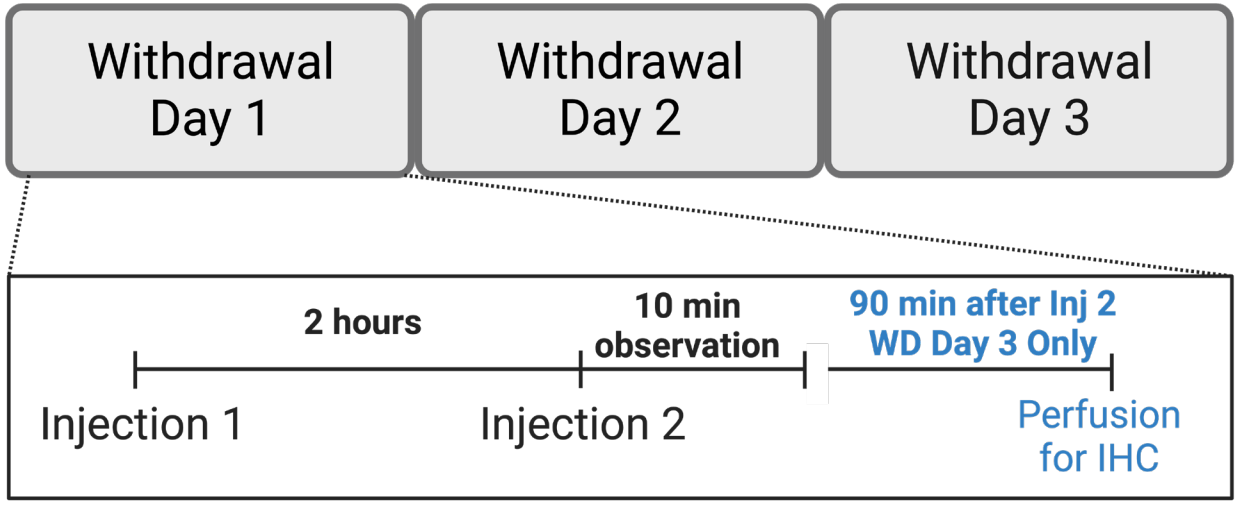
UNC SCHOOL OF MEDICINE

- “See, the tr*nq like extends the high, it gives the dope more of a heroin effect”
- “the worst detox right now, because the rehabs can't seem to find something to help”
- “you’re waking up 2–3 h later in a weird position”

- Does xylazine alter the PK/PD of fentanyl? Give fentanyl “legs”?
- Does naloxone reverse the effects of xylazine+fentanyl? Are there better antagonist options?
- What doses of xylazine are sedative in C57 mice?

Friedman et al. (2022)

Antagonist - Precipitated Withdrawal



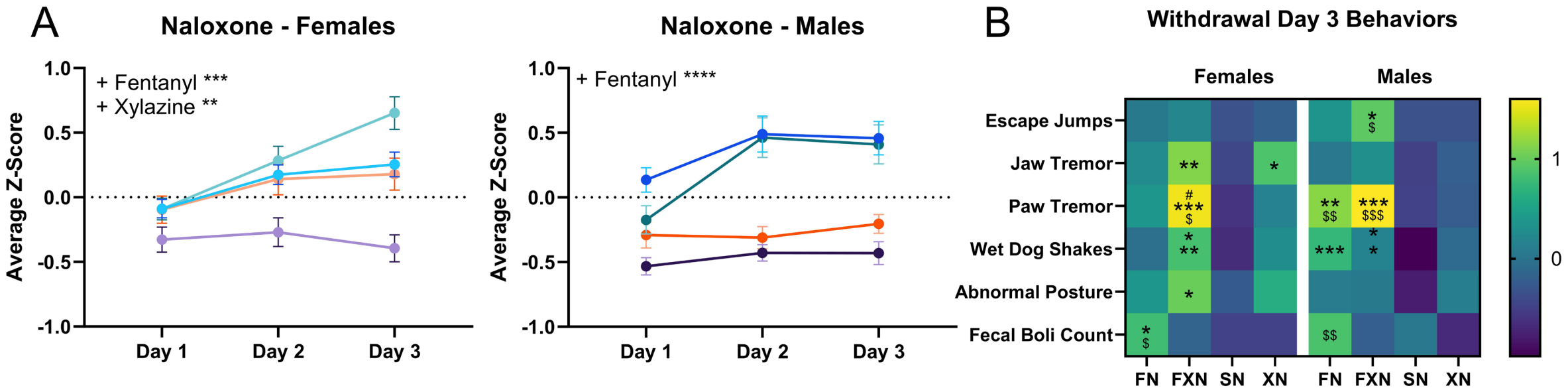
Withdrawal Behaviors

- Escape Jumps
- Paw Tremors
- Jaw Tremors
- Wet Dog Shakes
- Abnormal Posture
- Fecal Boli Count

Injection 1 = agonist
Injection 2 = antagonist

Bravo et al. (2019)
Luster, Cogan et al. (2019)
Bedard et al. (2023a,b)
Bedard et al. (2023, biorxiv)

Naloxone - Precipitated Withdrawal

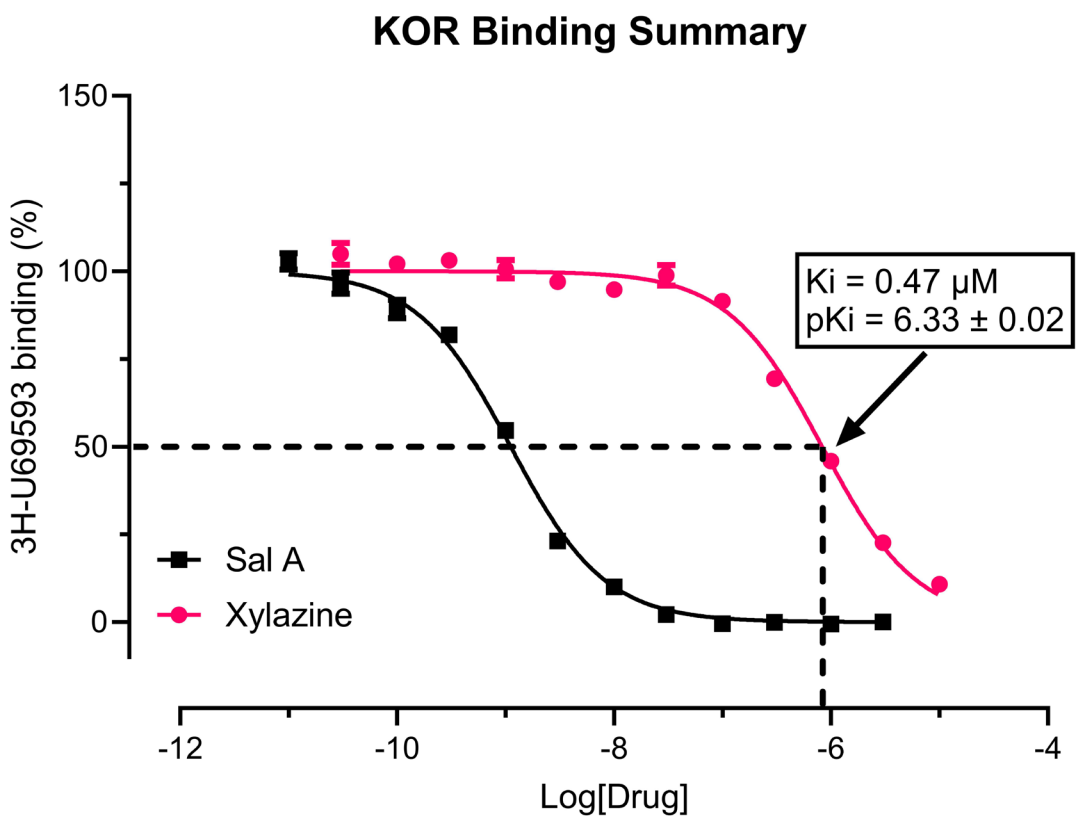


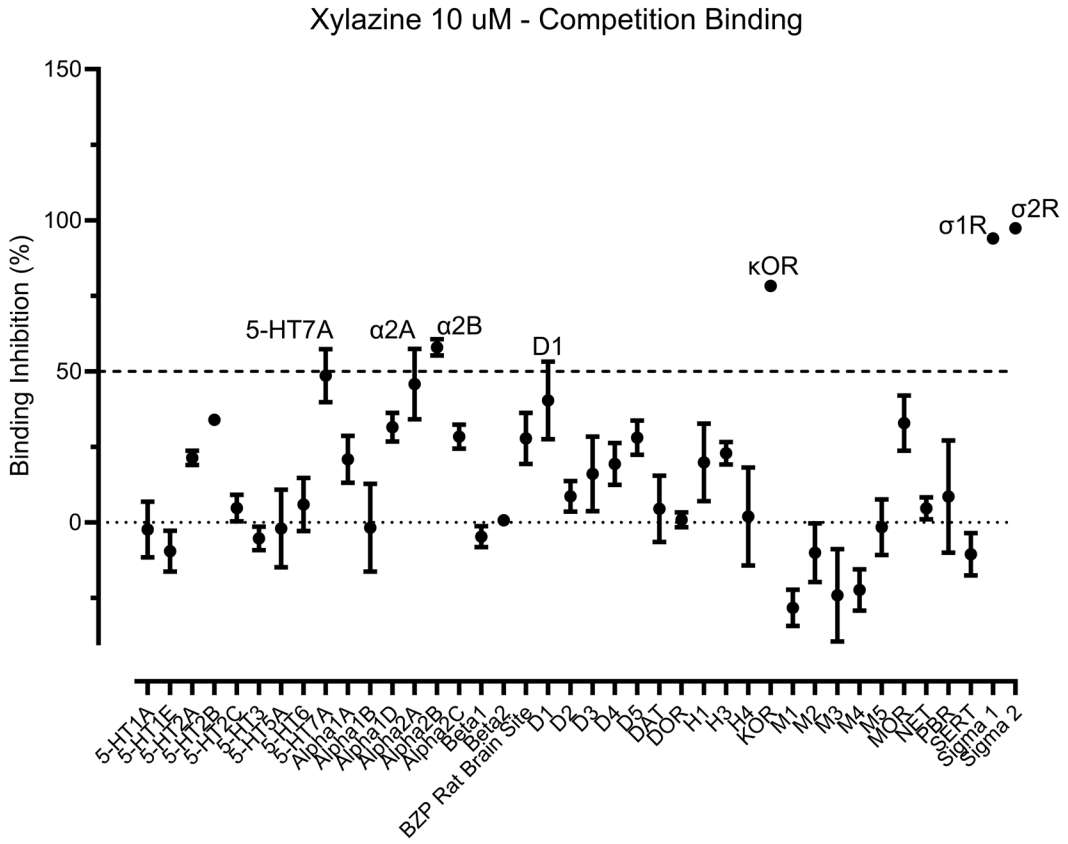
Naloxone = opioid receptor antagonist
Differential brain region activation in males and females
Bedard et al. (2023, biorxiv)

Females
Fentanyl — Saline
Xylazine — Fentanyl + Xylazine

Males
Fentanyl — Saline
Xylazine — Fentanyl + Xylazine

Radioligand Binding Assays



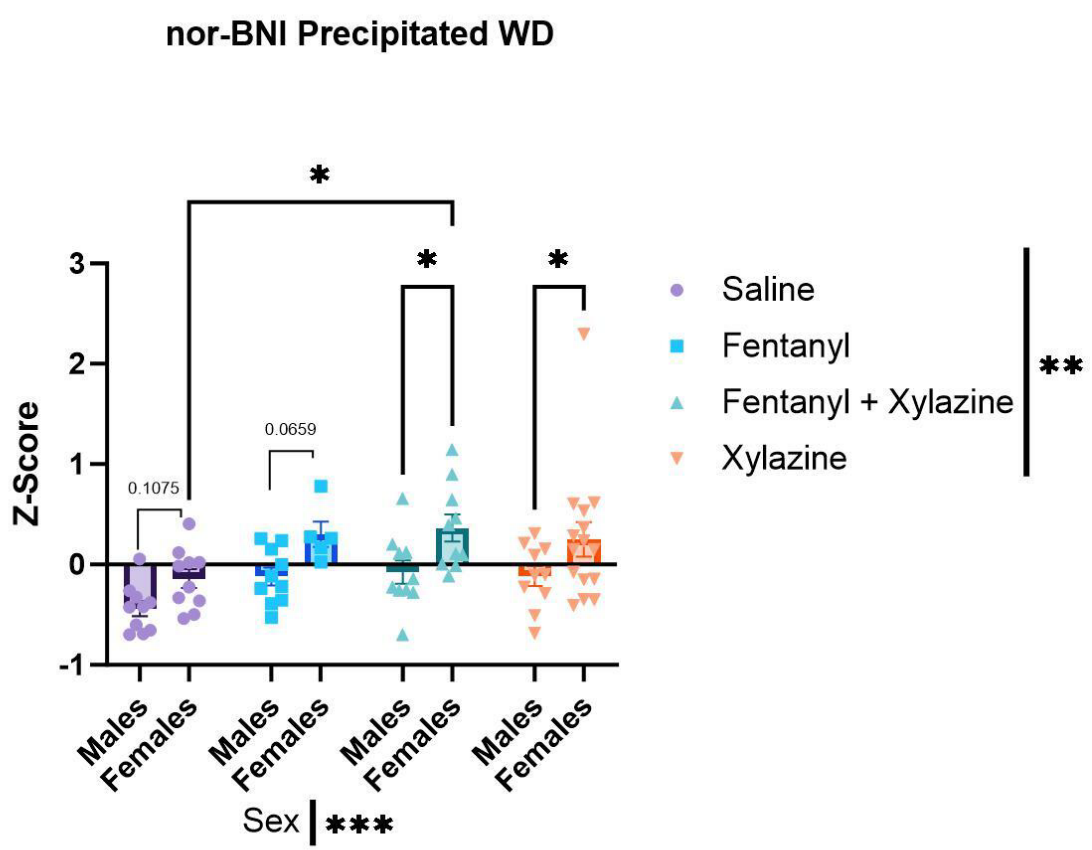


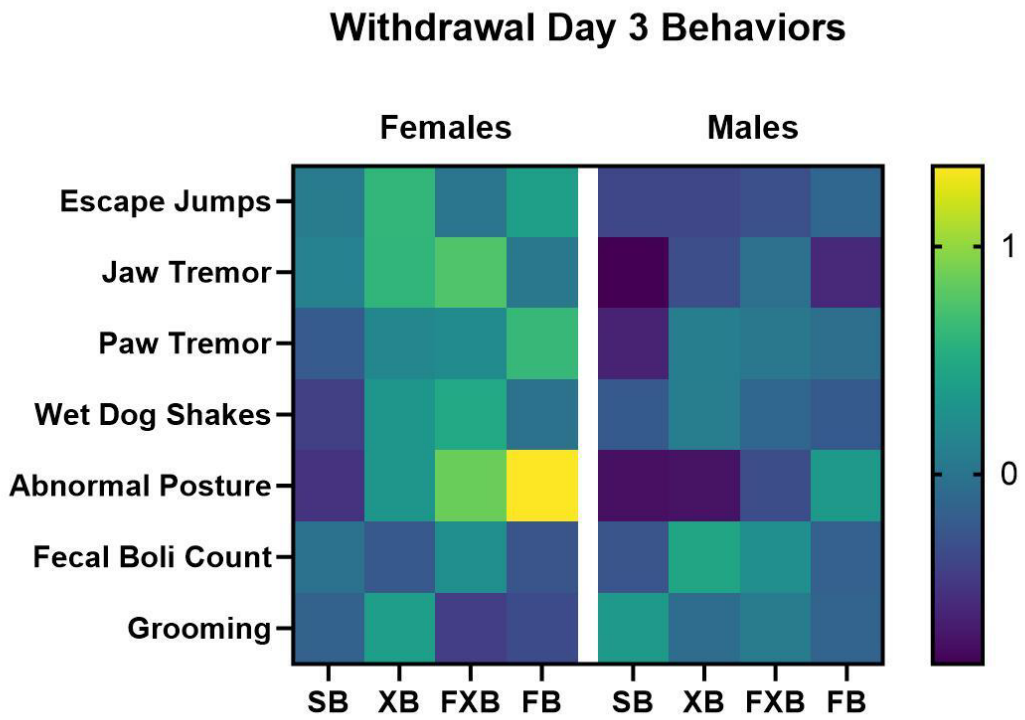
Bedard et al. (2023, biorxiv), XP Huang

Xylazine withdrawal in females to KOR antagonist

UNC SCHOOL OF MEDICINE

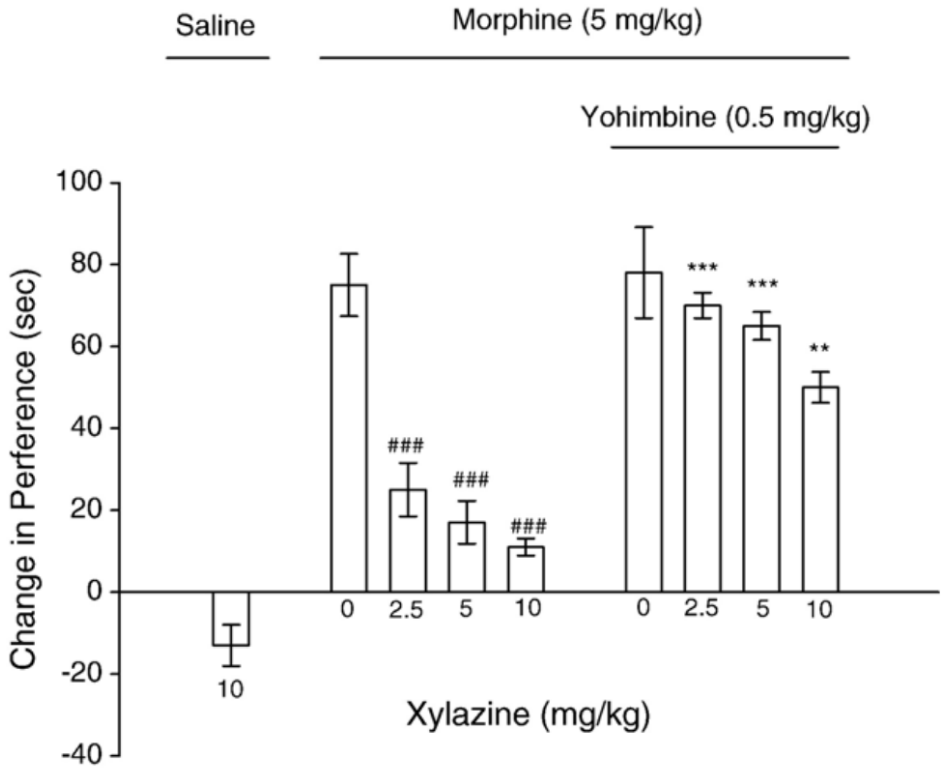
- 3 days of drug treatment, single injection norBNI for withdrawal



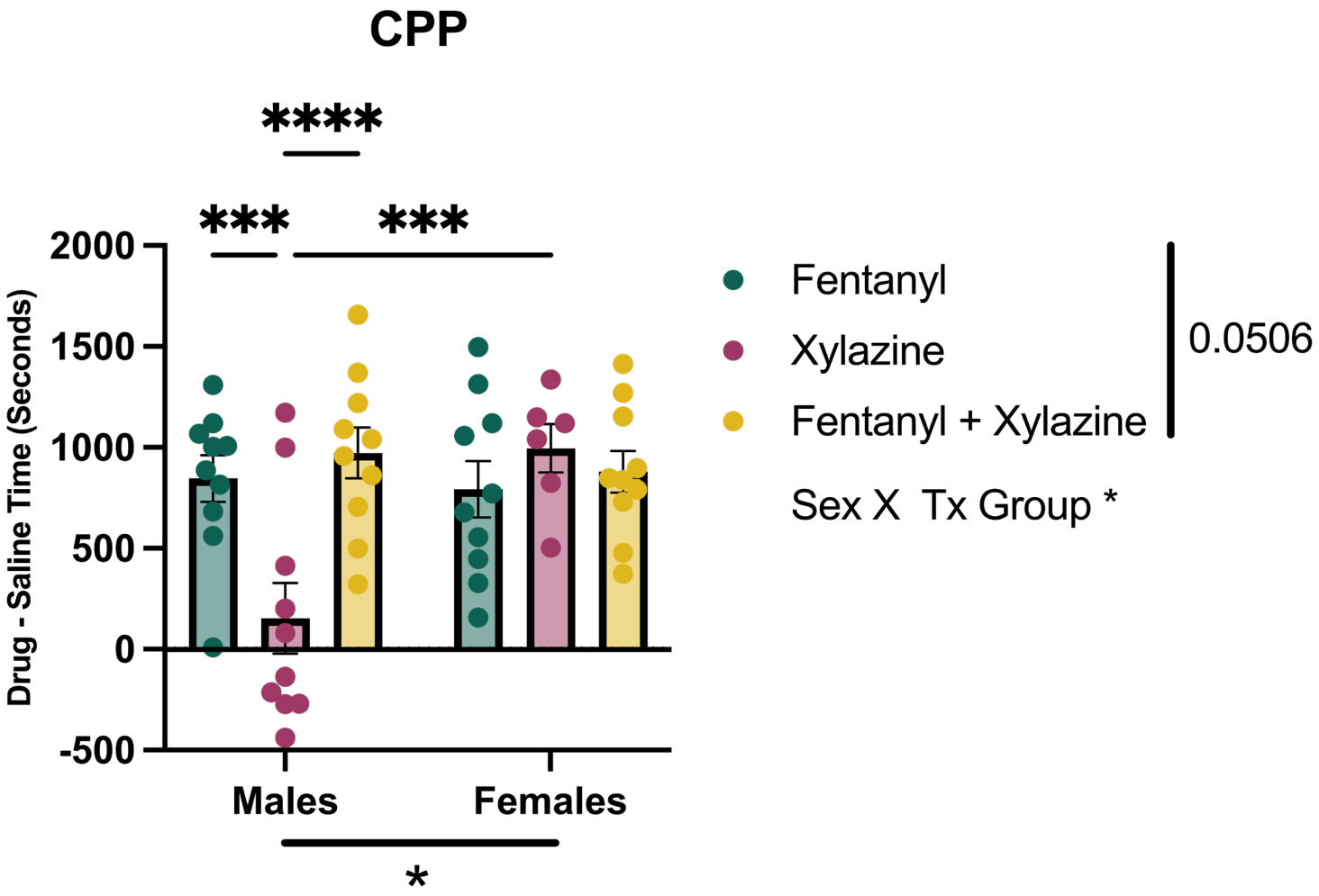


Madigan Bedard

Conditioned Place Preference



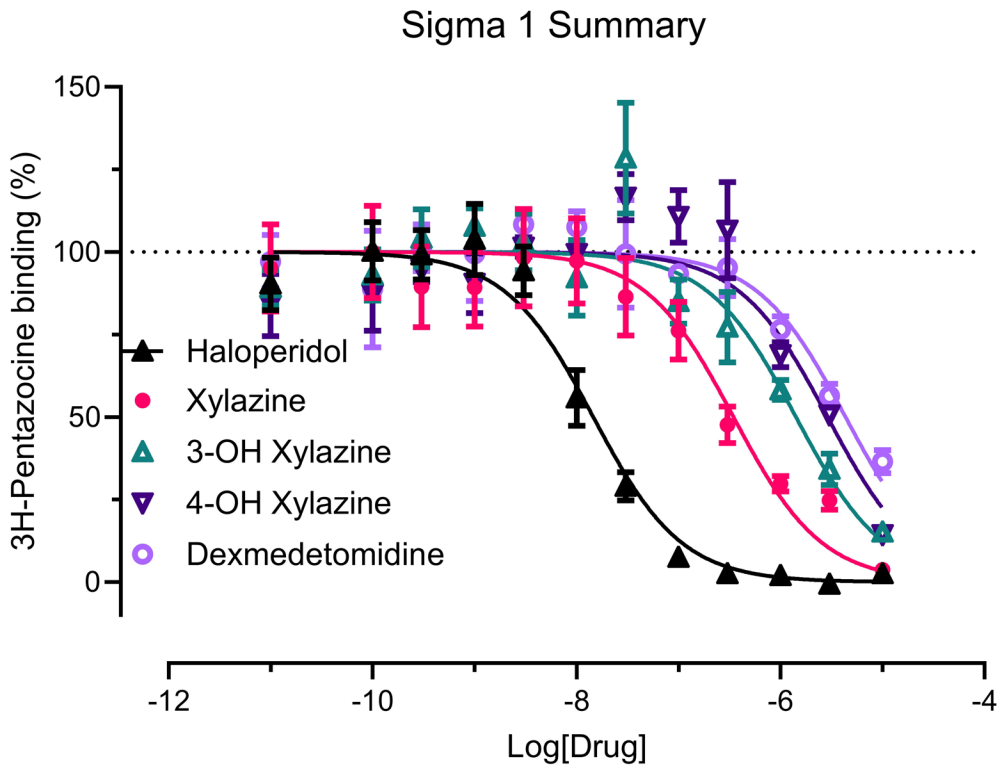
A2A-agonists decreased morphine CPP
Samini et al. (2008)

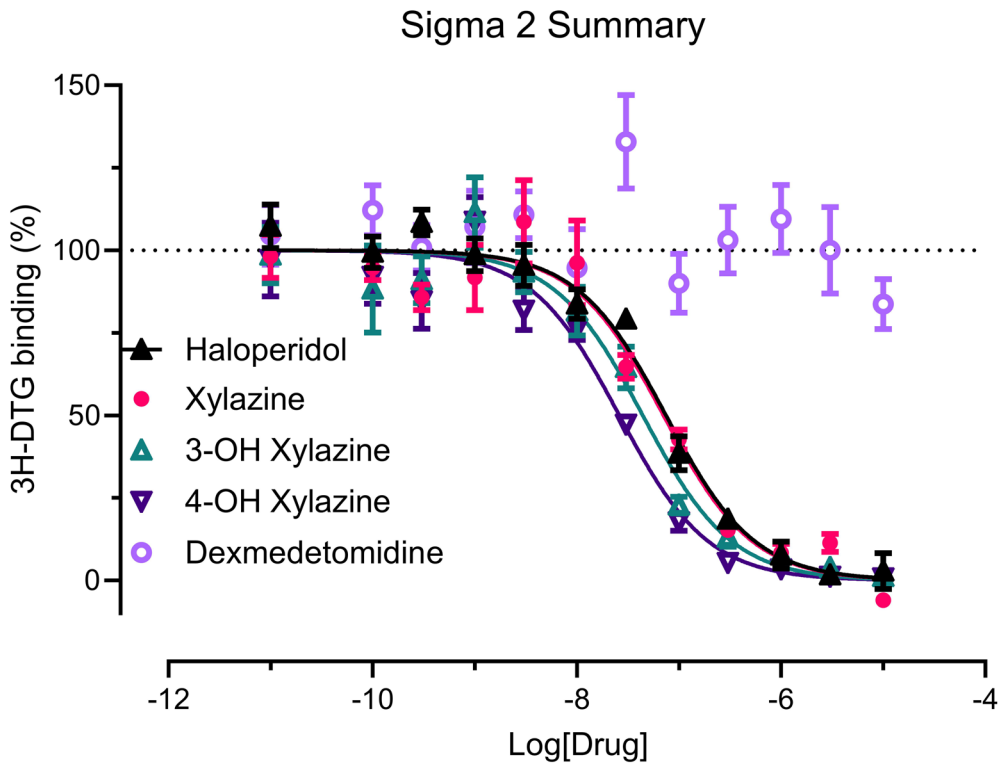


Mitch Huffstickler

Xylazine and Dex bind Sigma 1, Xyl binds Sigma 2

UNC SCHOOL OF MEDICINE





XP Huang

Summary of today's presentation

UNC SCHOOL OF MEDICINE

- Bedard et al., biorxiv.org, 2023
  - Low dose xylazine stimulates locomotion in female mice
  - Xylazine exacerbates naloxone precipitated withdrawal in female but not male mice
  - Xylazine has full agonist activity at K-opioid receptors

- New data
  - K-opioid receptor antagonist norBNI precipitates withdrawal from xylazine only in female mice
  - Low dose xylazine promotes conditioned place preference – an index of reward learning – only in female mice
  - Xylazine, and it's metabolites, bind additional targets including sigma receptors

Acknowledgments

UNC SCHOOL OF MEDICINE

McElligott Lab

Madigan Bedard

Anthony Downs, PhD

Alexandra Nowlan, PhD

Sarah Sizer, PhD

Gray Gereau

Sara Conley

Mitch Huffstickler

Jackson Murray

Zoë Martin del Campo

Calista Cline

Caroline Clodfelter

Samuel Loyack

Gracie Kmiec

Diana Zhou

Luke Wykoff

Madhura Manjunath

Isabella Girgis

Collaborators

Xi-Ping Huang, PhD

Bryan Roth, MD/PhD

Bryan Krumm, PhD

Nab Dasgupta, PhD, MPH

Joyce Besheer, PhD

Kate Reissner, PhD

Sarah Mott

- Triangle CERSI: U01FD0078857
- R01DA049261

UNC SCHOOL OF MEDICINE Pharmacology

bio RENDER

FDA U.S. FOOD & DRUG ADMINISTRATION

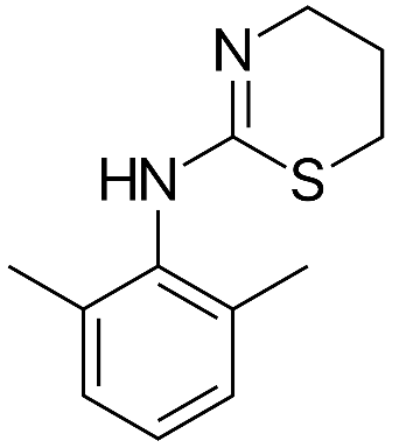
NIH National Institute on Drug Abuse

FDA Research on Xylazine

FDA Office of the Chief Scientist
National Center for Toxicological Research

Gonçalo Gamboa da Costa, Ph.D.

This presentation reflects the views of the presenter and should not be construed to represent the views or policies of the U.S. Food and Drug Administration.



Xylazine

Xylazine was originally developed in 1962 by the Bayer Corporation, Leverkusen, Germany as an antihypertensive agent.

Xylazine was approved by the U.S. FDA in 1972 as a non-opioid sedative and analgesic for use in veterinary medicine, where it finds widespread use. Very recent data indicates that xylazine binds to the human kappa opioid receptor.

There are no approved uses of xylazine for humans.

Xylazine has been used as an adulterant of heroin since 2000 in Puerto Rico.

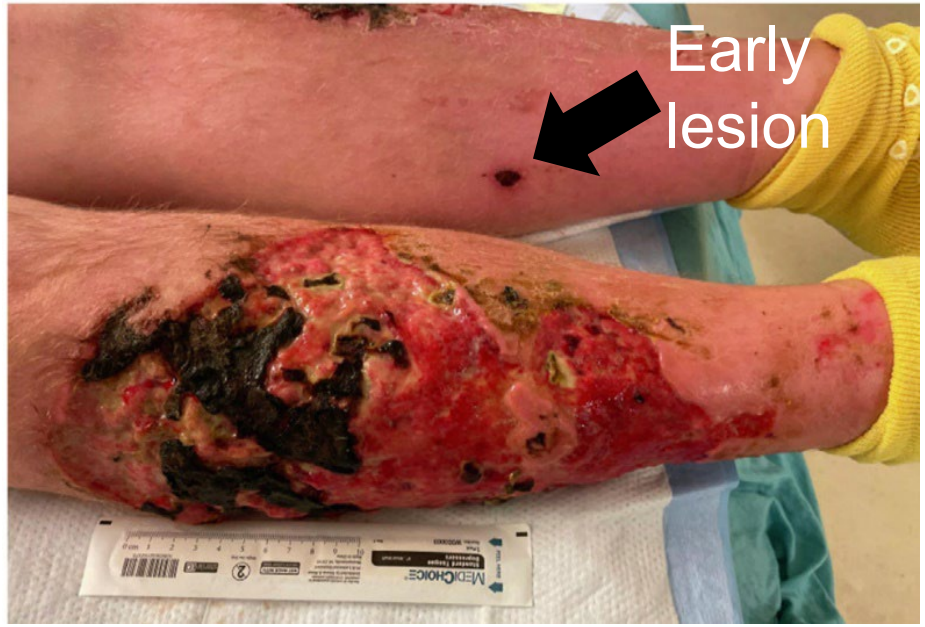
More recently, xylazine gained ground as an adulterant of fentanyl in the U.S. with particular prevalence in Philadelphia, PA, but is expanding to other states. Xylazine is reported to lengthen the short duration of fentanyl injection's effects.

Induction of necrotic skin lesions following injectable use of xylazine + fentanyl

Induction of necrotic skin ulcerations on site of injection, typically further complicated by secondary infection.

Wounds often arise away from the injection sites.

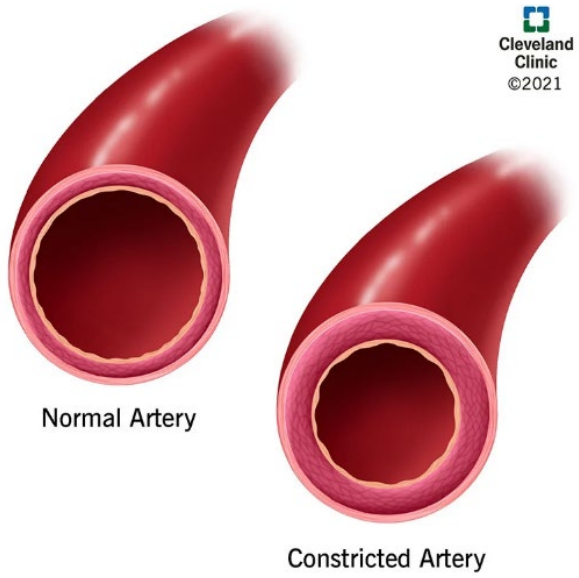
Anecdotal reports that “missing the vein” leads to increased chance of developing the lesions.



*Adapted from Wei et al. (2023) JAAD Case Reports, **36**, 89-91.*

Developing a model for xylazine + fentanyl-induced skin lesions

- Mechanism thought to involve prolonged peripheral vasoconstriction and hypoxia of the tissues mediated by α2-receptor activation by xylazine.
- Possible involvement of the kappa opioid receptor in the skin has been hypothesized. Reports of comparable lesions following injection of pentazocine, another kappa opioid receptor agonist.
- The natural history of the lesions remains poorly understood because most patients only seek medical care on very advanced stages of the lesions.



From: Cleveland Clinic

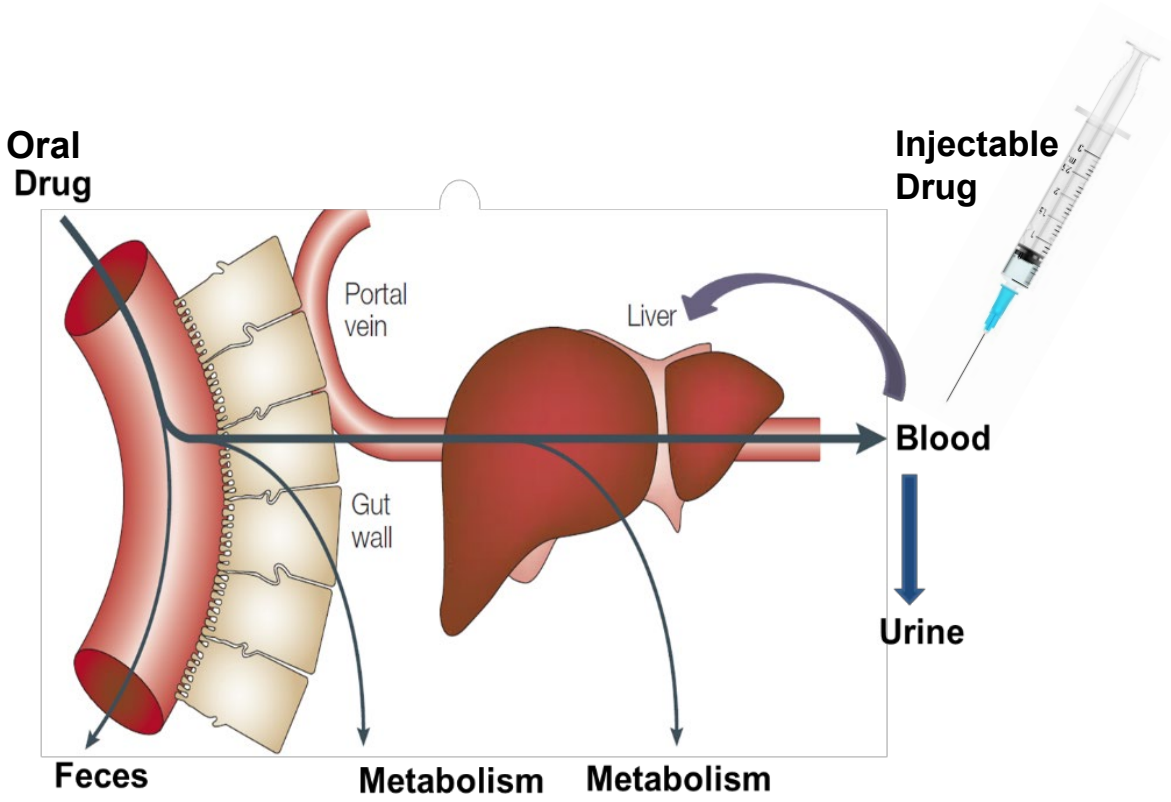
Clear need to develop a model to investigate the mechanisms behind the induction of skin lesions and enable the study of possible clinical interventions

Steps FDA is taking to develop a model for skin lesions induced by injectable use of xylazine + fentanyl

A model to investigate the formation of skin lesions needs to reflect receptor activation, potential immune mediated responses, and metabolites formed in humans.

Most drugs undergo metabolism in the body to facilitate elimination. The resulting drug metabolites can differ between humans and laboratory animals.

The extent to which the drugs are metabolized, the nature of the specific metabolites, and how long these compounds remain in circulation before elimination can be determinants to the mechanism of toxicity.

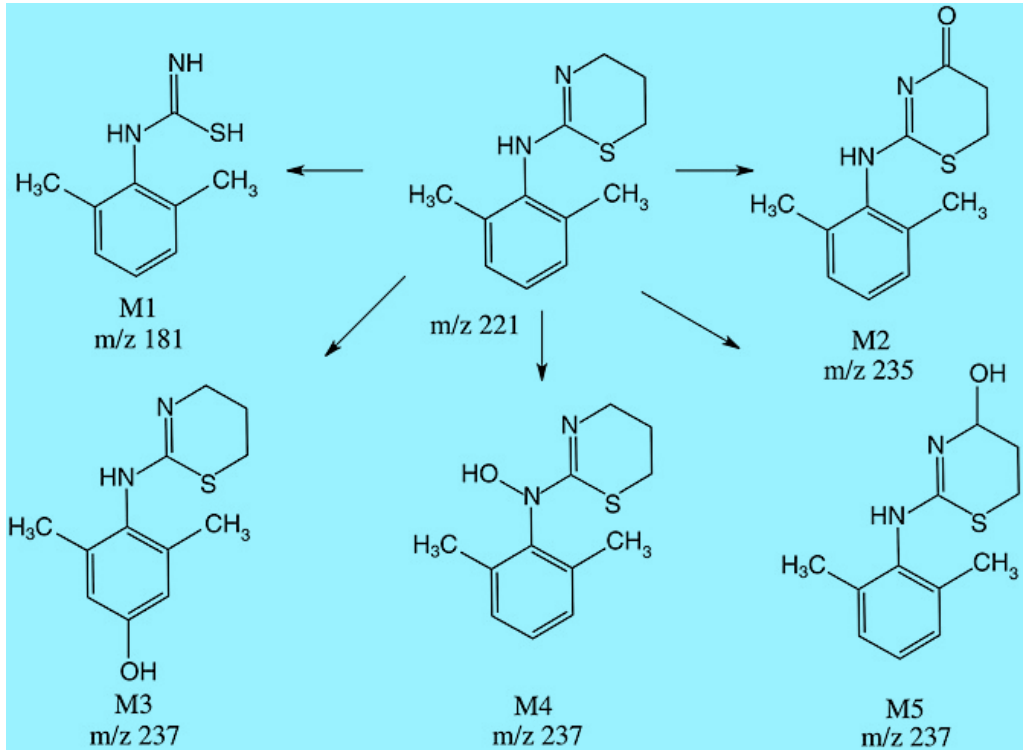


Adapted from Nat Rev Drug Discov. 2003;2(3):192–204

Steps FDA is taking to develop a model for skin lesions induced by injectable use of xylazine + fentanyl

FDA is currently conducting in vitro studies to understand how comparable the xylazine and fentanyl human liver metabolism is to that of select laboratory species

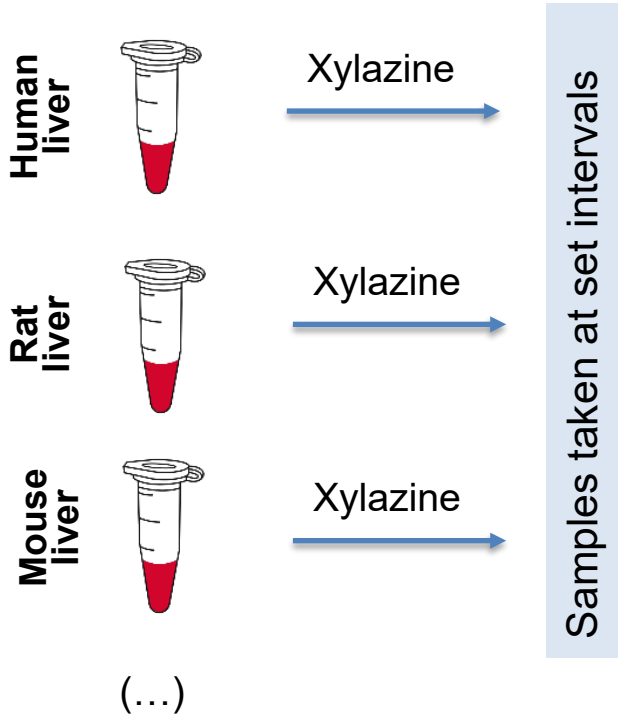
- Selection and use of most human-relevant model.
- Biologic diversity covered – species, strain, sex, etc.
- Avoids use of live animals in this screening process.

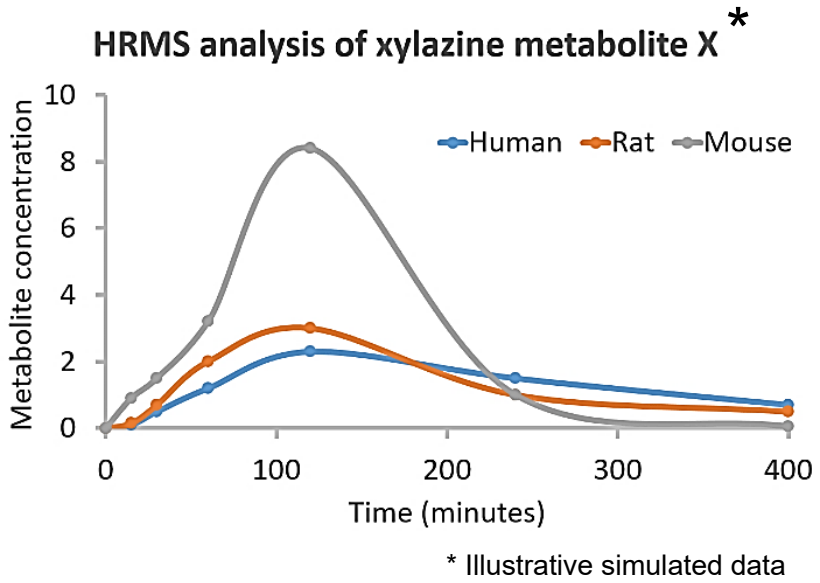


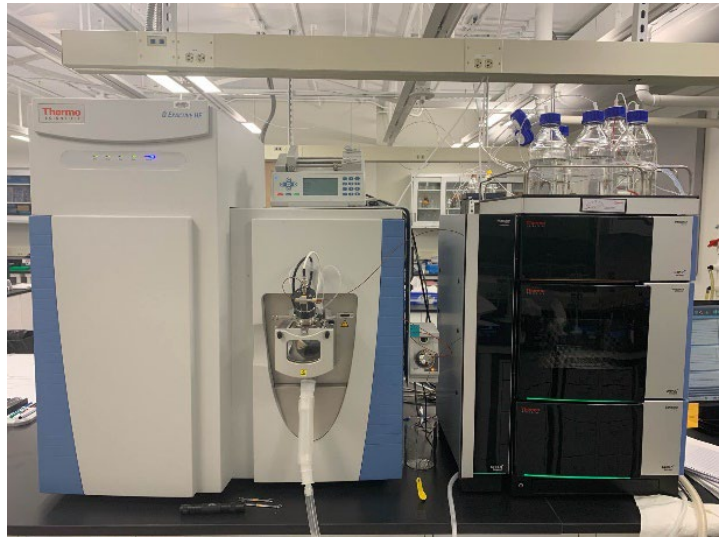
Metabolism of xylazine by the rat liver

*From St-Germain Lavoie et al (2012) Biomed. Chromatogr., **27**, 882-888*

Steps FDA is taking to develop a model for skin lesions induced by injectable use of xylazine + fentanyl





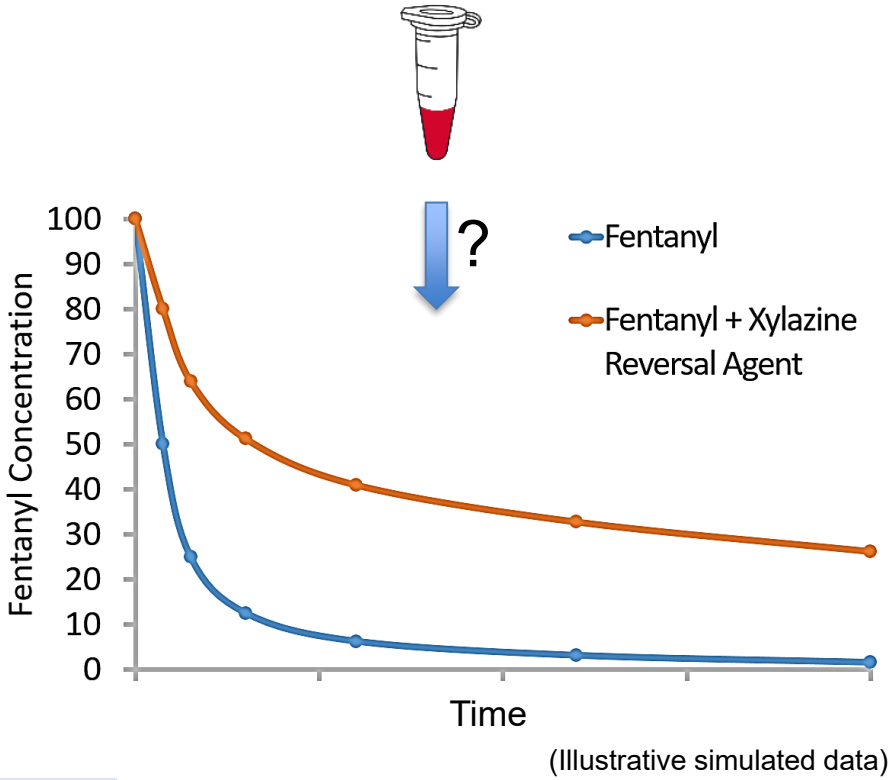


High Resolution Mass Spectrometer (HRMS)
FDA's National Center for Toxicological Research

Other research on xylazine and fentanyl metabolism at FDA

In vitro metabolism experiments to help understand:

- If xylazine modulates the metabolism of fentanyl (and vice versa) in the human liver and liver of relevant laboratory animal species.
- If potential human reversal agents for xylazine can impair the clearance of fentanyl by the human liver and liver of relevant laboratory animal species.



These studies can guide subsequent in vivo pharmacokinetic studies, reducing animal experimentation


FDA
U.S. FOOD & DRUG
ADMINISTRATION

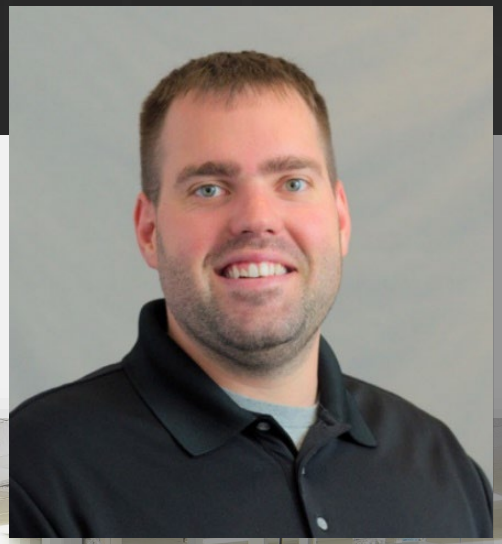
Xylazine

Perspectives from Forensic and Clinical Toxicology

Session 2: Pharmacological and Clinical Research Needs – October 4, 2023 (Washington, DC)

Alex J. Krotulski, Ph.D.
Center for Forensic Science Research and Education, Fredric Rieders Family Foundation, Willow Grove, PA

INTRODUCTION



- **Center for Forensic Science Research & Education**
  - Associate Director
    - Toxicology & Chemistry
  - Program Manager
    - NPS Discovery
- **Thomas Jefferson University**
  - Program Director
    - MS in Forensic Toxicology
  - Faculty / Lecturer
- **Journal of Analytical Toxicology**
  - Associate Editor

DISCLOSURES

- I have no conflicts of interest to disclose.
- I am a scientist and employee of FRFF / CFSRE, a 501(c)(3) non-profit research facility.
- Our research programs receive funding from a variety of federal agencies including the National Institute of Justice (DOJ), National Institutes of Health, Centers for Disease Control and Prevention, Food and Drug Administration, and others.
  - The opinions, findings, conclusions and/or recommendations expressed in this presentation are those of the author(s) and do not necessarily represent the official position or policies of NIJ, NIH, CDC, or FDA.

NIJ | National Institute of Justice
STRENGTHEN SCIENCE. ADVANCE JUSTICE.

NIH National Institutes of Health
Turning Discovery Into Health

CDC Centers for Disease Control and Prevention

FDA U.S. FOOD & DRUG ADMINISTRATION

CFSRE'S NPS DISCOVERY

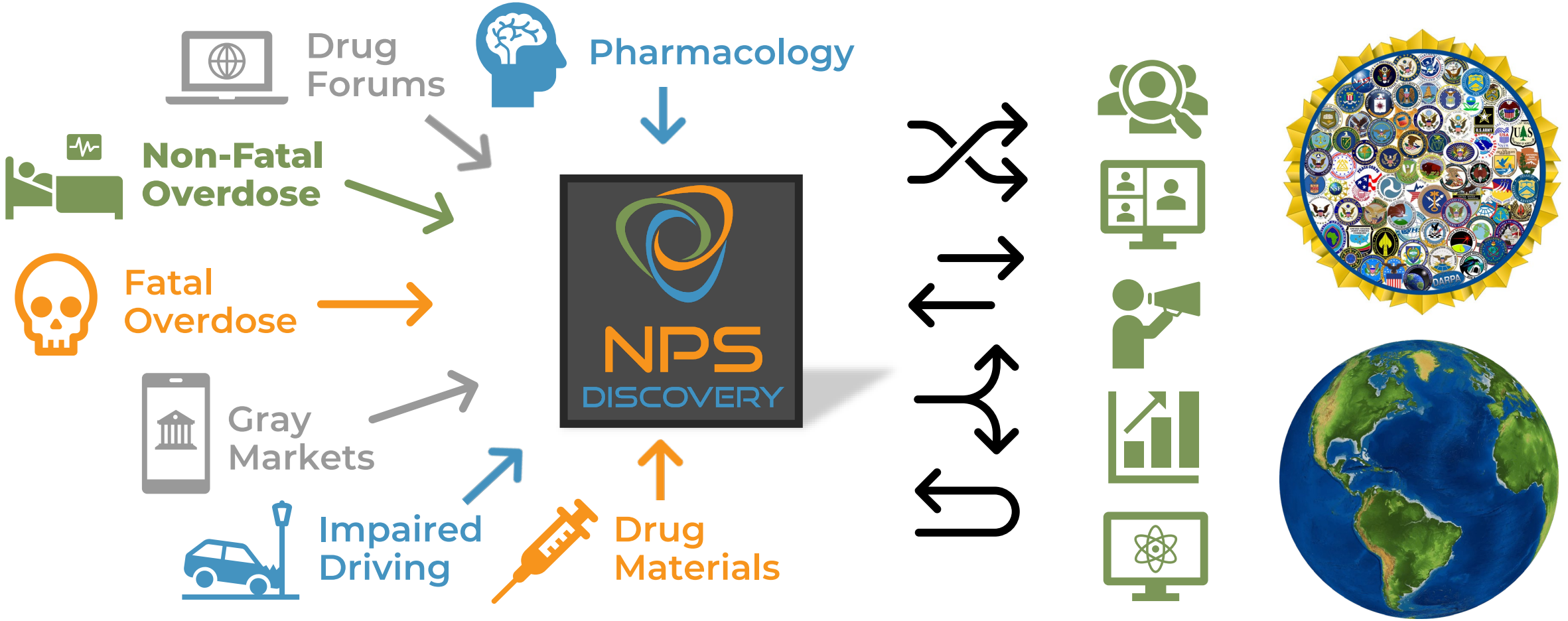
cfsre | NPS DISCOVERY

DRUG EARLY WARNING SYSTEM (EWS)

- Drug early warning systems are a multidisciplinary network with aims to exchange information, identify emerging drugs and changes in drug markets, and assess risks
  - Have become an integral part of public health efforts
  - Primary goal – **reduce harms**
  - Several EWS exist internationally

- **In 2018, the CFSRE launched NPS Discovery**
  - Open-access drug early warning system
  - Combine aspects of surveillance, casework, and research
  - Analyze samples and generate data in-house
  - Develop a panel of high impact reports
  - Disseminate results and reports widely to stakeholders

CFSRE'S NPS DISCOVERY



FORENSIC LABORATORY

- The Center for Forensic Science Research and Education (CFSRE)
  - 501(c)(3) non-profit research and educational facility
  - *Surveillance vs. Research*

Waters Xevo® G2-S LC-QTOF-MS

Sciex X500R LC-QTOF-MS

Sciex TripleTOF® 5600+ LC-QTOF-MS

Agilent 6495 LC-QQQ-MS

Agilent 6430 LC-QQQ-MS

Waters TQS LC-QQQ-MS

Waters TQD LC-QQQ-MS

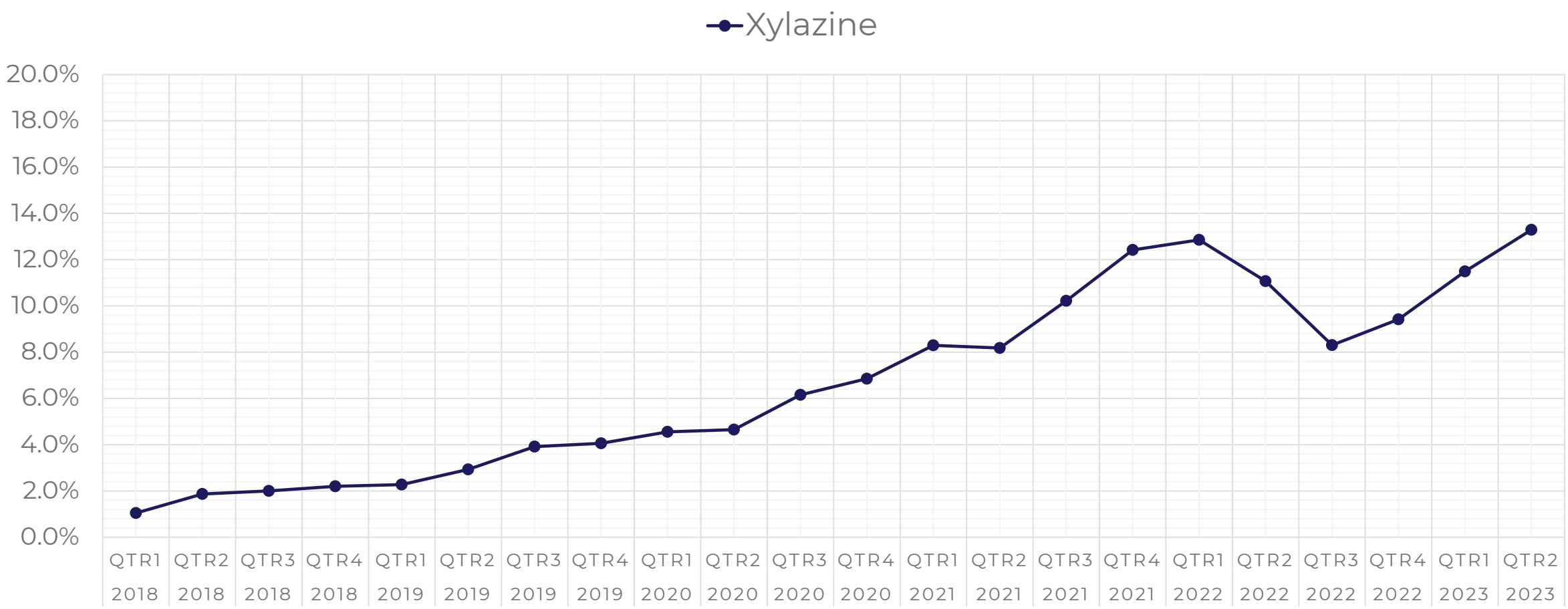
Agilent 5975 GC-MS

Agilent 5975 GC-MS

XYLAZINE SITUATION IN THE U.S.

cfsre | NPS DISCOVERY

POSITIVITY IN TOXICOLOGY SPECIMENS

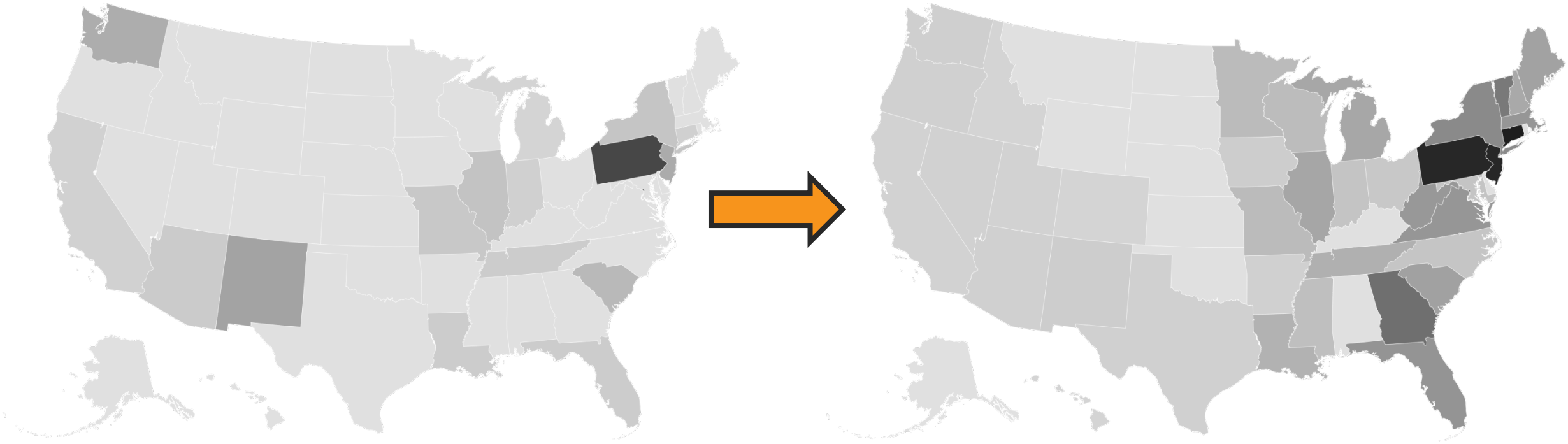


*Surveillance data in collaboration with NMS Labs (Horsham, PA).

INCREASED GEOGRAPHICAL DISTRIBUTION

Q1 2019

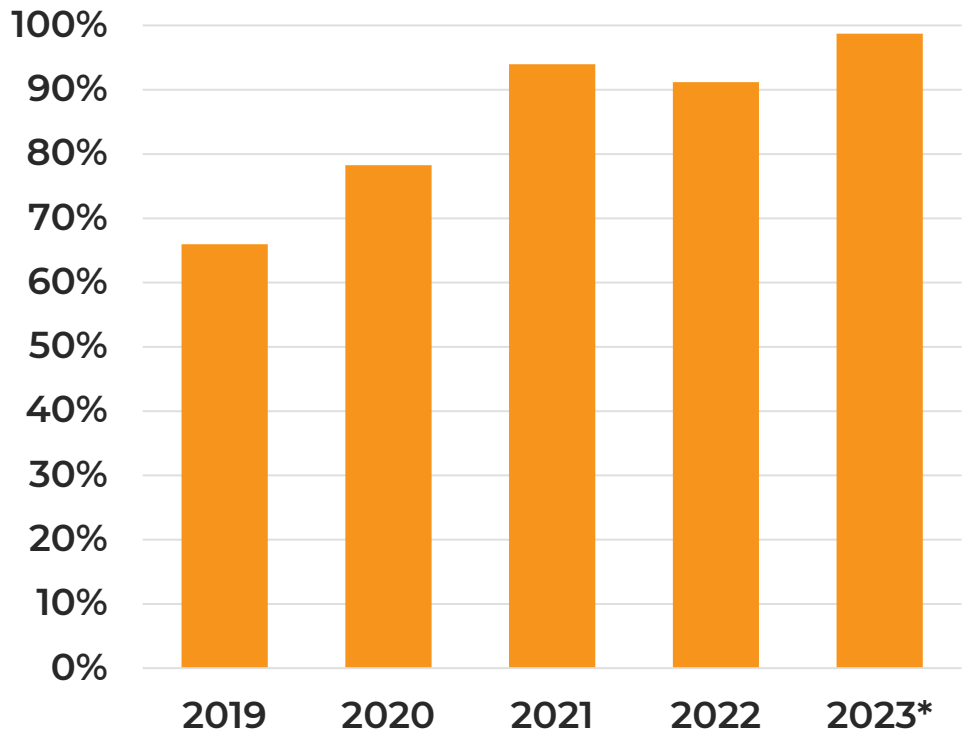
Q4 2022



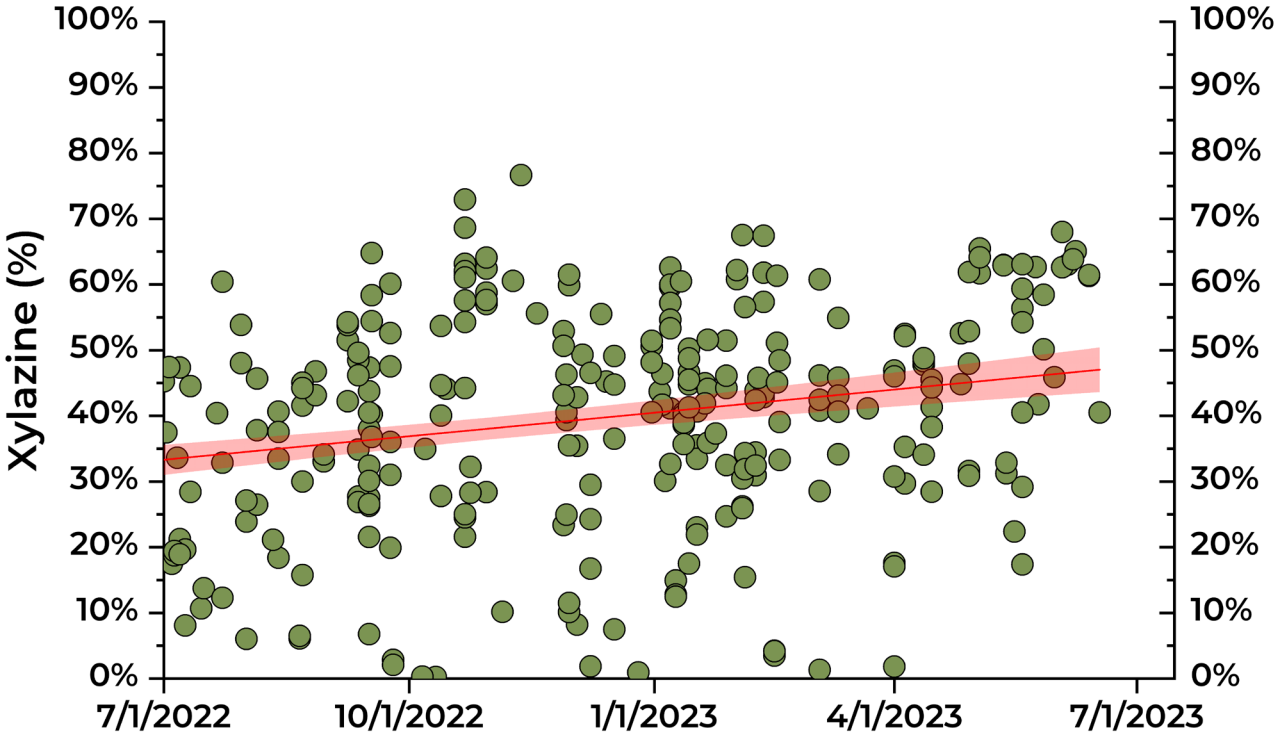
*Forensic data in collaboration with NMS Labs (Horsham, PA).

DOMINATING DRUG SUPPLIES – PHILADELPHIA, PA

Opioid samples containing xylazine



Xylazine purity/content in opioid samples



cfsre | NPS DISCOVERY

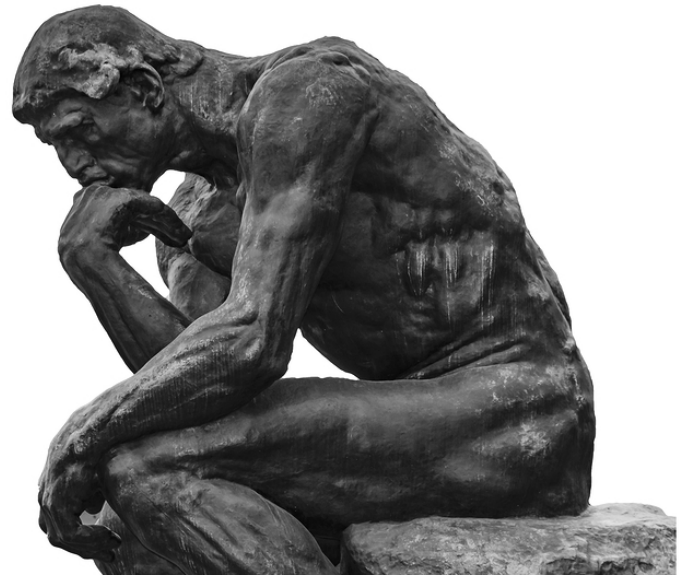
*In collaboration with the Philadelphia Department of Public Health (PDPH).

XYLAZINE'S UNANSWERED QUESTIONS

cfsre | NPS DISCOVERY

XYLAZINE'S UNANSWERED QUESTIONS

- Where is xylazine coming from?
  - Does the source dictate outcome?
  - How much xylazine are humans consuming?
- What is the pharmacokinetic profile in humans?
  - What is the half life? Is it affected by co-ingestion?
- How does xylazine metabolize in humans?
  - What's the significance of xylazine's metabolites?
- How much xylazine (and metabolites) is circulating in blood?
- What is best clinical practice for patients presenting after xylazine exposure?
  - What's the best way to address wound care? Dependence? Sedation?



ANALYTICAL RESEARCH EFFORTS

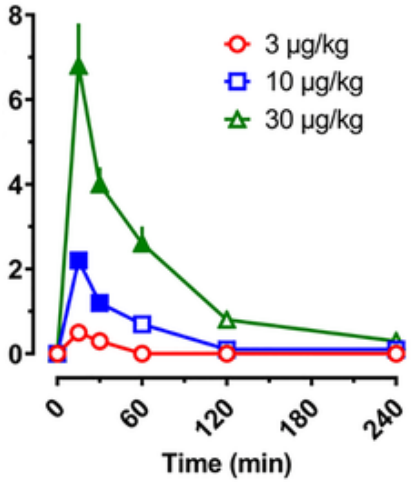
cfsre | NPS DISCOVERY

ANALYTICAL RESEARCH EFFORTS

- Current testing method for toxicology specimens
  - Scope: fentanyl, **xylazine**, cocaine, methamphetamine, etc.

- Future testing method for toxicology specimens
  - Scope: **xylazine and 4-OH, 3-OH, 2,6-xylidine metabolites**

- **Pending studies:**
  - Human quantitative data for xylazine in blood
  - Pharmacokinetic studies
  - Tying clinical findings with toxicology results

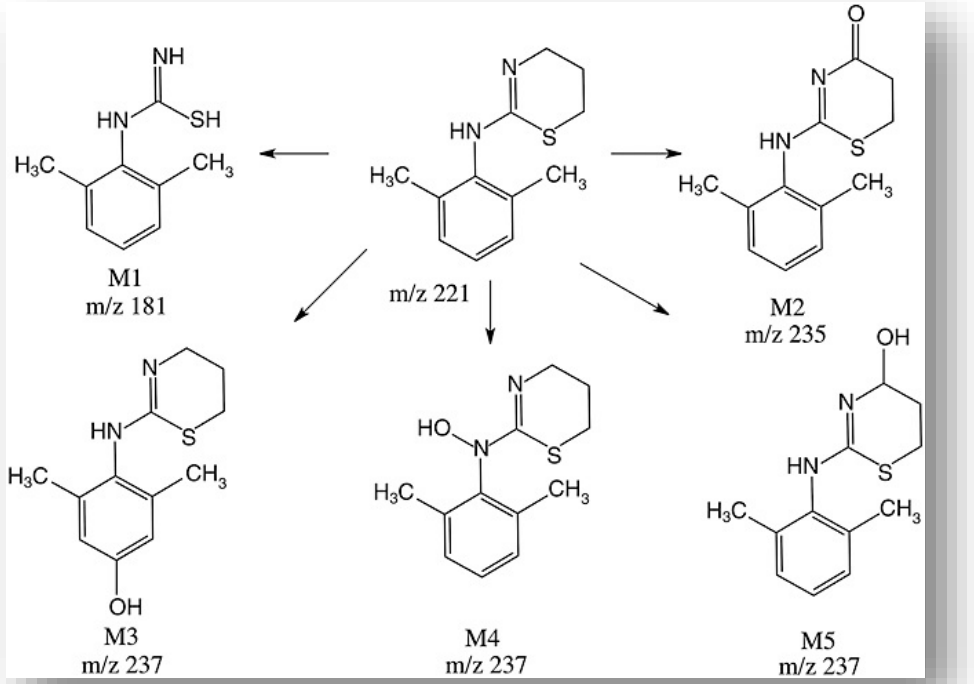


Walton *et al.* https://doi.org/10.1007/s00213-022-06292-5

ANALYTICAL RESEARCH EFFORTS

- ***In vitro* characterization of xylazine metabolism**
  - Corroborate previous studies
  - Allow for expanded scope of preliminary testing
  - Identification of new metabolites

- ***In vivo* characterization of xylazine metabolism**
  - Analyzed approximately 400 urine samples to date
  - 88% positive for xylazine
  - 53% positive for 4-OH/3-OH metabolite(s)
  - 13% positive for 2,6-xylidine
  - 46% negative for metabolites



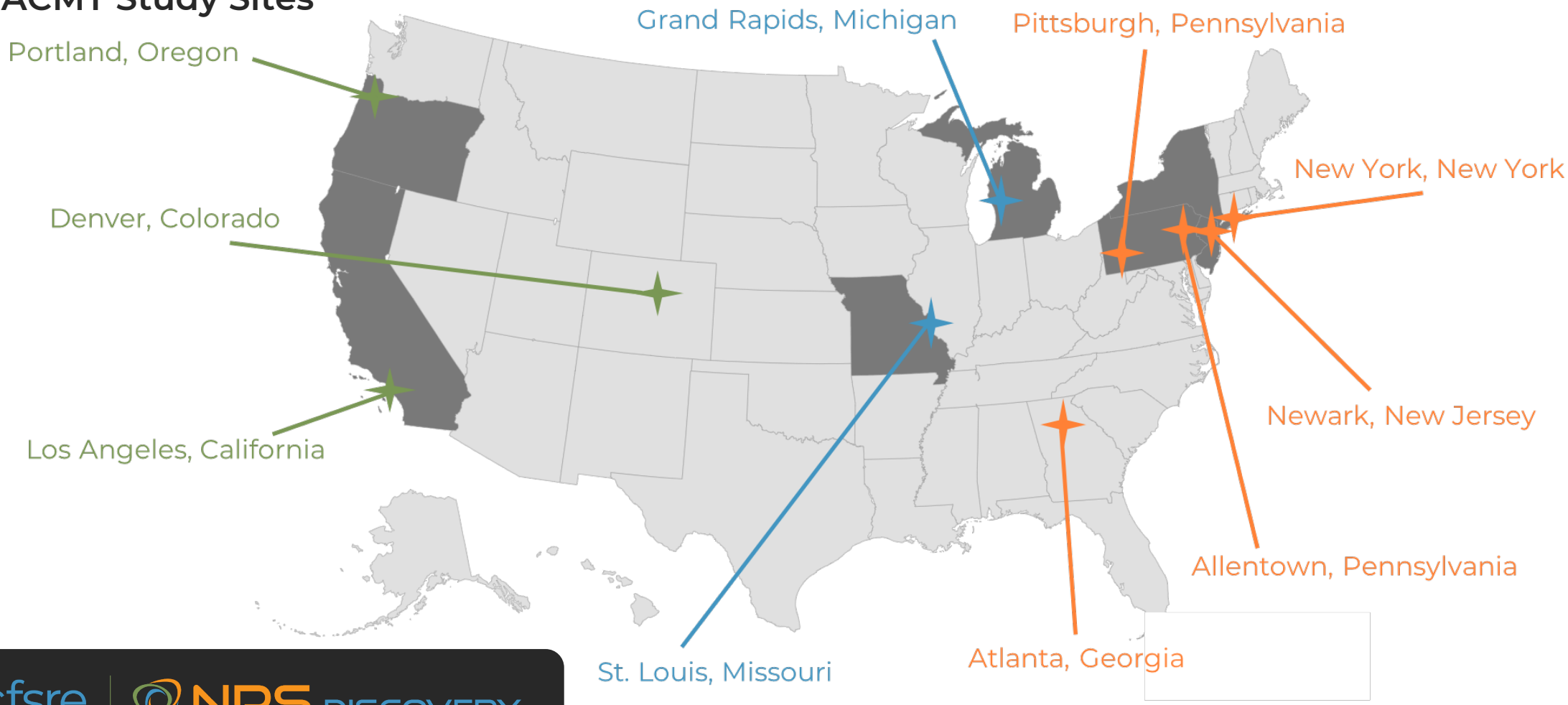
St-Germain Lavoie *et al.* https://doi.org/10.1002/bmc.2875

CLINICAL RESEARCH EFFORTS

cfsre | NPS DISCOVERY

CLINICAL RESEARCH EFFORTS

- **ACMT Study Sites**



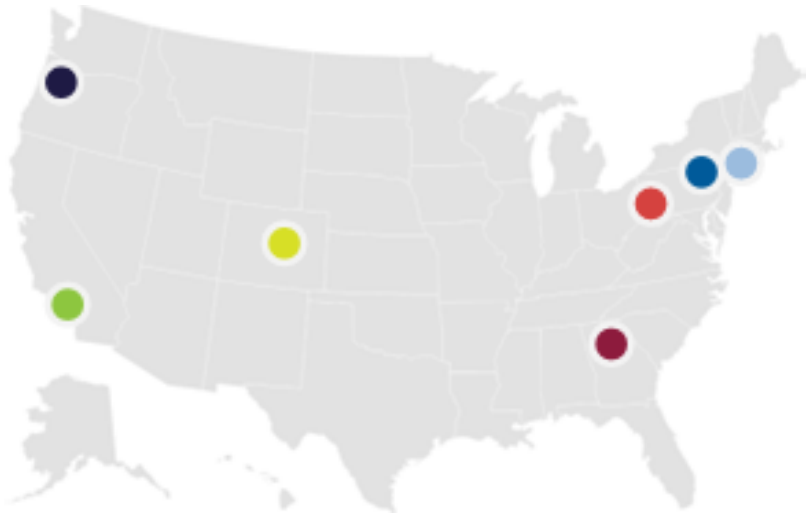
CLINICAL RESEARCH EFFORTS

- Xylazine Distribution – Q2 2023 (ACMT Study)

Portland, OR
Xylazine not detected

Los Angeles, CA
Xylazine not detected

Denver, CO
Xylazine not detected



New York, NY
Xylazine alongside fentanyl (26%)

Bethlehem, PA
Xylazine alongside fentanyl (25%)

Pittsburgh, PA
Xylazine alongside fentanyl (45%)

Atlanta, GA
Xylazine alongside fentanyl (12%)

https://www.cfsre.org/nps-discovery/clinical-reports

CLINICAL RESEARCH EFFORTS

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

- **Methods:**
  - Multicenter, prospective cohort study
  - Patient serum analyzed via LC-QTOF-MS
  - Overdose severity surrogate outcomes: (a) cardiac arrest requiring cardiopulmonary resuscitation (primary); and (b) coma within 4 h of arrival (secondary)

- **Results:**
  - 321 patients: 90 positive for xylazine and 231 negative
  - **Patients positive for xylazine had significantly lower adjusted odds of cardiac arrest and coma**

CLINICAL TOXICOLOGY
2023, VOL. 61, NO. 3, 173–180
https://doi.org/10.1080/15563650.2022.2159427

Taylor & Francis
Taylor & Francis Group

CLINICAL RESEARCH

Check for updates

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

Jennifer S. Love[a], Michael Levine[b], Kim Aldy[c,d], Jeffrey Brent[e], Alex J. Krotulski[f], Barry K. Logan[f], Carmen Vargas-Torres[a], Sara E. Walton[f], Alexandra Amaducci[a], Diane Calello[h], Robert Hendrickson[i], Adrienne Hughes[j], Anita Kurt[g], Bryan Judge[j], Anthony Pizon[k], Evan Schwarz[l], Joshua Shulman[k], Timothy Wiegan[m], Paul Wax[c,d] and Alex F. Manini[a]

[a]Department of Emergency Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [b]Department of Emergency Medicine, University of California, Los Angeles, CA, USA; [c]Department of Emergency Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA; [d]American College of Medical Toxicology, Phoenix, AZ, USA; [e]University of Colorado School of Medicine, Aurora, CO, USA; [f]Center for Forensic Science Research and Education, Fredric Rieders Family Foundation Willow Grove, Willow Grove, PA, USA; [g]Lehigh Valley Health Network, Bethlehem, PA, USA; [h]Rutgers New Jersey School of Medicine, Newark, NJ, USA; [i]Oregon Health & Science University, Portland, OR, USA; [j]Spectrum Health, Grand Rapids, MI, USA; [k]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [l]Washington University School of Medicine in St. Louis, St. Louis, MO, USA; [m]University of Rochester Medical Center, Rochester, NY, USA

ABSTRACT

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

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

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

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

ARTICLE HISTORY
Received 27 September 2022
Revised 9 December 2022
Accepted 12 December 2022

KEYWORDS
Opioids; fentanyl; adulterants; xylazine; toxicosurveillance

Introduction

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

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

CONTACT Jennifer S. Love jennifer.love@mountsinai.org Research Division, Department of Emergency Medicine, Icahn School of Medicine at Mount Sinai, 555 West 57th St, 5th Floor, Suite 5-25, New York, 10019, NY, USA

Love *et al.* https://doi.org/10.1080/15563650.2022.2159427

CLINICAL RESEARCH EFFORTS

- Collaborative study with Babu *et al.* at UMass Chan Medical School

- **Case #1:**
  - 40 yo M presented to ED for a suspected opioid overdose
  - Received 1 mg of IN naloxone by EMS → positive response
  - Reported using fentanyl (IV) and cocaine
  - Prolonged period of somnolence; treated for a benzodiazepine overdose
  - Did not require supplemental oxygen / respiratory support
  - Discharged to treatment facility

- **Toxicology:**
  - **Fentanyl (8.2 ng/mL)**, Norfentanyl (17 ng/mL), Methamphetamine (27 ng/mL), Cocaine (22 ng/mL), BZE (570 ng/mL), and **Xylazine (13 ng/mL)**

CLINICAL RESEARCH EFFORTS

- Collaborative study with Babu *et al.* at UMass Chan Medical School

- **Case #2:**
  - 27 yo M presented to ED for suspected opioid overdose
  - Found somnolent but responsive to voice and maintaining own airway
  - At ED, mental status declined, hypoxic despite being on 6 L of oxygen via nasal cannula
  - Administered 0.4 mg naloxone intravenously twice (0.8 mg total)
  - Clinical course complicated by acute hypoxemic respiratory failure and suspected non-cardiogenic pulmonary edema – set to be admitted to ICU but improved
    - Left against medical advice

- **Toxicology:**
  - **Fentanyl (27 ng/mL)**, Norfentanyl (15 ng/mL), Cocaine (Positive, <1 ng/mL), BZE (3.6 ng/mL), **Xylazine (11 ng/mL)**, and Naloxone (8 ng/mL)

CLINICAL RESEARCH EFFORTS

- Collaborative study with Babu *et al.* at UMass Chan Medical School

- **Case #3:**
  - 26 yo M presented to ED for suspected opioid overdose *(EMS dispatched for a motor vehicle crash)*
  - Patient symptoms consistent with opioid overdose (unresponsive, decreased respiratory drive, cyanosis, miosis) → EMS administered 0.4 mg of IN naloxone with positive response
  - Patient reported snorting what he thought was cocaine prior to period of unresponsiveness
  - No additional medications administered
  - Did not require supplemental oxygen / respiratory support adjuncts
  - Discharged to home

- **Toxicology:**
  - **Fentanyl (8.7 ng/mL)**, Norfentanyl (2.2 ng/mL), Cocaine (81 ng/mL), BZE (210 ng/mL), Naloxone (3.5 ng/mL)

CLINICAL RESEARCH EFFORTS

- Collaborative study with Babu *et al.* at UMass Chan Medical School

- **Case #4:**
  - 41 yo M presented to the ED for a suspected opioid overdose (injected supposed fentanyl)
  - Received a total of 12 mg of naloxone in the field (8 mg IN → 2 mg IM → 2 mg IM)
  - Ventilated with a bag valve mask
  - At ED, patient was altered but easily arousable to verbal stimuli / did not require supplemental O2/RS
  - Mental status improved but exhibit symptoms of alcohol withdrawal
  - Left against medical advice

- **Toxicology:**
  - **Fentanyl (4.8 ng/mL)** and Naloxone (24 ng/mL), **Ethanol (160 mg/dL)**

WHERE TO FROM HERE?

cfsre | NPS DISCOVERY

WHERE TO FROM HERE?

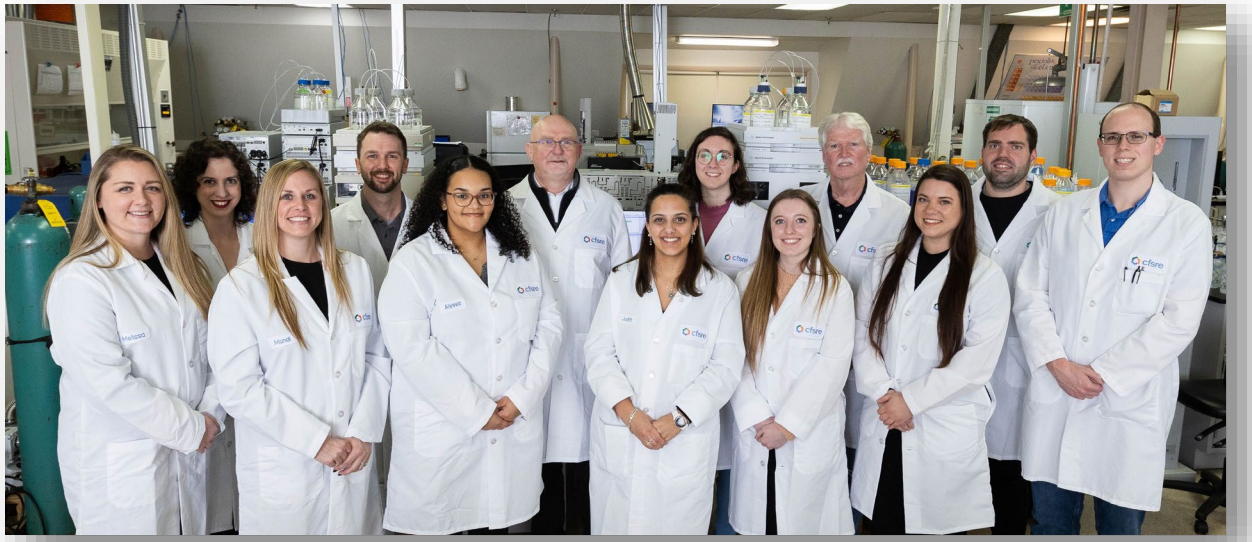
- There is A LOT of **research** left to do!
  - We don't know more than we know
  - Cross-field collaborations will be most successful

- **Good news:** Increased awareness, attention, funding, etc.
- **Bad news:** Timing might be too late

- The end goal remains to **reduce harms**

ACKNOWLEDGEMENTS

- CFSRE Team
- UMass Team
- ACMT Team
- NMS Labs
- Funding Agencies
- Collaborators



NIJ | National Institute of Justice
STRENGTHEN SCIENCE. ADVANCE JUSTICE.

NIH National Institutes of Health
Turning Discovery Into Health

CDC Centers for Disease Control and Prevention

FDA U.S. FOOD & DRUG ADMINISTRATION

THANK YOU! QUESTIONS?

Alex J. Krotulski, Ph.D.
Associate Director – CFSRE
Program Manager – NPS Discovery
alex.krotulski@cfsre.org

Break for lunch

The meeting will resume at 1:10 pm ET

REAGAN-UDALL FOUNDATION FOR THE FDA

Mitigating Risks from Human Xylazine Exposure

REAGAN-UDALL FOUNDATION FOR THE FDA

Session 3: Exploring Product Development Research Needs

- **Jeanmarie Perrone, MD,** Perelman School of Medicine, University of Pennsylvania
- **CAPT Christopher Jones, PharmD, DrPH, MPH,** Substance Abuse and Mental Health Services Administration
- **Nabarun Dasgupta, PhD, MPH**, Remedy Alliance/For the People
- **Timothy Stenzel, MD, PhD**, Center for Devices and Radiological Health, FDA
- **Zachary Dezman, MD, MS**, Center for Drug Evaluation and Research, FDA

Xylazine: Philadelphia Clinical experience

Jeanmarie Perrone, MD, FACMT

Professor, Emergency Medicine, Medical Toxicology and Addiction Medicine

Director, Center for Addiction Medicine and Policy

Perelman School of Medicine at the University of Pennsylvania

Opioid-Xylazine Overdose Data

321 pts w opioid overdose 9 EDs in TOXiC registry 9/2020-8/2021

- xylazine detected in 90/321
- not detected in 231/321

- No differences in bradycardia or intubation rates
- Overdose manifestations similar in both
- CPR and “coma within 4 hours” were ***more common in the patients with “xylazine not detected”***
- Combined xylazine/opioid might be less toxic than fentanyl alone

Love JS, Manini AF et al: Opioid overdoses involving xylazine in emergency department patients: a multicenter study. Clin Toxicol. 2023;61:173-180.

Multicenter cohort study of opioid overdose +/- xylazine

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

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

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

Love, et. al., Clinical Toxicology, 2023

Penn
University of Pennsylvania

Center for Addiction Medicine and Policy

Clinical Manifestations – Discussion

- Preliminary studies suggest that vital signs of people with xylazine+opioids are not significantly different than those exposed to opioids alone
- When sedation continues after opioid overdose reversal with naloxone, likely due to unreversed sedatives such as benzodiazepines, post stimulant wash-out or other sedatives
- **Is there a role for a xylazine reversal agent?**
  - May cause precipitated withdrawal
    - similar to flumazenil-benzodiazepine reversal
  - Contribution of the opioid to respiratory depression and death is **substantially more significant** than that from xylazine
- In most cases symptomatic or supportive care has been sufficient

Clinical Manifestations: Is there a withdrawal syndrome?

Major Phenotypes from Expert Chart Review

52 of 73 patients (71.3%) with no signs of a new withdrawal syndrome

- Mixed opioid and/or benzodiazepine withdrawal, course as expected
- Aggressive withdrawal & pain management, improved with opioids

19 patients (26.4%) with a possible withdrawal syndrome

- Agitated delirium/toxidrome with other substances, +/- ICU admission
- Naloxone or buprenorphine precipitated withdrawal
- Insufficiently treated opioid withdrawal, low doses methadone/oxycodone

2 patients (2.7%) with otherwise unexplained symptoms

- Unexplained hypertension (~180/100s) and/or tachycardia (<100)

How Much Opioid is in a Bag of Philadelphia Heroin/Fentanyl?

Net Weight (g)	Purity (%)	Number of Bags	Weight per bag (mg)	Fentanyl per Bag (mg)
22	6.9	767	28.68	1.98
26	1.4	731	35.57	0.50
29	8	684	42.40	3.39
20.1	7	450	44.67	3.13
18	9	449	40.09	3.61
13	5	400	32.50	1.63
14.9	6	390	38.21	2.30
15.8	5	224	70.54	3.53
7.4	10	195	37.95	3.79
7.57	3.5	192	39.43	1.38
10.3	3.2	182	56.60	1.81
5.1	7.4	172	29.65	2.19
4.93	6.5	166	29.70	1.93
9.95	3.3	165	60.30	1.99
4.32	10	159	27.17	2.72
3.98	12	140	28.43	3.41
5.5	6	140	39.29	2.36

Avg fentanyl mg per bag:	2.45
Low	0.50
High	3.80

Source: DEA

Xylazine withdrawal – Overlapping symptoms

Xylazine	Opioid	Benzodiazepine
Anxiety **Dysphoria** **Restlessness**	Tachycardia Diaphoresis **Restlessness** Mydriasis Body aches Rhinorrhea GI symptoms Tremor Yawning Piloerection **Anxiety** **Dysphoria**	Tachycardia Hypertension Diaphoresis **Anxiety** Tremor Altered mental status Seizures **Dysphoria**

Xylazine withdrawal – Prophylaxis and treatment

Prophylaxis and treatment

- Clonidine
- Antipsychotics
- Gabapentin
- Benzodiazepines

Resources

Xylazine Best Practices: Penn Medicine Center for Addiction Medicine and Policy PennCAMP.org

D'Orazio: Xylazine adulteration of the heroin-fentanyl supply. Ann Intern Med 2023

Xylazine Detection in a Hospitalized Cohort

Among 121 cases with testing sent within 48 hours, **xylazine positivity was associated with:**

- Younger age
- White race
- Fentanyl detection
- Methadone detection
- Less frequent ICU admission

	Xylazine Tests Sent Within 48h of ED Arrival	Xylazine Negative	Xylazine Positive	*p*-value
	n=121	*n=48 (39.7%)*	*n=73 (60.3%)*	
Age, mean (SD)	44.6 (1.2)	51.0 (2.1)	40.4 (1.1)	<0.001
Female	40 (33.1%)	14 (29.2%)	26 (35.6%)	0.461
Race				0.001
Black	37 (30.6%)	24 (50.0%)	13 (17.8%)	
White	72 (59.5%)	21 (43.8%)	51 (69.9%)	
Other	12 (9.9%)	3 (6.3%)	9 (12.3%)	
Hispanic ethnicity	5 (4.1%)	1 (2.1%)	4 (5.5%)	0.456
Other drugs detected				
Fentanyl or norfentanyl	102 (84.3%)	32 (66.7%)	70 (95.9%)	<0.001
Methadone	15 (12.4%)	2 (4.2%)	13 (17.8%)	0.026
Buprenorphine	2 (1.7%)	0 (0.0%)	2 (2.7%)	0.248
Other opioids	42 (34.7%)	12 (25.0%)	30 (41.1%)	0.069
Benzodiazepines	54 (44.6%)	18 (37.5%)	36 (49.3%)	0.201
Methamphetamine or Cocaine	28 (23.1%)	14 (29.2%)	14 (19.2%)	0.202
Intensive Care Unit admission	39 (32.2%)	24 (50.0%)	15 (20.5%)	0.001
Length of stay, median (IQR) days	5 (2, 11.5)	7 (4, 21)	5 (1, 9)	0.059
Discharge disposition				0.13
Standard Discharge	78 (64.4%)	35 (72.9%)	43 (58.9%)	
AMA	35 (28.9%)	9 (18.8%)	26 (35.6%)	
Died	8 (6.6%)	4 (8.3%)	4 (5.5%)	

Thakrar AP, Perrone J, Lowenstein M: Society of General Internal Medicine National Conference. Aurora, CO. May 12, 2023.

REAGAN-UDALL FOUNDATION FOR THE FDA

CAPT Christopher Jones, PharmD, DrPH, MPH
Center for Substance Abuse Prevention
Substance Abuse and Mental Health Services Administration

Exploring Product Development Research Needs

Harm Reduction Needs Related to Xylazine

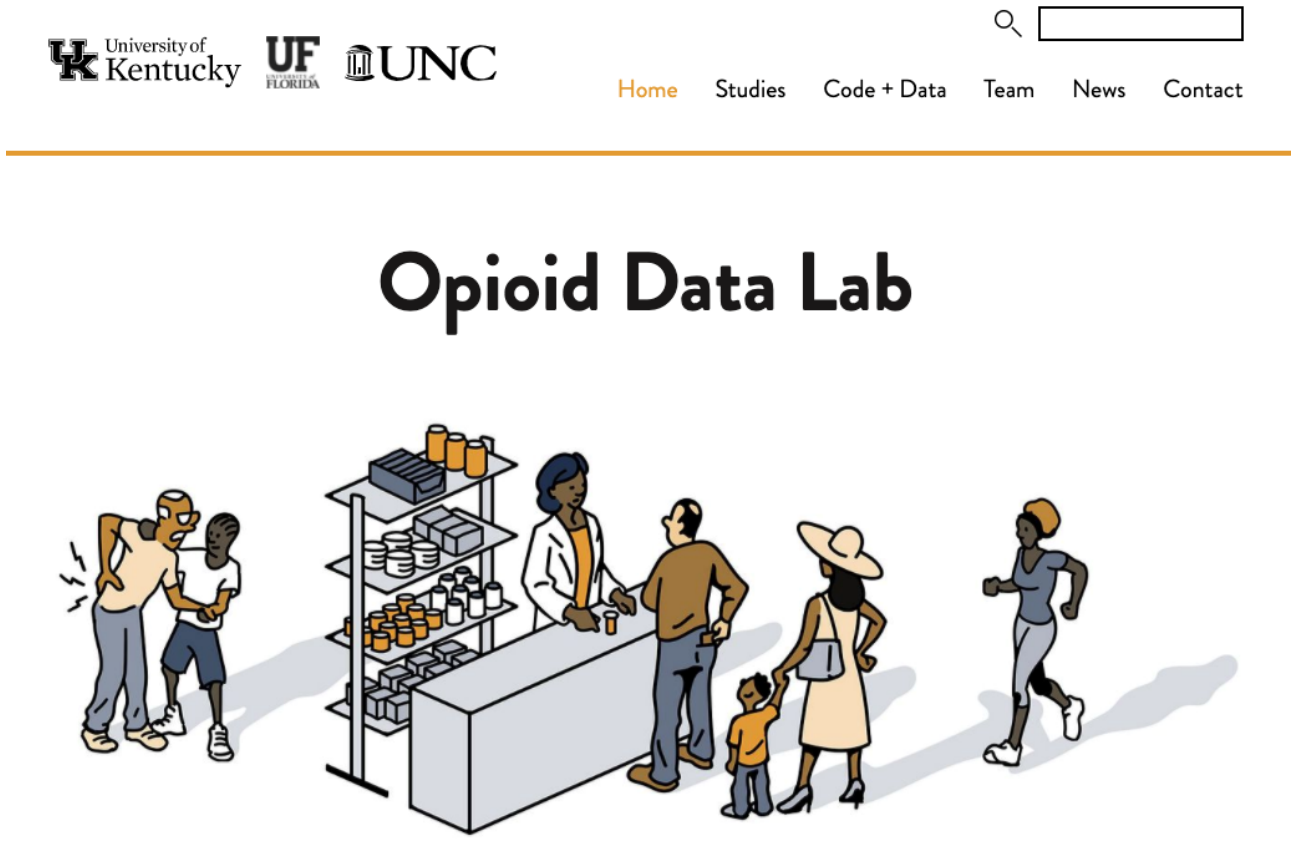
Nabarun Dasgupta, MPH, PhD

Remedy Alliance For The People

UNC Chapel Hill

October 4, 2023

Reagan-Udall Foundation for the FDA



Agenda

- Xylazine test strips
- Drug checking data
- Wound Care needs
- Public health implications

Detecting Xylazine

Figgatt *et al. Harm Reduct J* (2021) 18:80
https://doi.org/10.1186/s12954-021-00528-x

Harm Reduction Journal

RESEARCH Open Access

Treatment experiences for skin and soft tissue infections among participants of syringe service programs in North Carolina

Mary C. Figgatt[1,2*], Zach R. Salazar[3], Louise Vincent[3], Diannee Carden-Glenn[4], Kelly Link[5], Lauren Kestner[6], Tyler Yates[7], Asher Schranz[8], Elizabeth Joniak-Grant[1] and Nabarun Dasgupta[2]

Abstract

Introduction: Bacterial and fungal infections, such as skin and soft tissue infections (SSTIs) and infective endocarditis (IE), are increasing among people who use drugs in the United States. Traditional healthcare settings can be inaccessible and unwelcoming to people who use drugs, leading to delays in getting necessary care. The objective of this study was to examine SSTI treatment experiences among people utilizing services from syringe services programs. This study was initiated by people with lived experience of drug use to improve quality of care.

Methods: We conducted a cross-sectional survey among participants of five syringe services programs in North Carolina from July through September 2020. Surveys collected information on each participant's history of SSTIs and IE, drug use and healthcare access characteristics, and SSTI treatment experiences. We examined participant characteristics using counts and percentages. We also examined associations between participant characteristics and SSTI history using binomial linear regression models.

Results: Overall, 46% of participants reported an SSTI in the previous 12 months and 10% reported having IE in the previous 12 months. Those with a doctor they trusted with drug use-related concerns had 27 fewer (95% confidence interval = − 51.8, − 2.1) SSTIs per every 100 participants compared to those without a trusted doctor. Most participants with a SSTI history reported delaying (98%) or not seeking treatment (72%) for their infections. Concerns surrounding judgment or mistreatment by medical staff and self-treating the infection were common reasons for delaying or not seeking care. 13% of participants used antibiotics obtained from sources other than a medical provider to treat their most recent SSTI. Many participants suggested increased access to free antibiotics and on-site clinical care based at syringe service programs to improve treatment for SSTIs.

Conclusions: Many participants had delayed or not received care for SSTIs due to poor healthcare experiences. However, having a trusted doctor was associated with fewer people with SSTIs. Improved access to non-judgmental healthcare for people who use drugs with SSTIs is needed. Expansion of syringe services program-based SSTI prevention and treatment programs is likely a necessary approach to improve outcomes among those with SSTI and IE.

Summer 2020 Something unexpected was happening in the drug supply. We thought it was SSTIs.

January 2021 Don Jackson at a local SSP first identified xylazine using FTIR-based point-of-care drug checking.

Drug Checking Tech

Test strips

Anywhere
1 min

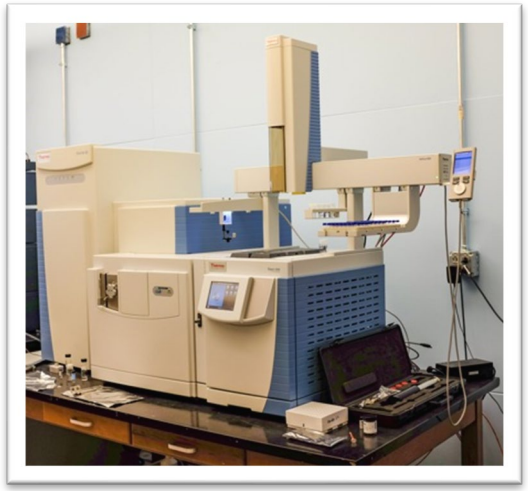
Reagents

table top
10 mins

FTIR

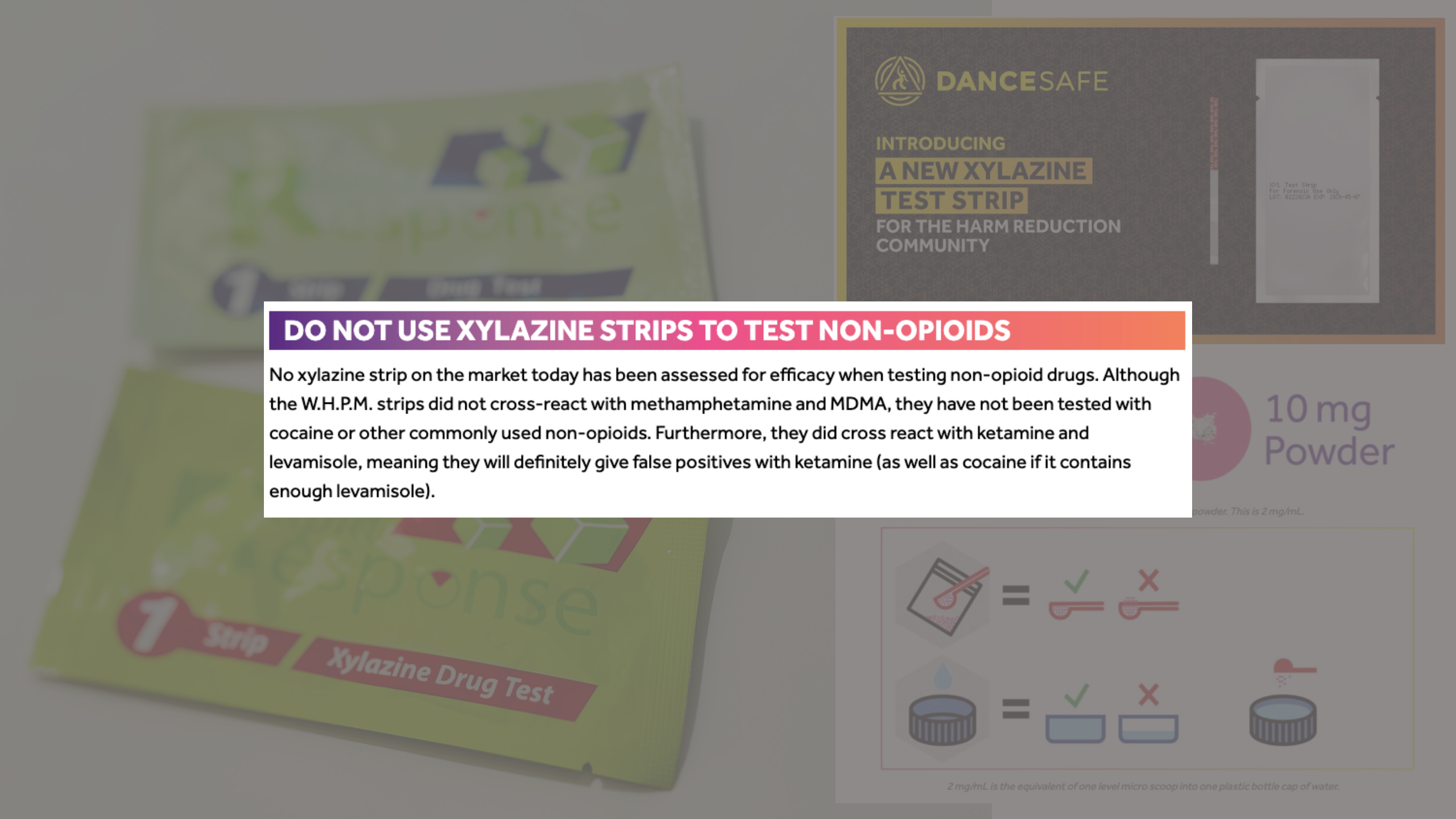
program sites
10 mins

LC/GCMS, QTOF



lab
1 week

cost, time, complexity



DO NOT USE XYLAZINE STRIPS TO TEST NON-OPIOIDS

No xylazine strip on the market today has been assessed for efficacy when testing non-opioid drugs. Although the W.H.P.M. strips did not cross-react with methamphetamine and MDMA, they have not been tested with cocaine or other commonly used non-opioids. Furthermore, they did cross react with ketamine and levamisole, meaning they will definitely give false positives with ketamine (as well as cocaine if it contains enough levamisole).

Total NC drug samples analayzed
787

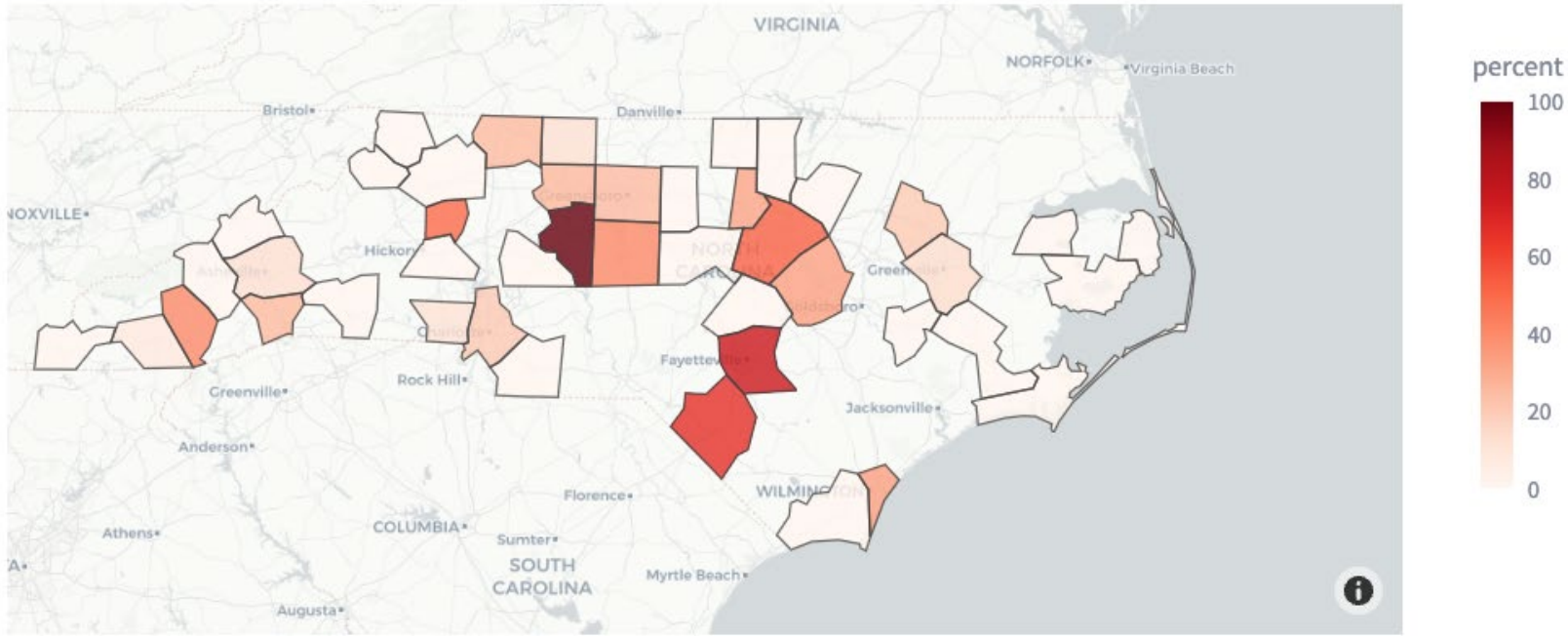
Counties with any drug samples
44

Samples with xylazine
190

Counties with xylazine
21

Our samples do not represent the entire drug supply. People may send us samples because they suspect xylazine or have unexpected reactions.

Percent of Samples Testing Positive for Xylazine in NC



rank	substance	samples
1	xylazine	190
2	fentanyl	185
3	4-ANPP	174
4	phenethyl 4-ANPP	91
5	p-fluorofentanyl	69
6	heroin	52
7	cocaine	50
8	lidocaine	37
9	despropionyl p-fluorofentanyl	36
10	ethyl-4-ANPP	33
11	dimethyl sulfone (methylsulfonylmetha	32
12	methamphetamine	31
13	N-phenylpropanamide	29
14	1,3-Diacetin	26
15	p-fluoro phenethyl 4-ANPP	25
16	6-monoacetylmorphine (6-MAM)	23
17	acetylcodeine	22
18	caffeine	22
19	tramadol	20
20	non-specific sugars	17
21	acetaminophen	16
22	diphenhydramine	14
23	procaine	10
24	phenethyl bromide	10
25	1-phenethyl-4-propionyloxypiperidine	7

Xylazine prevalence varies. East Coast primarily affected.

Samples analyzed
N=3,081

Expected opioids
n=1,570

Xylazine in any amount (including trace)
n=453

Xylazine as **primary** constituent
n=317 (20%)

state	xylazine	total	percent
CT	2	2	100
MS	1	1	100
NJ	1	1	100
OR	3	48	6.3
AZ	1	19	5.3
WA	5	256	2
CO	0	6	0
VA	0	5	0
MT	0	1	0
IN	0	2	0
NV	0	3	0
NM	0	18	0
GA	0	3	0
CA	0	37	0

Caveat: Overestimation

People may send us samples *because* they suspect xylazine.

Data current through Monday October 2, 2023

Zagorski *et al. Harm Reduction Journal* (2023) 20:141
https://doi.org/10.1186/s12954-023-00879-7

PERSPECTIVE Open Access

Reducing the harms of xylazine: clinical approaches, research deficits, and public health context

Claire M. Zagorski[1*], Rebecca A. Hosey[2], Christopher Moraff[3], Aaron Ferguson[4], Mary Figgatt[5], Shoshana Aronowitz[6], Natalie E. Stahl[7], Lucas G. Hill[1], Zoe McElligott[8] and Nabarun Dasgupta[9]

Table 1 Xylazine harm domains and clinical approaches

Harm domain	Mechanism	Clinical implications	Harm reduction strategies
Heavy sedation	Alpha-2 receptor agonism	Continued sedation after naloxone administration Pressure ulcers and skin breakdown likely Elevated risk for DVT Elevated risk of compartment syndrome Nerve, muscle, and soft tissue injury Rhabdomyolysis	Encourage using drugs with a friend Roll people nodding onto their side Move people nodding every two hours Pad under bony areas (sacrum, heels, shoulders, etc.) Avoid wrinkled or hard surfaces under nodding person
Skin wounds	Unknown	Bacterial superinfection possible Ensure adequate longitudinal wound care Can cause shame and reduced care-seeking Individuals may be deemed ineligible for in-patient substance use disorder care due to untreated wounds	Coach to avoid injecting into or near wounds Facilitate wound care access Teach individual and friends/family how to care for wounds Provide wound care supplies Teach on signs of worsening condition
Anemia	Unknown; perhaps sympathetic antagonism	Vague symptoms may delay care-seeking Important to rule out dietary or other causes	Coach communities on signs and symptoms; when care-seeking is necessary Encourage and facilitate community support to identify changes in health status in self and others
Dysglycemia	Unknown	Vague symptoms may delay care-seeking Important to rule out other causes of metabolic derangement Potential to worsen skin wound progress	Coach communities on signs and symptoms; when care-seeking is necessary Encourage and facilitate community support to identify changes in health status in self and others

Graphic Images of Skin Wounds on Next Slide

Kappa opioid receptor agonists

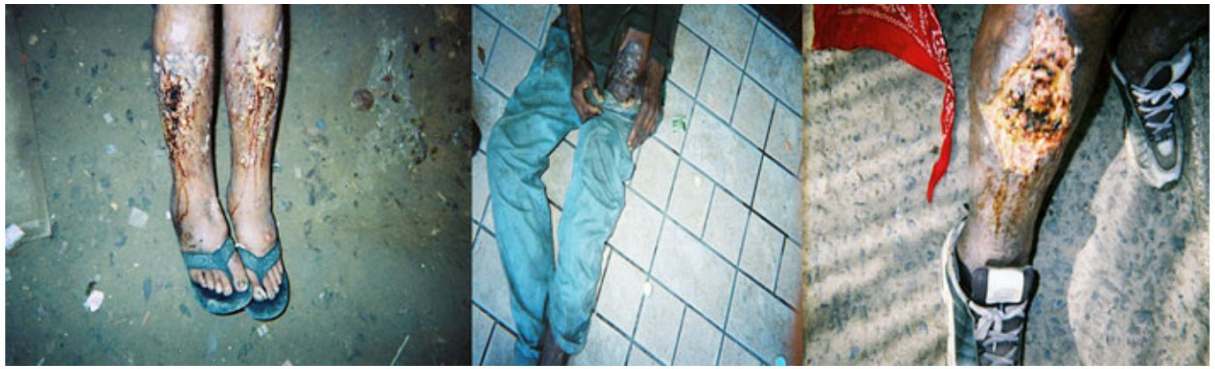
Ts & Blues: Chicago/STL 1979-81

Pentazocine liquid: India & Nigeria

Xylazine: Puerto Rico 2012

Xylazine fentanyl: Philadelphia 2022

Puerto Rico 2012
Xylazine



Reyes et al. 10.1007/s11524-011-9662-6

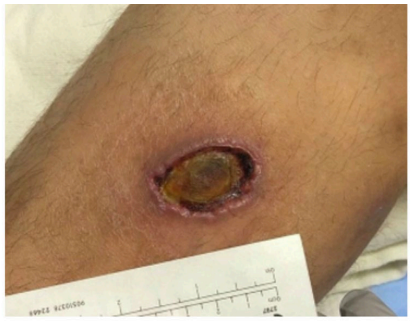
Nigeria 2020

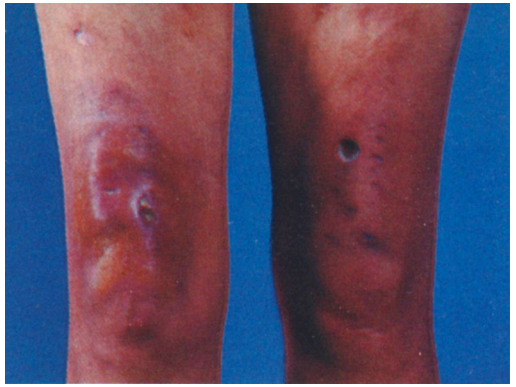
Parenteral pentazocine

Otene et al.
Nigerian J of Plastic Surgery

Philadelphia 2022
Xylazine + Fentanyl

Rose et al. 10.1016/j.jdcr.2023.04.010

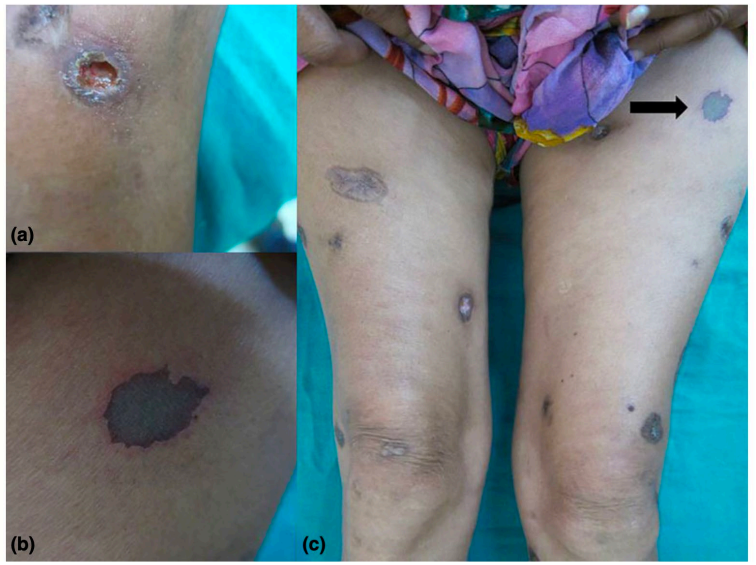




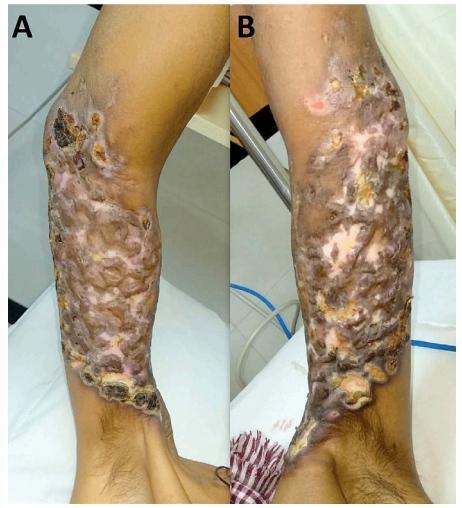
Chicago 1979
pentazocine & tripelennamine

Padilla et al. Arch Dermatol

India 2016-22
Parenteral pentazocine



Sethi Int. J of Dermatology



Yelne et al. 10.7759/cureus.27046

Wound Care Kits

Alonza Lasher, Ainsley Bryce, Bayla Ostrach
Holler Harm Reduction
Madison, North Carolina

Xylazine-Associated Wounds and Related Health Concerns Among People Who Use Drugs: Reports from 7 U.S. States

21 Pages
Posted: 15 Jun 2023

Jennifer J. Carroll
North Carolina State University; Warren Alpert Medical School

Date Written: May 30, 2023

Abstract

Background and Aims: Xylazine, an adrenergic alpha-2 agonist increasingly present in the U.S. drug supply, has not been studied in humans and is associated with severe skin ulcers. The purpose of this study is to describe the progression and treatment of xylazine-associated wounds, other xylazine-related health concerns, and the most urgent research priorities, according to front line healthcare and harm reduction professionals.

Design: This is an exploratory, qualitative study.

Setting: Participants were in the U.S. states of Maryland, Massachusetts, Michigan, Minnesota, North Carolina, Pennsylvania, and Texas

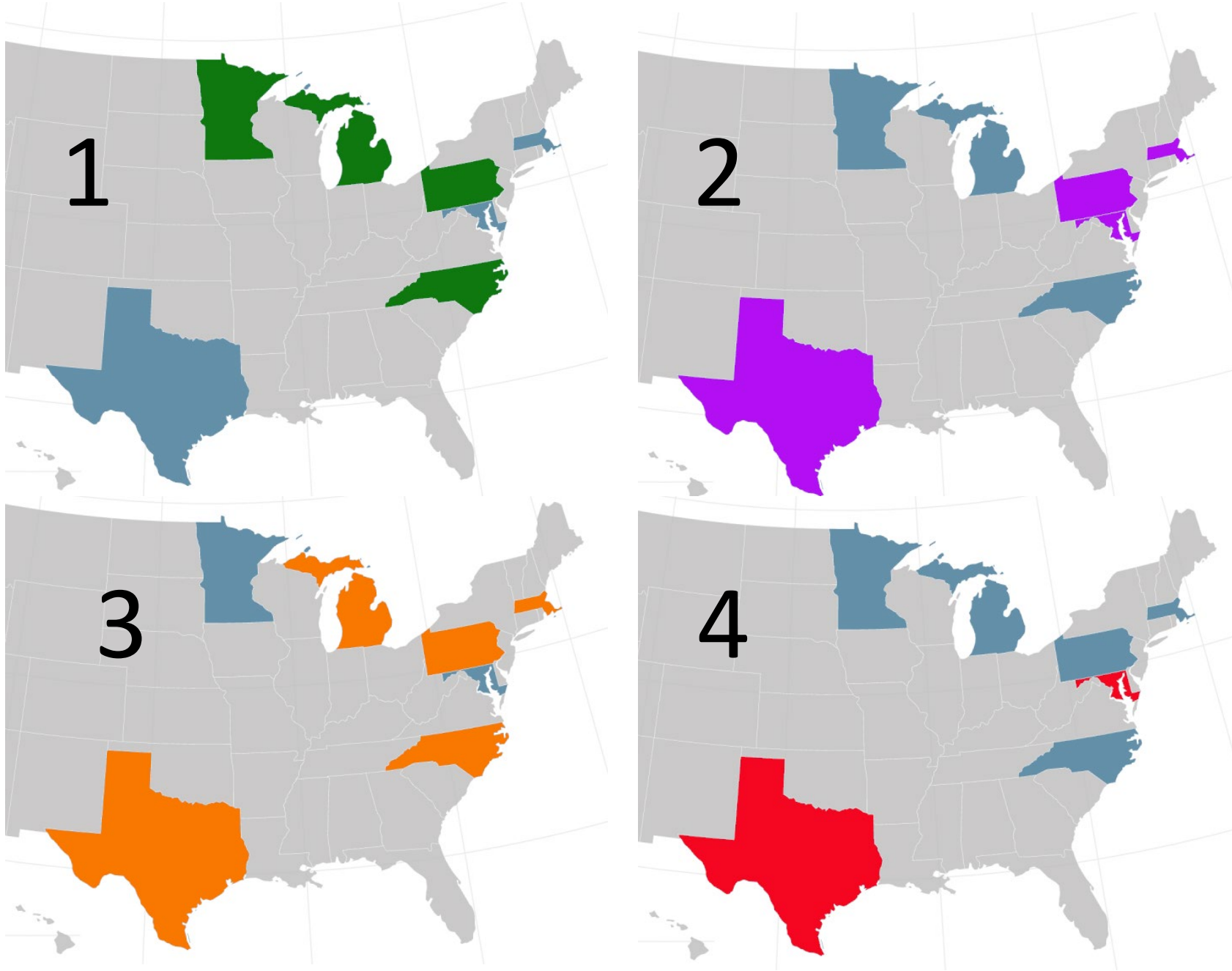
Wound care supplies	Benefits of use	Drawbacks of use
Xeroform (occlusive petrolatum/bismuth tribromophenate gauze)	Can be cut to size Easier to use than non-adherent pads Participants like it, ask for it. Effective at debriding over time.	Hard for community members to manage alone. Can cause surrounding skin to macerate and slow healing if not cut and placed properly.
Calcium alginate and **silver alginate** dressings	Protects wound bed Non-adherent	Can harden in a few days and become difficult to remove without damaging the wound bed
Medihoney hydrogel	Excellent at softening eschar Reliable, if slow, debriding agent	Attracts bugs. Stickiness a problem for unhoused persons. It slides off the wound in cold temperatures.
SANTYL (collagenase) ointment	Excellent debriding agent	Expensive. Available by prescription only. Not in NC Medicaid formulary
Vashe Wound Solution	Effective agent for cleaning and hygiene	Expensive. Large quantities needed Hard to distribute (liquid)

NO CONSISTENT CASE DEFINITION OF XYLAZINE-RELATED WOUNDS IS EMERGING

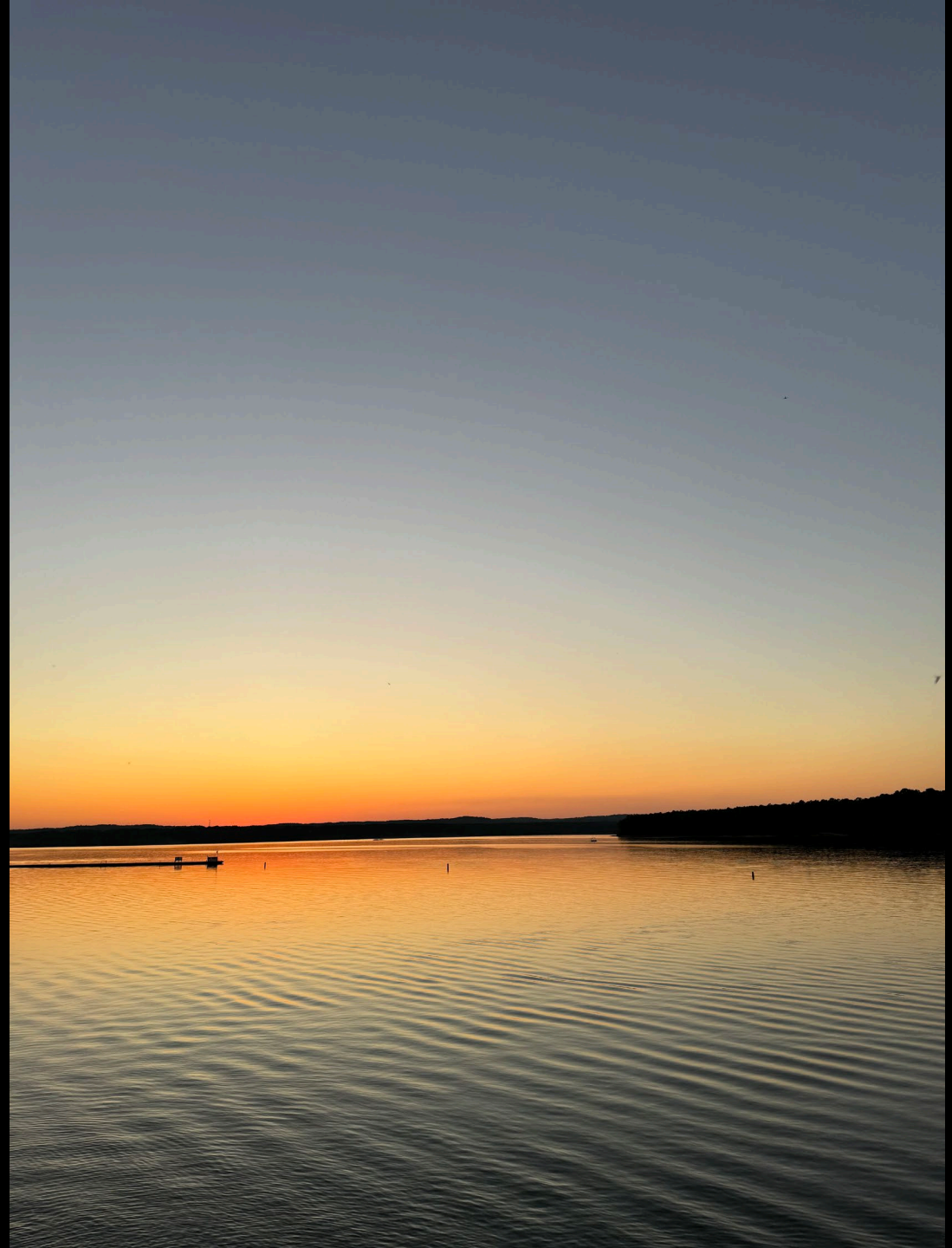
Harm reduction and wound care specialists in 7 states universally described xylazine wounds as:
--Necrotic
--Slow to heal
--First presenting as blisters or birdshot-like wounds

BUT:

1) Only described in MI, MN, NC, and PA as almost <u>always infected.</u>
2) Only described in MA, MD, PA, and TX as almost <u>never infected</u>
3) Only described in MA, MI, NC, PA, and TX as <u>macule-like/granulated</u>
4) Only described in TX and MD as <u>almost always small, never large.</u>



Carroll, Jennifer J. "Xylazine-associated wounds and related health concerns among people who use drugs: Reports from front-line health workers in 7 U.S. states." *In review.* Pre-print available at https://papers.ssrn.com/abstract_id=4470098



Thanks from and to our team!

UNC INJURY PREVENTION RESEARCH CENTER (IPRC)

UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH

UNC HUSSMAN SCHOOL OF JOURNALISM AND MEDIA

UNC CHEMISTRY MASS SPECTROMETRY LAB

NORTH CAROLINA SURVIVORS UNION NCSU THE COMMUNITY VOICE


Illyana


Allison


Don


Louise


Drew


Brandie


Maryalice


LaMonda


Zoë


Nabarun


Colin


Erin

Nabarun Dasgupta

@nabarund

https://streetsafe.supply

Session 3: Opportunities to Address Product Development Research Needs

Tim Stenzel, M.D., Ph.D.

Director, Office of In Vitro Diagnostics, OPEQ, CDRH, FDA

Mitigating Risks from Human Xylazine Exposure meeting hosted by Reagan-Udall Foundation for the FDA and FDA's Center for Drug Evaluation and Research

October 4, 2023

Important In Vitro Diagnostic Test Research Needs

- Determine needed clinical sample type(s)
- Determine clinically valid positive/negative cutoffs by sample type
- Inexpensive POC/CLIA waived and OTC tests
- Dual Xylazine/Fentanyl tests likely to be helpful
- Reference materials can help harmonize tests

Thank You!!!!

Exploring Product Development Research Needs

Zachary Dezman, MD, MS
Medical Officer
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Food and Drug Administration

October 4th, 2023

Pharmacology of Xylazine

- Pharmacology
  - α_2-agonist
  - Pharmacokinetics, pharmacodynamics
  - Off-receptor effects?

Epidemiology

- Epidemiology
- Clinical outcomes in xylazine overdose
  - Characteristics and complications
  - Efficacy of existing treatments

Product development for overdose management

- Reversal agents
  - Other models of overdose
  - Pharmacology
- Product development
  - Intravenous
  - Subcutaneous/intramuscular, intranasal

Complications of chronic use

- Xylazine withdrawal
  - Characterize syndrome
  - Mechanistic explanation
  - Treatments
- Xylazine-associated wounds
  - Pathophysiology
  - Surgical management

Complications of chronic use

- Most xylazine is mixed with fentanyl/heroin
  - Complicate transition to medication for opioid use disorder (MOUD)?
  - Does xylazine impact MOUD retention rates?
- Does xylazine use disorder exist?
  - Characteristics
  - What treatments work?

Current Thoughts on Overdose Product Development

- Overdose Prevention Framework
- Guidance: Expedited Programs for Serious Conditions – Drugs and Biologics
- Webpage: Investigational New Drug (IND) Application

Thank you!

- Additional thanks
  - Rigo Roca, MD
  - Celia Winchell, MD

Session 4: On the Ground Response to Xylazine

Presenter:

- **Martín Lina Alcaraz**, Sanos Corporation Puerto Rico

Panelists:

- **Alice Bell**, **LCSW**, Prevention Point Pittsburgh
- **Malik Burnett, MD, MBA, MPH**, Maryland Department of Health
- **Luis Roman, PsyD**, Intercambios Puerto Rico
- **Lewis Nelson, MD, MBA**, Rutgers New Jersey Medical School
- **Jennifer Tuerke**, Voices of Hope Maryland

REAGAN-UDALL FOUNDATION FOR THE FDA

Session 5: Future Directions

- **Rachel S. Wightman, MD**, Alpert Medical School of Brown University
- **Jane Acri, PhD**, National Institute on Drug Abuse, NIH
- **Elizabeth M. Oliva, PhD**, Veterans Health Administration, VA
- **Laurie Konsella, MPA**, Office of Assistant Secretary for Health, HHS
- **Marta Sokolowska, PhD,** Center for Drug Evaluation and Research

Drug Overdose Testing (DOT): Xylazine

Rachel S. Wightman, MD FACMT
Associate Professor of Emergency Medicine and Epidemiology
Alpert Medical School of Brown University
Emergency Medicine Director of Medical Toxicology and Addiction
Consultant Medical Director, Rhode Island Department of Health

BROWN PHYSICIANS, INC.

BROWN
Alpert Medical School

Disclosures

- This work was supported by:

  RI COBRE on Opioid and Overdose, NIGMS/P20GM125507

Xylazine Detection in Urine and Blood Post Overdose

February to August 2022	Xylazine (n)	Fentanyl (n)	Percent fentanyl positive samples with xylazine
76 Urine samples	25 (33%)	67 (88%)	37%
76 Blood samples	11 (14%)	58 (76%)	19%
Both Urine and Blood samples	10 (13%)	58 (76%)	17%
Not Detected	50 (66%)	9 (12%)	

Median time to collection of blood from ED triage time was approximately 4 hours and 50 minutes
Median time to collection of urine from ED triage time was approximately 4 hours and 30 minutes
* Every sample positive for xylazine also tested positive for fentanyl

Real world considerations in SUD research

- Context of use
  - Route of use (Xylazine in blood: 6 snorted, 2 smoked, 2 ingested, 1 injection)
  - Frequency of use
  - Time since use or since triage
- Comorbidities and presenting status (e.g. mental health, cardiac history)
  - 2/3rds of sample self reported psychiatric illness
- Toxicology testing in isolation (breadth and depth)
  - Transparency in testing libraries and limitations of methods
- Generalizability

Practical directions for xylazine research

- Treatment with longer inpatient observation periods (e.g. impact of adulterants)
- Safety considerations given chronic and high levels of use
- Follow up should leverage links to state administrative databases when possible

Thank you

- Rachel_Wightman@brown.edu

- Special Thanks

Dr. Francesca Beaudoin, Dr. Adina Badea

Rhode Island Department of Health

Providence RI Public Schools

National Institute on Drug Abuse

Xylazine: Future Directions for NIDA

Jane B. Acri, Ph.D
Deputy Director (acting)
Division of Therapeutics and Medical Consequences
National Institute on Drug Abuse

Federal Response - NIDA

In April 2023, the Director of the White House Office of National Drug Control Policy (ONDCP) designated fentanyl adulterated or associated with xylazine as an emerging threat to the United States.

ONDCP released a National Response Plan in July to coordinate a government-wide response.

NIDA is part of the **Fentanyl Adulterated or Associated with Xylazine Interagency Working Group** that includes HRSA, SAMHSA, NIH, FDA, CDC

EPIDEMIOLOGY AND COMPREHENSIVE DATA SYSTEMS

NIDA proposed response includes National Institute on Drug Abuse (NIDA)'s National Drug Early Warning System (NDEWS) is evaluating novel xylazine surveillance methods, including EMS call data and wastewater epidemiology (WBE). NDEWS has 16 sentinel sites across the U.S. that use a variety of drug surveillance technologies covering several states (FL, KY, MI, MN, TX) and many large metro areas including Atlanta, Chicago, Denver, Detroit, Los Angeles, New York City, Phoenix, San Diego, San Francisco, Seattle, St. Louis, and Washington, D.C. NIDA provided supplemental funding to NDEWS to expand wastewater sampling for xylazine and other drugs within its network and harmonize WBE data with other surveillance data. NIDA has also funded a service contract to the small business Biobot to evaluate the distribution of xylazine and other substances in ~70 wastewater treatment facilities across the U.S. In addition, a NIDA-funded project is using AI to mine social media data for self-reported substance use, including xylazine exposures.

Federal Response - NIDA

- **NIH** NIDA's new harm reduction research network, funded through the NIH HEAL Initiative, is poised to develop and evaluate harm reduction strategies for xylazine exposure. Common measures that were identified for collection by all studies in the network include questions on xylazine and xylazine test strip use. Lead network sites are located in Baltimore, Chicago, New York City, and other locations where xylazine has become highly prevalent. Current NIDA-funded research is engaging people who use opioids to understand their experiences with xylazine exposure to inform harm reduction strategies.

- **REGULATORY CONTROL AND MONITORING OPTIONS**
- **NIH**/NIDA is expanding research on the pharmacology and physiological effects of xylazine that could help inform novel harm reduction and treatment interventions. In addition, NIDA has solicited research on whether other alpha-2 adrenergic agonists in addition to xylazine are emerging in the illicit drug supply

- **BASIC AND APPLIED RESEARCH**
- NIDA intramural and extramural researchers are conducting preclinical studies to investigate the effects of xylazine and xylazine/opioids on respiratory function, withdrawal, and overdose risk, and potential overdose reversal agents specific for xylazine.

NIDA NOSI

Notice of Special Interest (NOSI): Xylazine: Understanding Its Use and the Consequences

Notice Number:
NOT-DA-24-012

Key Dates

Release Date:	August 28, 2023
First Available Due Date:	October 16, 2023
Expiration Date:	January 08, 2025

Division of Therapeutics and Medical Consequences Scientific/Research Contacts

Jana Drgonova, PhD
jana.drgonova@nih.gov

Aidan Hampson, PhD
aidan.hampson@nih.gov

In June 2023, **NIH/NIDA** released a Notice of Special Interest (NOSI) and a subsequent expanded NOSI in August 2023, calling for more research on xylazine pharmacology and physiological effects; clinical manifestations of xylazine exposure, including its impact on opioid overdose, outcomes from chronic exposure, and potential for unique xylazine withdrawal symptoms; possible pharmacotherapies for xylazine exposure; patterns of xylazine use (including seeking vs. avoidance); its presence in the drug supply; and psychosocial consequences of xylazine exposure.

https://grants.nih.gov/grants/guide/notice-files/NOT-DA-24-009.html
https://grants.nih.gov/grants/guide/notice-files/NOT-DA-24-012.html

NIDA'S NATIONAL DRUG ABUSE TREATMENT CLINICAL TRIALS NETWORK

Managing Patients Taking Xylazine-Adulterated Opioids in Emergency, Hospital, & Addiction Care Settings

June 14, 2023
9 a.m. - 12:30 p.m.

National Institute on Drug Abuse

Meeting Organizer: Kristen Huntley, Ph.D., NIDA CCTN

Co-chairpersons:

Jeanmarie Perrone, M.D., Professor, Emergency Medicine & Addiction Medicine; Director, Center for Addiction Medicine and Policy, University of Pennsylvania

Rachel Haroz, M.D., Associate Professor, Emergency Medicine & Addiction Medicine, Cooper Medical School of Rowan University

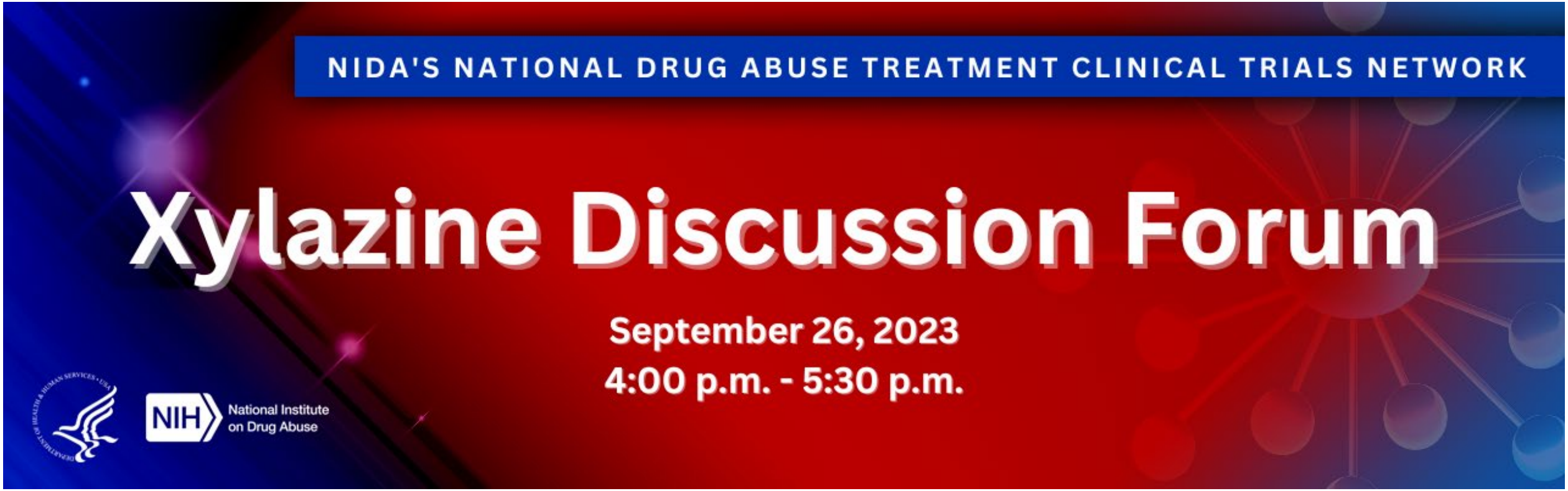
Meeting Focus:

- **Clinical manifestations of withdrawal and overdose**
- **Wounds**
- **Testing**

Meeting Goals:

Identify emerging practices and research needs

Meeting Recording and Summary



Meeting Organizer: Kristen Huntley, Ph.D., NIDA CCTN

Speakers:

Jeanmarie Perrone, M.D., Professor of Emergency Medicine, Hospital of the University of Pennsylvania; Director, Division of Medical Toxicology and Addiction Medicine Initiatives, Department of Emergency Medicine, University of Pennsylvania; Founding Director, Penn Medicine Center for Addiction Medicine and Policy

Rachel Haroz, M.D., Associate Professor, Emergency Medicine & Addiction Medicine; Medical Director, Center for Healing, Cooper University Health Care, Cooper Medical School of Rowan University

Paul Wax, M.D., Executive Director, American College of Medical Toxicology, Adjunct Professor, UT Southwestern School of Medicine

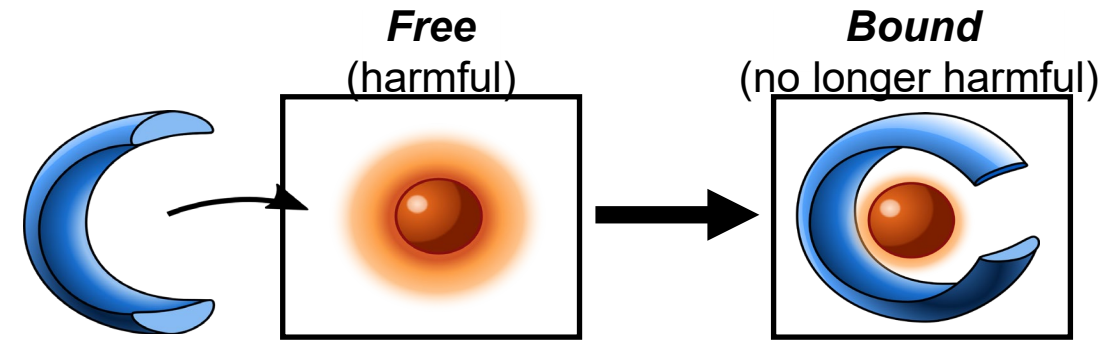
OTHER RESEARCH - NIDA

NIDA has issued a supplement to a cooperative agreement UG3DA056892 (Sentanyl II: A Multi-State Analysis of Fentanyl/Analogs, Naloxone, and Clinical Features of Non-Fatal Opioid Overdose, PI Roland Merchant) which is in progress. The project involves obtaining demographic and clinical data and blood samples from University of Massachusetts Medical Center Emergency Department (ED) opioid overdose patients. Blood samples undergo extensive assessment for opioids and other substances by the Center for Forensic Science Research and Education (CFSRE). Xylazine has been detected in the blood of 10 of 26 (38.5%) Sentanyl II participants to date.

This research program provides a naturalistic and practical opportunity to study xylazine pharmacokinetics among recently exposed human participants. Supplement Aim 1 will recruit twelve UMass ED patients who (1) present after opioid overdose via injection use, and (2) whose initial blood sample obtained on arrival at the ED indicates a probable xylazine exposure, per the Randox Laboratories Evidence MultiSTAT xylazine assay. Participants will provide additional blood samples hourly for up to six hours. CFSRE will perform quantitative analyses of these samples to produce xylazine pharmacokinetic profiles of these participants.

From NIH Reporter: https://reporter.nih.gov/search/vH0FvkzrZUKBi-ssRHHtkQ/project-details/10904337#similar-Projects

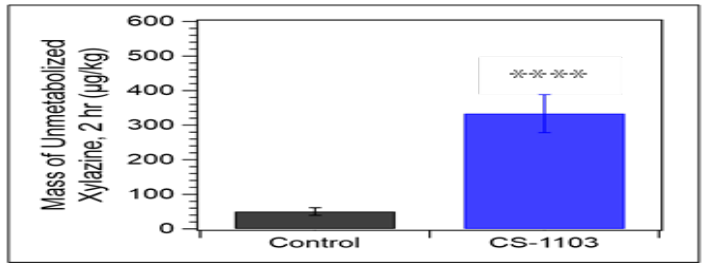
Med Development - NIDA



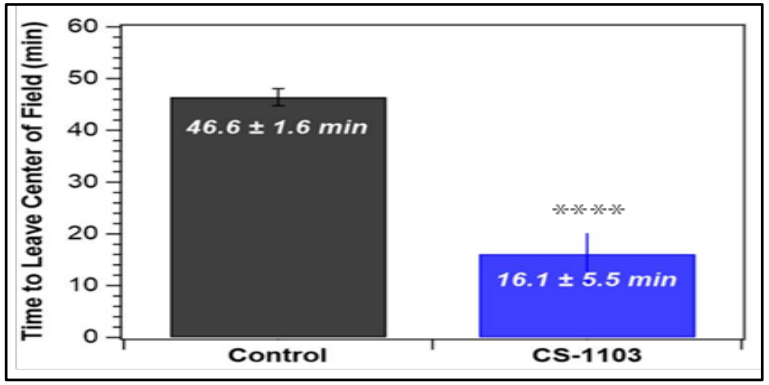
CS-1103 binds, inactivates, and clears xylazine, accelerating emergence from sedation

- CS-1103 is a small-molecule sequestrant
- ***It binds, inactivates, and clears*** small molecules from the body with high specificity
- Anticipate First-in-Human studies in 2024

- **accelerates clearance** of xylazine into urine 6-fold vs saline control in 2 hr, in rat
- **accelerates emergence** from sedation nearly 3-fold, in rat
- also **works when fentanyl is present**, reversing both respiratory depression and sedation



IV CS-1103 **accelerates clearance** of xylazine from plasma into urine, in rat. ****p-value <0.0001



IV CS-1103 **reduces duration** of xylazine-induced sedation, in rat. ****p-value <0.0001

Sedation experiments conducted in collaboration with Joseph Cotten, MD PhD, Department of Anesthesia, Critical Care, and Pain Medicine, Mass General Hospital

VA | U.S. Department of Veterans Affairs

Xylazine: VA's Response

Elizabeth Oliva, PhD
VA National Opioid Overdose Education and Naloxone Distribution (OEND) Coordinator
VA Office of Mental Health and Suicide Prevention
Veterans Health Administration
Department of Veterans Affairs (VA)

October 4, 2023
Public Meeting: Mitigating Risks from Human Xylazine Exposure
Reagan-Udall Foundation for the Food and Drug Administration

Testing

- VA has mandated that fentanyl be included as part of VA's basic panel for urine drug tests
- VA will integrate point of care testing, including a urine drug screen test for xylazine, if/when they become available
  - Will convene national workgroup to develop clinical guidance
  - Will weigh feasibility of mandating confirmatory xylazine testing for all fentanyl positive specimens at sites with access to confirmatory testing
- Consultation with Office of General Counsel (OGC) Related to Drug Test Strips
  - Engaging with OGC to examine how to support implementation of fentanyl and xylazine drug test strips—a potential barrier to national implementation is that drug test strips vary in legality across the country
- Consultation with National Institute of Standards and Technology (NIST)
  - Will request a consultation with NIST related to testing and evaluation of fentanyl and xylazine test strips—the other major barrier to implementation is that fentanyl and xylazine drug test strips, unlike drug testing for human specimens—which have federal agencies involved in evaluating and overseeing performance of those drug tests—do not have a corollary federal agency that evaluates or oversees drug test strip performance to ensure minimal standards of detecting the presence of the drug itself in drug specimens

Evidence-based Prevention, Harm Reduction, and Treatment Implementation and Capacity Building (1 of 2)

- Informed by award-winning approach to implementing VA's Rapid Naloxone Initiative[1] which used theory-based approach to mapping barriers to implementation strategies[2]
- Development of Patient and Provider Education
  - Developed a Xylazine Patient Guide and Xylazine Provider Guide that have been integrated into VA Academic Detailing Services' Substance Use Disorder Harm Reduction Campaign (https://www.pbm.va.gov/PBM/academicdetailingservicehome.asp)
  - Will work with Academic Detailing Services to deliver knowledge translation services and support dissemination across the enterprise
  - Will work with Office of Nursing Services to develop xylazine-related wound care guidance
- Dissemination of Emerging Practices to Address Xylazine Exposure
  - Will continue to disseminate the most up-to-date emerging practices to support clinical care to patients exposed to xylazine to relevant national communities of practices and listservs (e.g., Emergency Medicine, Nursing, Substance Use Disorder Treatment, Pain Management, Surgery, and Primary Care)
- Communications Plan
  - Will coordinate across clinical services and communication offices to develop a communications plan to increase awareness of xylazine among both providers and patients

VA | U.S. Department of Veterans Affairs

[1]Oliva et al., 2021, *Jt Comm J Qual Patient Saf;* [2]Goodrich et al., 2020, *The QUERI Roadmap*

Evidence-based Prevention, Harm Reduction, and Treatment Implementation and Capacity Building (2 of 2)

- Examine distribution pathways
  - If/when there is a federal recommendation to distribute drug test strips that meet a minimum standard, VA will examine feasibility of procurement and distribution via pharmacy and logistics
- Tracking
  - When clinical tests for xylazine become available, will use frequency and geographic data of positive results to track prevalence of detected xylazine exposures within our patient population
- Standardized Collection of Xylazine Exposure in Documentation (e.g., clinical notes)
  - Xylazine is already included in VA's national Syringe Services Program note; will also add to national Suicide Behavior and Overdose Report note
- Using Natural Language Processing (NLP) Data for Xylazine Exposure Identification
  - Using NLP to help identify patients with potential xylazine exposure and track localities and populations with emerging cases; will integrate NLP data into clinical dashboards to improve treatment for Veterans
- Improved Coding of Injection Drug Use
  - VA supported a new ICD-10-CM code to track Injection Drug Use—was discussed at September 2023 ICD-10-CM Committee Meeting

Basic and Applied Research

- VA's Office of Research and Development (ORD) is a major funder of basic and applied research in the United States with an annual budget of $916 million
- ORD is committed to supporting the goals of the July 2023 Fentanyl Adulterated or Associated with Xylazine Response Plan via its Pain and Opioid Use Actively Managed Portfolio
  - This portfolio's funding announcements were amended to include studies of fentanyl adulterated or associated with xylazine as a research area of special interest effective Winter 2023
  - Announcements include special consideration of research identified in the Response Plan including treatment development, investigations of how xylazine impacts human physiology and behavior, research on social outcomes of xylazine use in humans, and research on use motivations, e.g.,
    - Research to evaluate as quickly as possible potential xylazine antidotes in humans, and identify the most promising clinical stabilization, detoxification, and treatment protocol(s)
    - Conduct basic research on drug-drug interactions to understand the pharmacology, chemistry, biology, and toxicology of how xylazine and fentanyl interact in humans and the behavioral consequences
    - Examine whether any of these effects vary across modes of xylazine administration (e.g., injecting, smoking, or inhalation)
    - Conduct applied research on population-level health, social, equity, and economic drivers and consequences of exposure to fentanyl adulterated with xylazine

Office of the Assistant Secretary for Health

Laurie Konsella, MPA
Senior Public Health Advisor
Office of Regional Health Operations, Region 8

OASH | Office of the Assistant Secretary for Health

October 4, 2023

What is the Office of the Assistant Secretary for Health (OASH)?

- **Vision: Healthy people, healthy communities, a healthy nation for all**

- **Mission**: To improve the health and well-being of all by leading on policy, practices, and programs through the application of science, innovation, education and a commitment to social justice and equity.

- **OASH oversees**:
    - the Department's key public health offices and programs
    - a number of Presidential and Secretarial advisory committees
    - 10 regional health offices across the nation
    - the Office of the Surgeon General and the U.S. Public Health Service Commissioned Corps

What is the Office of Regional Health Operations (ORHO)?

As the senior federal public health official in the region, the Regional Health Administrator (RHA) performs essential functions for the Department of Health and Human Services (HHS) in three major areas: prevention, preparedness, and agency-wide coordination.

Bi-directional: ORHO supports execution of national policies at regional/state level and we communicate on-the-ground intelligence back up to OASH and departmental leadership.

To find your Regional Health Administrator:
https://www.hhs.gov/ash/about-ash/regional-offices/index.html

Community and Stakeholders: Actions

People Who Use Drugs

- Understand the Risks
- No Overdose Reversal
- Wound Care and prevention of disfiguring infections and deep flesh wounds
- Test strips
- More severe withdrawal

Harm Reduction Advocates/ Organizations

- Add xylazine education to conversations
- Add xylazine test strips to kits and vending machines
- Add wound care education and supplies to kits
- Contribute to research via point in time study of xylazine presence and knowledge in community
- Build capacity

Healthcare Providers and Research Community

- Education and awareness: New threat = More to learn
- Wound identification and treatment
- Different high, severe withdrawal
    - Referral to treatment, Recovery process
- Research: Human physical impact of veterinary drug
  Sex/gender, Race/ethnicity. Co-morbidities
- Overdose response
- Include pharmacists as trusted community health care provider

Public Health and Policy Makers

- Develop and share communication tools and messages
- Increase surveillance efforts
- Overdose Fatalities
- Medical interventions (overdose, wound care)
- Coordinate surveillance data with law enforcement and first responders
- Support availability of xylazine education and supplies
- Work with HR organizations to support funding for supplies/education
- Health Equity Lens (always!)

Additional questions

Peers and first responders:

Fewer reversals = More vicarious trauma and burn-out

Community at large

More visible disfiguring wounds = more stigma

Funders

More Harm Reduction service/supply expenses = decreased services

Thank you!

Laurie.Konsella@hhs.gov

OASH | Office of the Assistant Secretary for Health

REAGAN-UDALL FOUNDATION FOR THE FDA

Closing Remarks

Marta Sokolowska, PhD
Deputy Center Director for Substance Use and Behavioral Health
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Thank you!

Meeting materials will be posted on our website: www.reaganudall.org

REAGAN-UDALL FOUNDATION FOR THE FDA