Xylazine

Perspectives from Forensic and Clinical Toxicology

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

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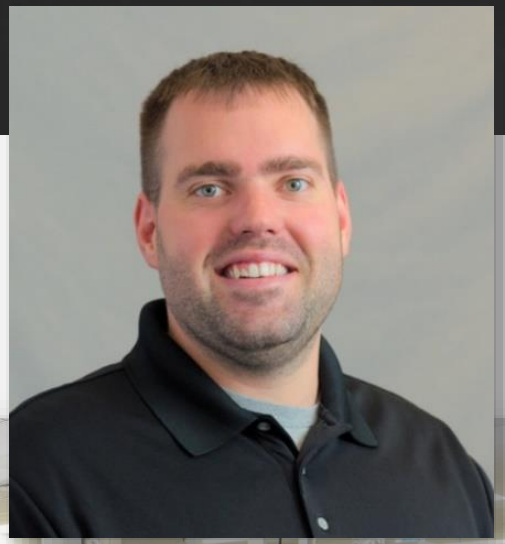
INTRODUCTION



- **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.

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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

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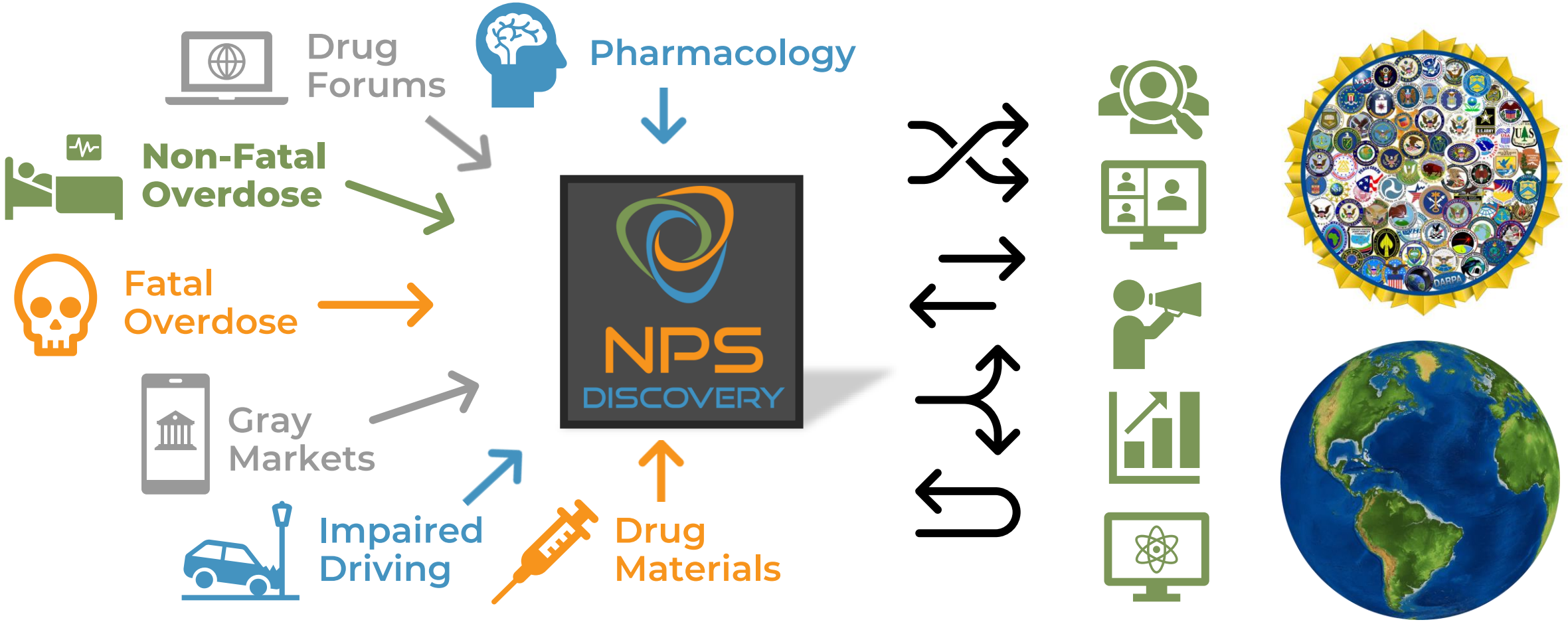
DRUG EARLY WARNING SYSTEM (EWS)

- 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.

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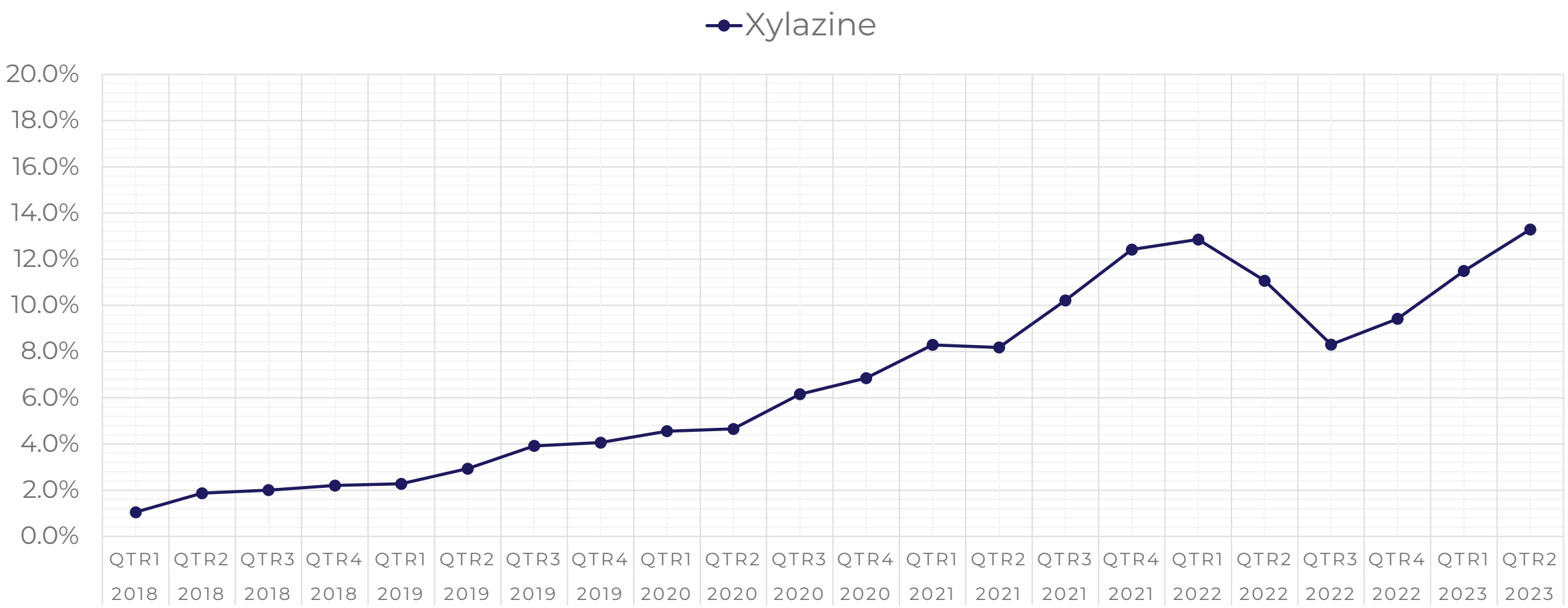
POSITIVITY IN TOXICOLOGY SPECIMENS

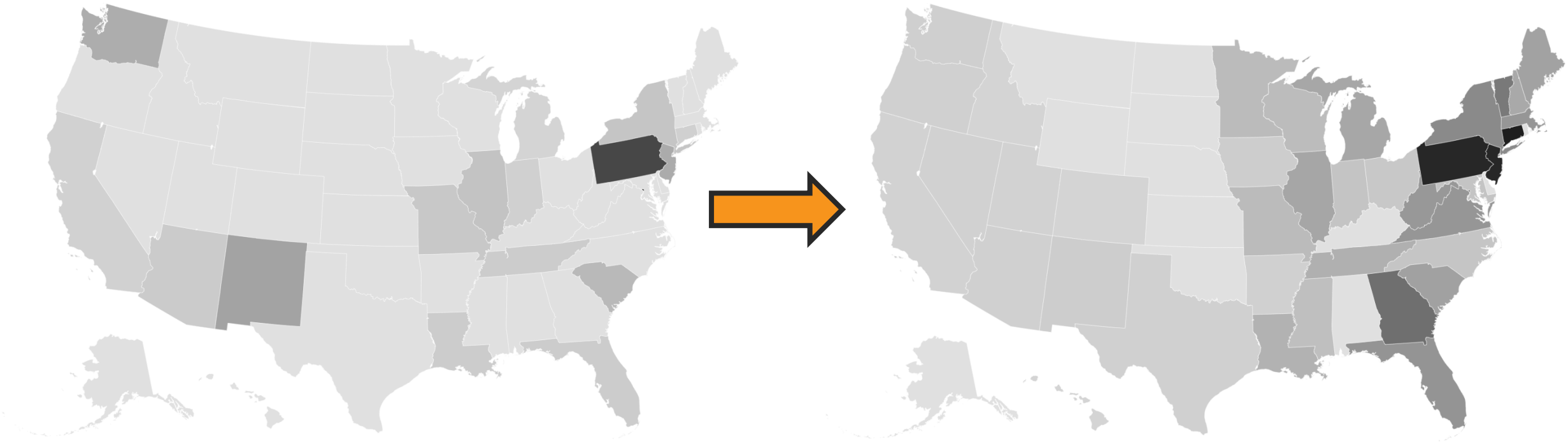


*Surveillance data in collaboration with NMS Labs (Horsham, PA).

INCREASED GEOGRAPHICAL DISTRIBUTION

Q1 2019

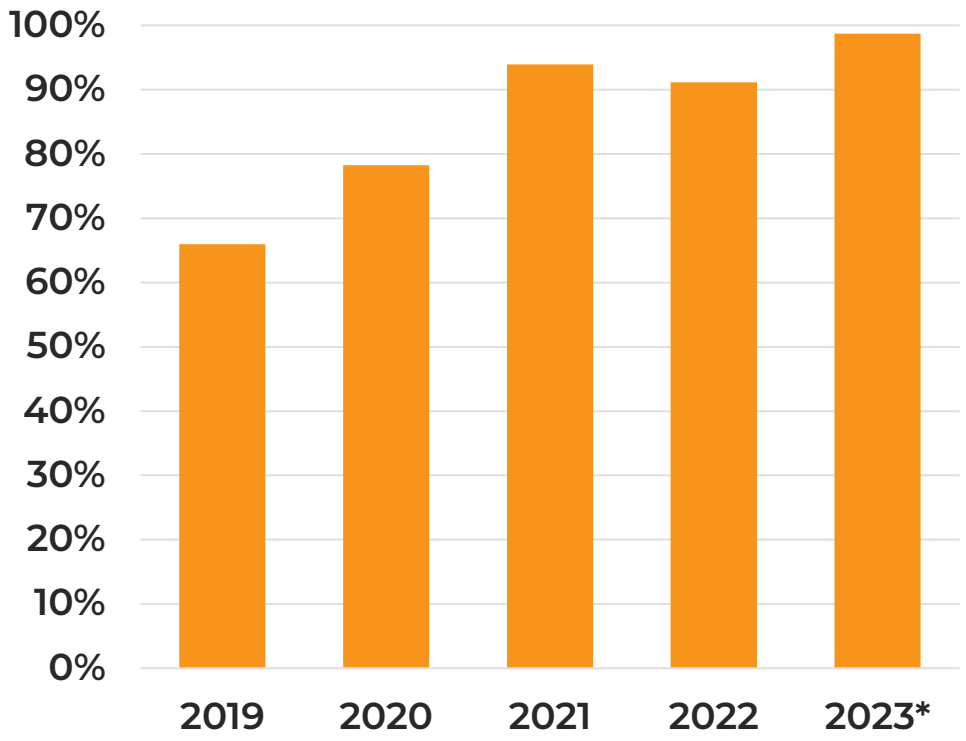
Q4 2022



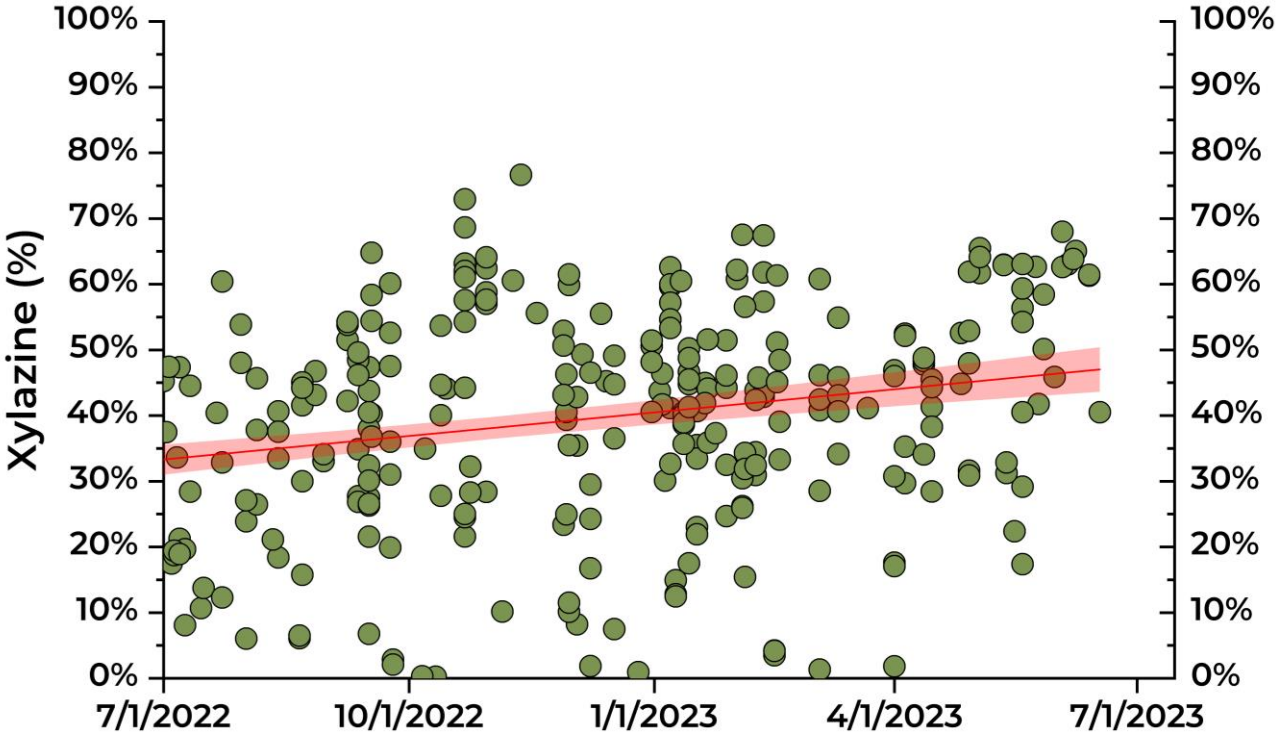
*Forensic data in collaboration with NMS Labs (Horsham, PA).

DOMINATING DRUG SUPPLIES – PHILADELPHIA, PA

Opioid samples containing xylazine



Xylazine purity/content in opioid samples



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

XYLAZINE'S UNANSWERED QUESTIONS

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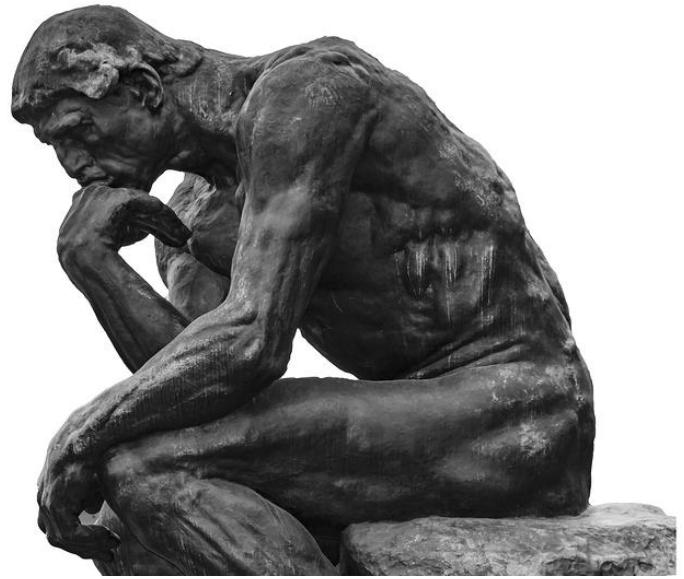
XYLAZINE'S UNANSWERED QUESTIONS

- 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

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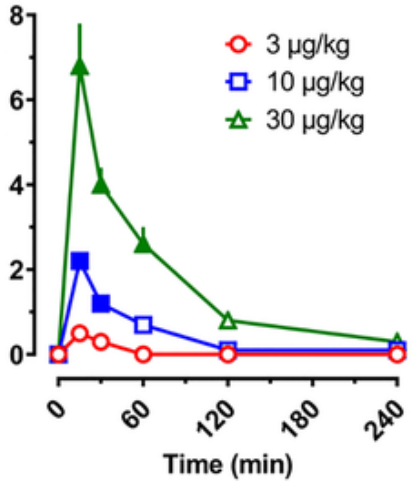
ANALYTICAL RESEARCH EFFORTS

- 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

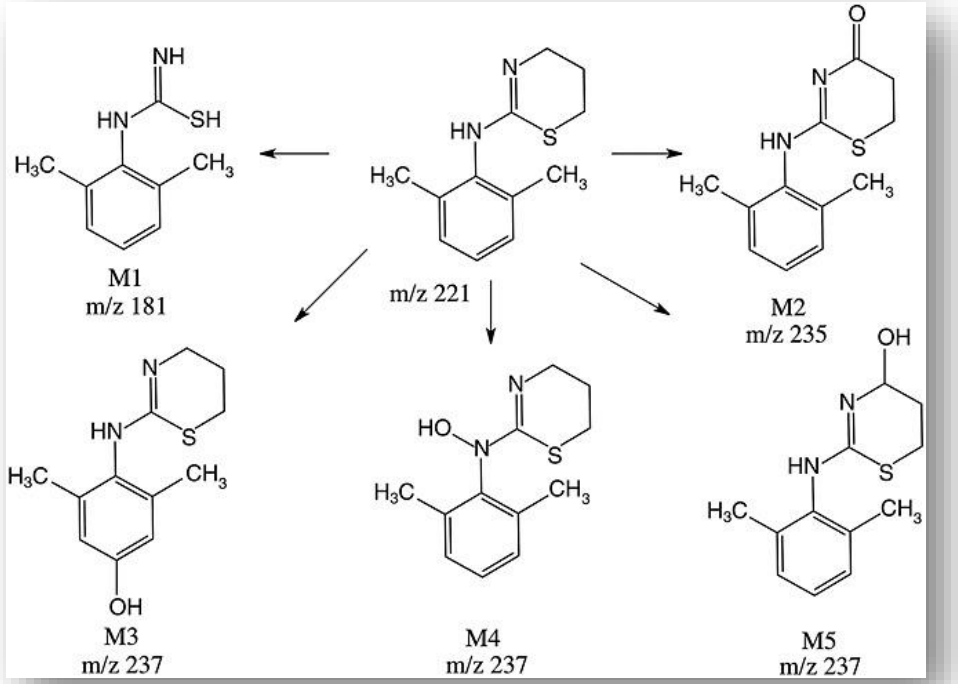


Walton *et al.* https://doi.org/10.1007/s00213-022-06292-5

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

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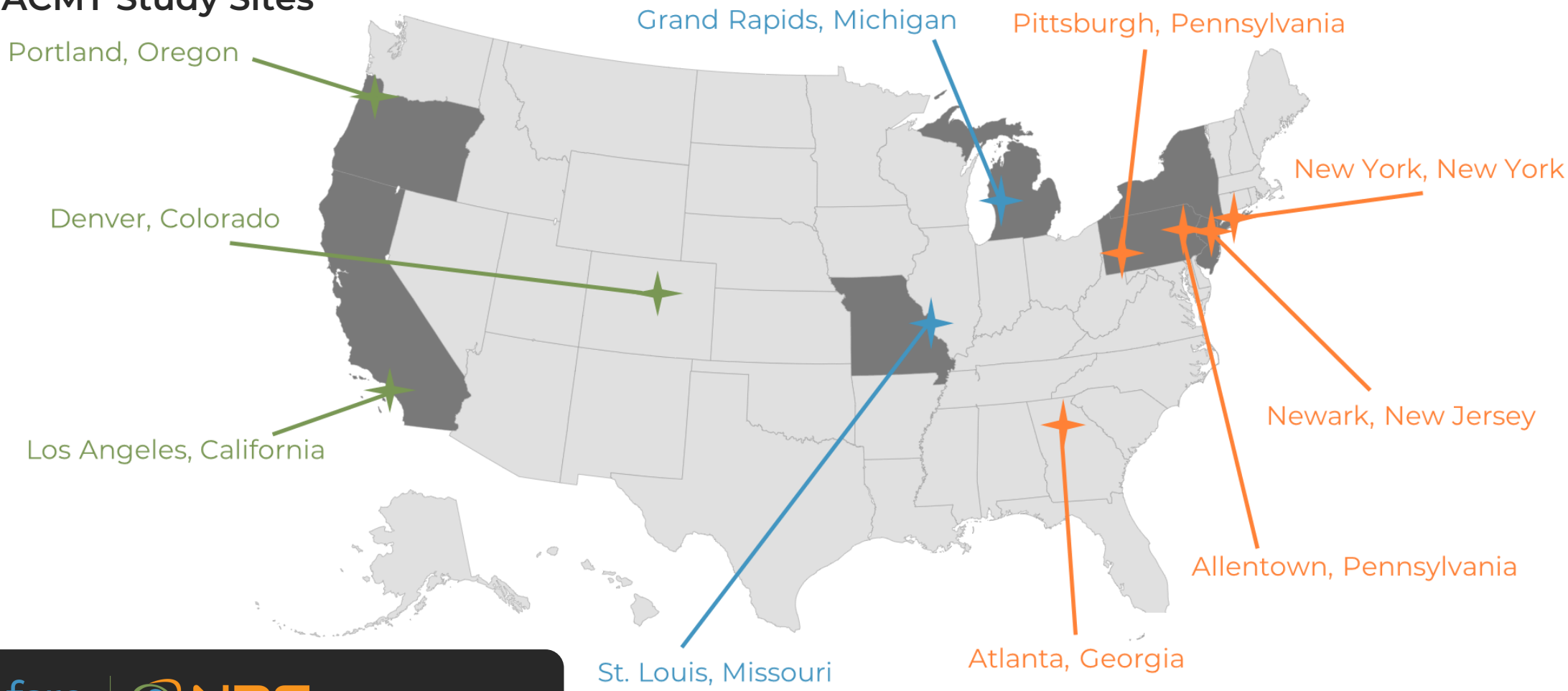
CLINICAL RESEARCH EFFORTS

- **ACMT Study Sites**



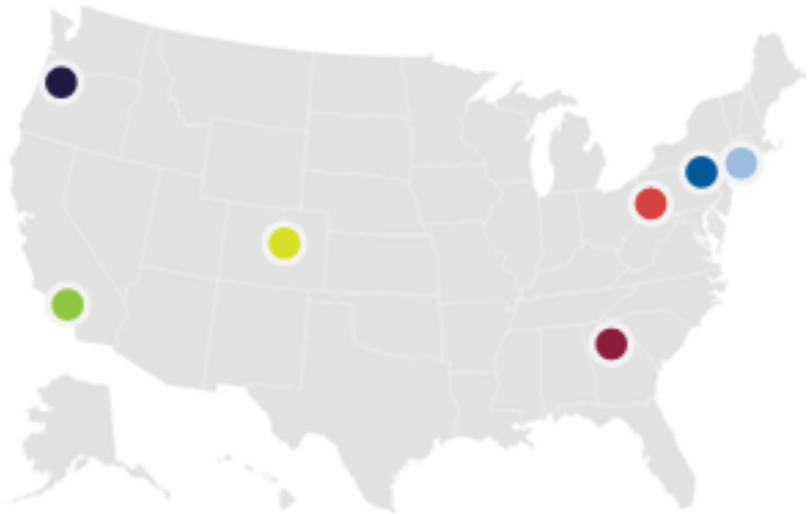
CLINICAL RESEARCH EFFORTS

- 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**

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CLINICAL RESEARCH

Check for updates

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

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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.

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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].

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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

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- **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?

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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**

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- UMass Team
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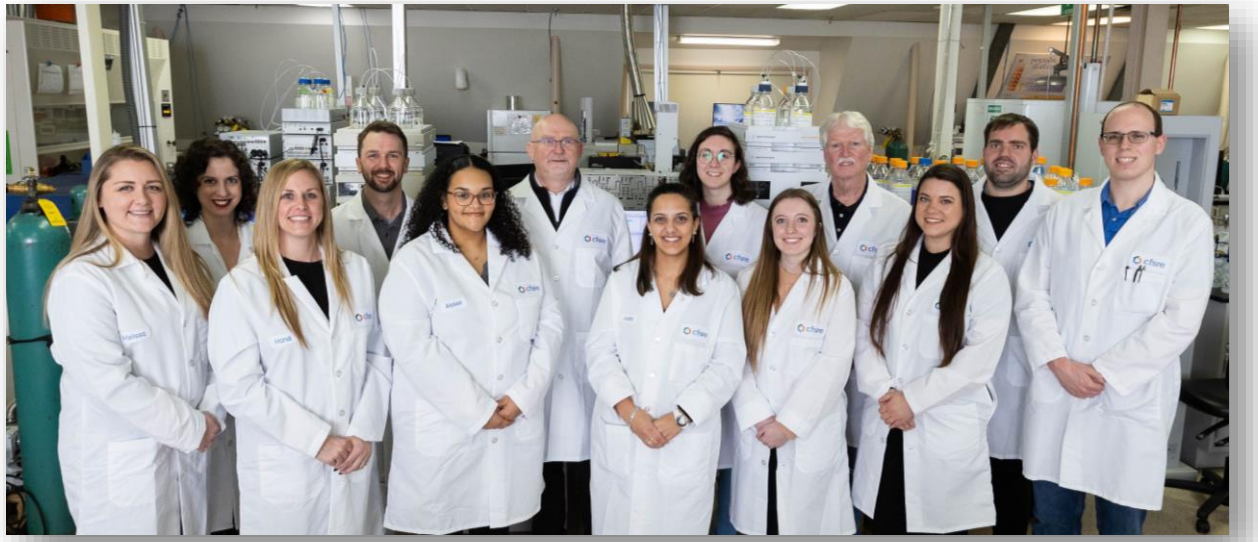
- Funding Agencies
- Collaborators



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THANK YOU! QUESTIONS?

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