# **Toxicity of Xylazine and How It Impacts Treatment for People Who Use Drugs**

#### Joseph D'Orazio, MD, FAAEM, FACMT, FCPP

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Horse tranquilizer is hitting the US as a dangerous street drug By Maria Morava and AJ Willingham, CNN

Updated 4:36 PM ET, Thu February 4, 2021





This undated photo provided by the Philadelphia Department of Public Health shows discarded boxes of xylazine seized in a raid.

Feb 2, 2021, 06:30pm EST | 5,829 views

### An Animal Tranquilizer Is Now Linked To One In Three Overdoses In Philadelphia



in

Misha Gajewski Contributor ① ① Healthcare I write about the brain and the body but sometimes other things.



PHILADELPHIA, PA - JULY 27: Micheal Rouwhorst, 28, prepares a shot of heroin and cocaine near the  $\dots$  [+] THE WASHINGTON POST VIA GETTY IMAGES



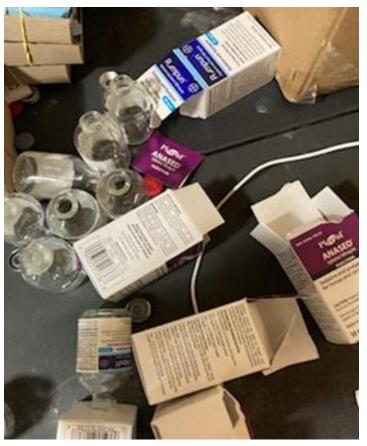
### **Historical Perspective**

- Used in veterinary medicine for procedural sedation
  - Used in both small and large animal medicine
  - Not a controlled substance
  - In combination with opioids
    - Enables use of lower doses and enhances sedation/analgesia
  - Ketamine-xylazine combination commonly used for sedation in rats, mice, hamster, and guinea pigs
  - Medetomidine and dexmedetomidine have replaced xylazine in dogs and cats – less vomiting as a side effect
- First reports of misuse in Puerto Rico in the 2000s known as 'anestesia de caballo'
  - Found in Philadelphia as early as 2006





#### Liquid $\rightarrow$ Solid ("salting") $\rightarrow$ added to heroin/fentanyl



Source: Drug Enforcement Administration Philadelphia Division

#### March 2019

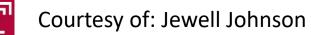
Philadelphia FD dismantled a large-scale heroin and fentanyl mill where 40 vials of xylazine were confiscated.

#### August 2020

The Kensington Initiative dismantled three drug trafficking organizations and seized 174 vials of xylazine.

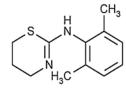


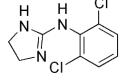
\*Xylazine is not a scheduled drug in PA



# Xylazine – Pharmacology/Clinical Effects

- Alpha-2 adrenergic agonist that stimulates central alpha-2 receptors
  - Decreases sympathetic outflow  $\rightarrow$  sedation
  - CNS DEPRESSION No effect on respiratory rate, blunted response to airway occlusion similar to other sedatives, synergistic effect with opioids
- Similar effects to *imidazoline* compounds such as clonidine, dexmedetomidine, oxymetazoline, tetrahydrazoline, tizanidine, and lofexidine
  - Major clinical effect is profound sedation
  - Imidazoline receptor activity → hypotension/bradycardia
- Pharmacokinetics
  - Typical anesthesia dose ranges (0.2-1 mg/kg IM or IV)
  - Time to effect is a 1-2 minutes
  - Duration of drug effect up to 4 hours

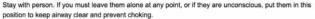




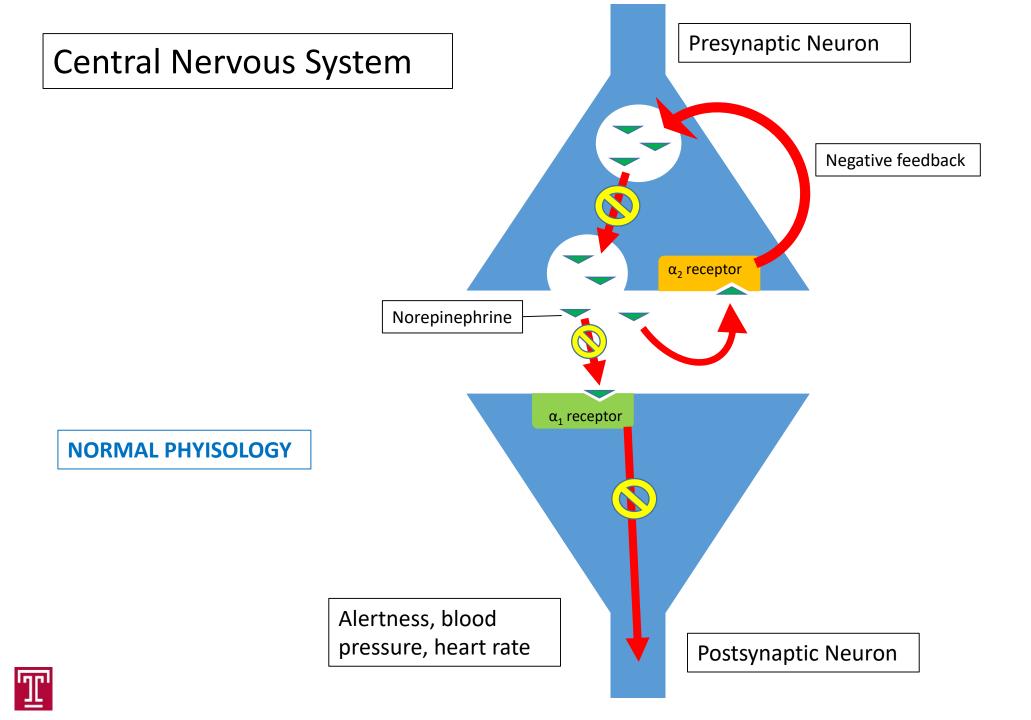
Xylazine

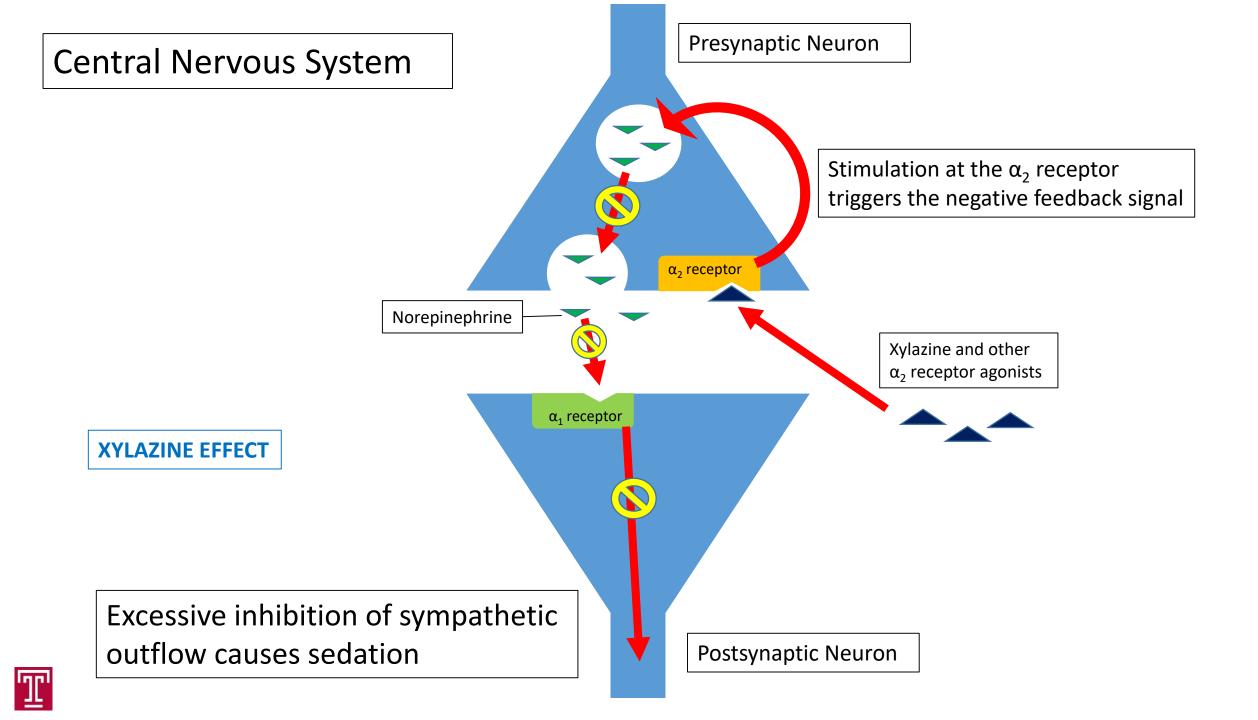










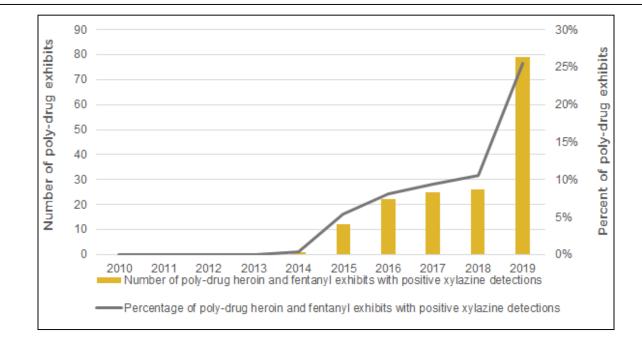




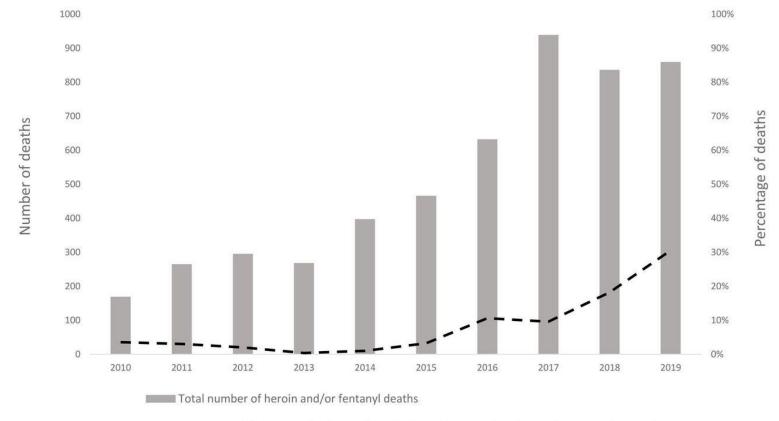
Increasing presence of xylazine in heroin and/or fentanyl deaths, Philadelphia, Pennsylvania, 2010– 2019

Jewell Johnson (0), Lia Pizzicato, Caroline Johnson, Kendra Viner

Number and percentage of xylazine detections in poly-drug exhibits seized where the primary drug detected was fentanyl or heroin, Pennsylvania, 2010-2019



Number and percentage of heroin and/or fentanyl unintentional overdose deaths involving xylazine, Philadelphia, Pennsylvania, 2010–2019.



- Percentage of heroin and/or fentanyl involved overdose deaths where xylazine was detected

Between 2010 and 2015, xylazine was detected in 40 (2%) of the 1854 unintentional overdose deaths with heroin and/or fentanyl detections. This increased to 67 (11%) in 2016, 90 (10%) in 2017, 152 (18%) in 2018, and 262 (31%) in 2019



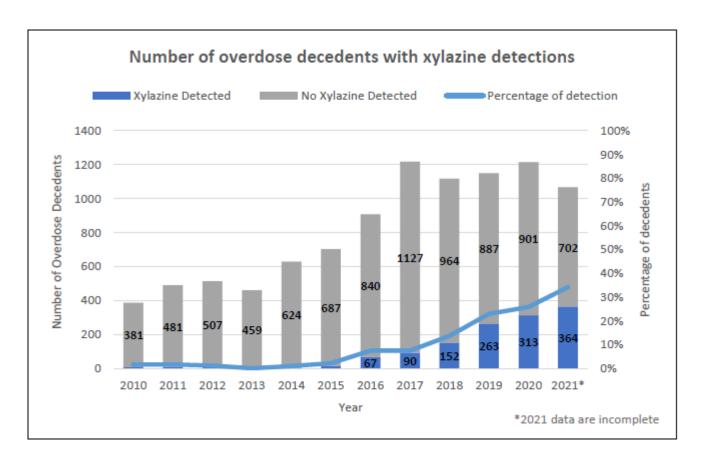


Philadelphia Department of Public Health Health Commissioner's Office

CHERYL BETTIGOLE, MD, MPH Health Commissioner FRANK FRANKLIN, PHD, JD Deputy Health Commissioner JEFFREY HOM, MD, MPH Acting Director, Division of Substance Use Prevention and Harm Reduction

#### Health Alert

Risks of Xylazine Use and Withdrawal in People Who Use Drugs in Philadelphia March 16, 2022



\*In 2021, 91% of samples of purported heroin or fentanyl from Philadelphia also contained xylazine, making it the most common adulterant in the drug supply



#### Drug Supply Assessment: Q4 2021

#### Philadelphia, Pennsylvania, USA

Purpose: This report provides up-to-date information regarding the drug supply in Philadelphia, Pennsylvania, United States.

**Overview:** Traditional drugs (e.g. heroin, fentanyl, cocaine, methamphetamine) are commonly identified among drug samples in cities across the United States, albeit at varying purities and combinations. Novel psychoactive substances (NPS) continue to appear within the drug supply, masked as traditional drugs or added to traditional drug preparations. The drug supply nationally remains a dynamic and changing environment, specifically relating to the active drugs contained within the preparations and the cutting agents or adulterants added. The drug supply can be different from city to city or even within a given community, requiring specific regional assessments. Accurate understanding of the drug supply in real-time is imperative for effective public health and public safety preparedness and response.

**Objective:** A partnership between the Center for Forensic Science Research and Education (CFSRE) and the Philadelphia Department of Public Health (PDPH) has been established to accurately assess the drug supply in Philadelphia, Pennsylvania. This initiative was established as a comprehensive effort. Select drug testing results from samples obtained within the city were compiled for preparation of this report. The results reported herein may not represent the entirety of the drug supply.

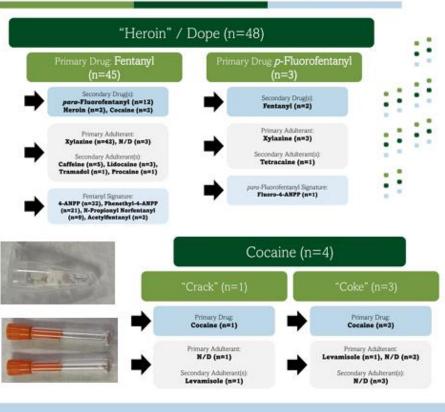
Acknowledgements: This report was prepared by Alex J. Krotulski, PhD; Jen Shinefeld, MS; Jeffrey Hom, MD, MPH; Sara E. Walton, MS; and Barry K. Logan, PhD, F-ABFT. The authors acknowledge CFSRE and PDPH personnel for their involvements. Funding for this study was provided internally by the Fredric Rieders Family Foundation, no external funding was received. The opinions, findings, conclusions, and/or recommendations expressed in this publication are those of the authors and do not necessarily reflect those of federal, state, local, and/or private agencies. For more information about NPS Discovery and its programs, please contact npsdiscovery/gefare.org or visit www.npsdiscovery.org.





#### Summary and Key Findings:

- 65 samples were reported between September & December 2021
- · Most "heroin" samples contained fentanyl cut with xylazine
- Cocaine and methamphetamine samples were not adulterated; fentanyl contamination was not observed in this sample set\*
- para-Fluorofentanyl was identified as the primary opioid in some "heroin" samples, once as the only opioid (without fentanyl or heroin)
- . Two "heroin" samples were found to contain fentanyl & stimulants
- · Counterfeit "Xanax" found to contain an NPS benzodiazepine







(Powder in Glassine Bag)



Powders / Crystals (E.g., Cocaine, Methamphetamine)







(E.g., Cannabis, Syringe)



#### Drug Checking Report: Q1 2022

Purpose: This report provides up-to-date information regarding the drug supply in Philadelphia, Pennsylvania, United States.

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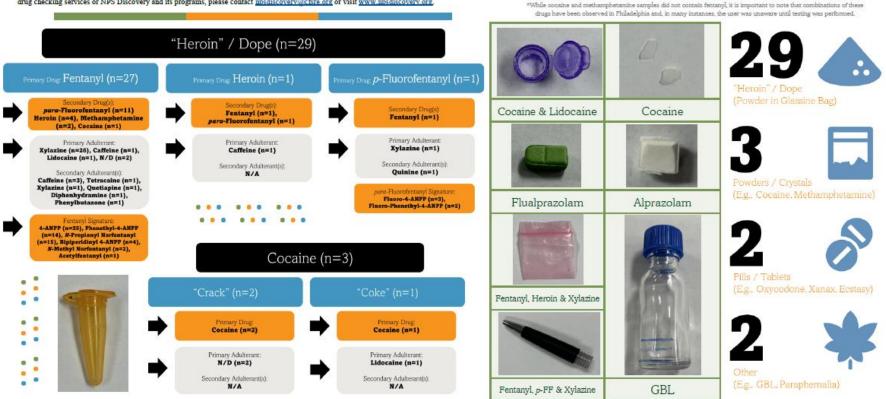
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#### Summary and Key Findings:

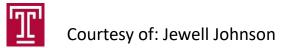
- 36 samples were reported between January and February 2022
- Most "heroin" samples contained fentanyl cut with xylazine
- Fentanyl combinations with methamphetamine and cocaine were observed in this sample set, however, not commonly
- Cocaine samples were not adulterated in this sample set\*
- para-Fluorofentanyl continues increasing in prevalence, being identified as the primary opioid in some "heroin" samples
- · A counterfeit tablet was found to contain an NPS benzodiazepine





### States/Jurisdictions Reporting Xylazine







Office of Drug Monitoring & Analysis 2021 Second Quarter Report

August 19, 2021

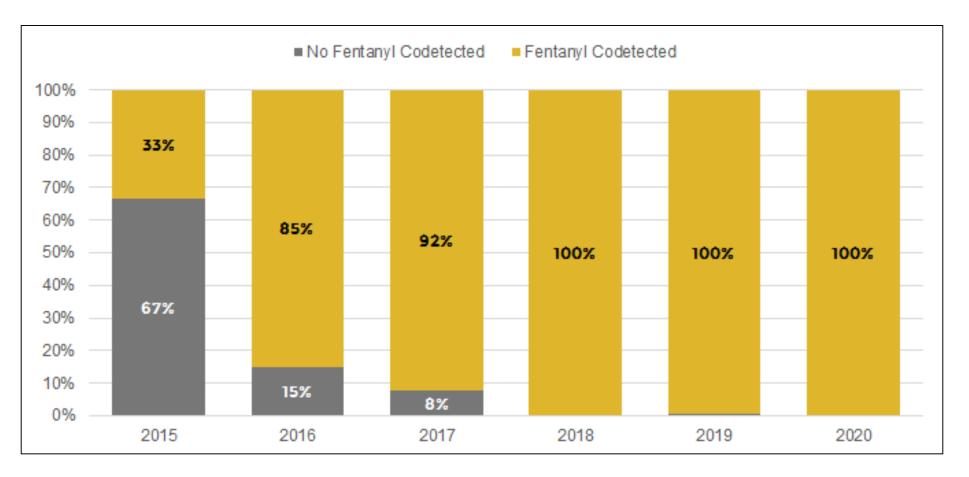


SUSPECTED HEROIN SUBMISSIONS CONTAINING XYLAZINE									
YEAR	SUBMI	SSIONS	GLASSINE BAGS						
2015	9	<b>0.3</b> %	84	0.1%					
2016	55	<b>2%</b>	1,615	1%					
2017	47	<b>2%</b>	2,420	<b>2%</b>					
2018	88	<b>3</b> %	3,260	<b>2%</b>					
2019	368	12%	9,038	<b>6%</b>					
2020	853	<b>29%</b>	30,231	22%					
2021 (TO 6/30)	1,532	<b>52</b> %	93,051	<b>67%</b>					
TOTAL	2,9	952	139,699						
From 2015 to 2020, there was a 9,378% increase in									
the presence of xylazine used as an adulterant in									
suspected heroin submissions.									

- In 2020, xylazine was found in 22% of suspected heroin glassine bags, compared 67% of glassine bags during the first two quarters of 2021 (Hudson, Ocean, and Union independent labs do not test for xylazine)
- The majority of suspected glassine bags containing xylazine were in combination with fentanyl

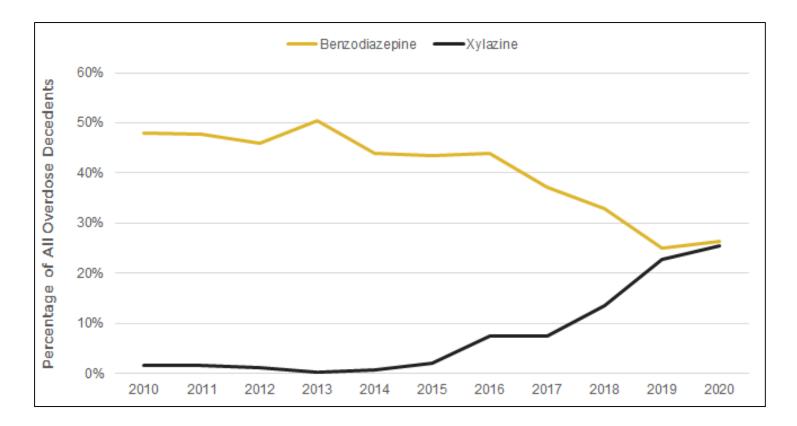


# Fentanyl codetections among xylazine positive overdose decedents by year, Philadelphia, PA 2015-2020



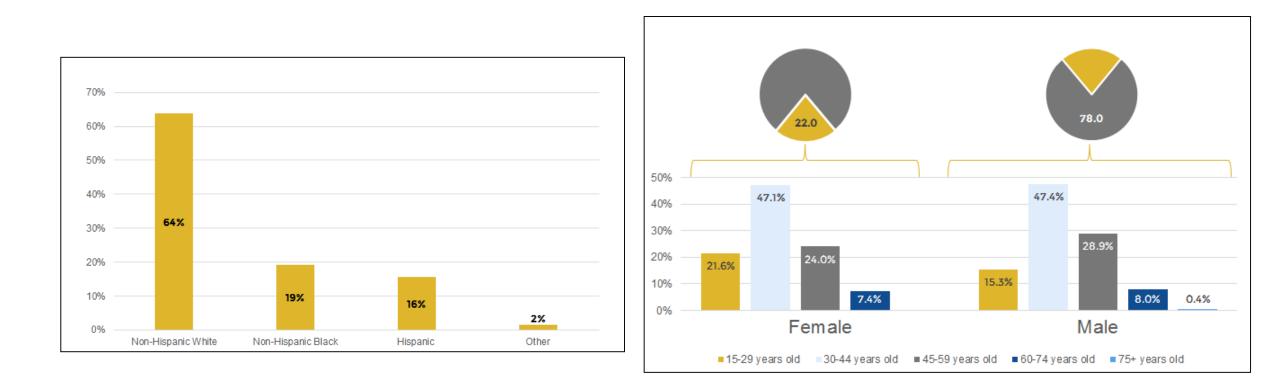


Courtesy of: Jewell Johnson Data source: Philadelphia Medical Examiner's Office Prevalence of benzodiazepines compared to xylazine among all overdose decedents, Philadelphia, PA 2010-2020





Demographic distribution of xylazine positive overdose decedents, Philadelphia, PA 2010-2020





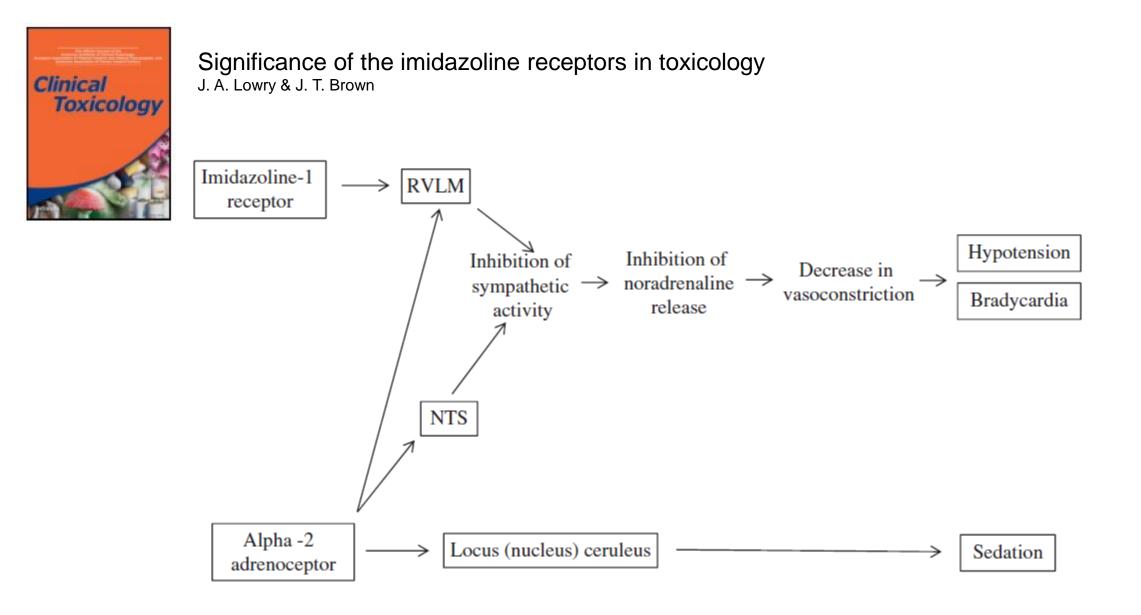
Courtesy of: Jewell Johnson Data source: Philadelphia Medical Examiner's Office

# Corollary to Clonidine Overdose

- Common adult and pediatric overdose addiction and ADHD adjacent med
- Therapeutic antihypertensive → sedation, miosis, bradycardia, hypotension in overdose
- Central  $\alpha_2$  receptor and *imidazoline receptor* activity
  - Imidazoline-1 receptor anti-hypertensive effect
    - Imidazoline- 1 receptors are responsible for bradycardia, hypotension in clonidine overdose
  - Central  $\alpha_2$  receptor agonist activity leads to sedation
    - Transient hypertension from peripheral alpha-2 stimulation causing vasoconstriction
    - Miosis caused by  $\alpha_2$  receptor agonism in the eye
  - Naloxone has been used to reverse sedation with mixed response, some controversy
    - Clonidine mediated hypotension leads to minor endogenous opioid release
    - Imidazoline-2 receptor potentiate opioid receptors







NTS: nucleus tractus solitarii

### Drug-facilitated assault with tetrahydrazoline

#### Adams County woman arrested after poisoning her 2 children with Visine, state police say

Updated Jan 05, 2019; Posted Jul 01, 2014

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#### By Jeffrey A. Johnson | jjohnson@pennlive.com

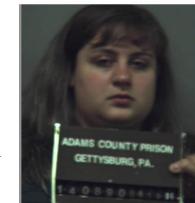
Samantha Elizabeth Unger

Samantha Elizabeth Unger, 23, is accused of poisoning her two children with Visine, according to state police.

#### (Adams County Prison)

A Franklin Township woman was recently arrested on several felony criminal charges after state police said she poisoned her two young children by putting Visine in their drinks.

Samantha Elizabeth Unger, 23, as of Tuesday morning was being held in lieu of \$50,000 bail in Adams County Prison.



#### Daily Mail

Arkansas woman, 56, is 'tried to poison husband with Visine eye drops'

Ariel Zilber For Dailymail.com 1/1/2021

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#### Woman Used Eye Drops to Kill Husband, Court Says

Lana Sue Clayton was sentenced to 25 years in prison after she added eye drops to her husband's drinks in such large amounts that the active chemical killed him, according to the authorities.

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Lana Sue Clayton in a 2018 booking photo. York County Sheriff's Office, via Associated Press

# Management of Xylazine Overdose

- Blunted response to hypoxia due to sedation airway occlusion is problematic
  - Field management
    - Recovery position, airway maneuvers
  - ED Management
    - Continuous pulse oximetry, airway monitoring/control
- No antidotal therapy available or recommended
  - Yohimbine (alpha-2-antagonist) not recommended
  - Atipamezole not FDA approved drug
  - Naloxone?



Stay with person. If you must leave them alone at any point, or if they are unconscious, put them in this position to keep airway clear and prevent choking.



### Narcan or Narcan't?

- "Narcan resistant overdose" Narcan unlikely to have a significant clinical effect directly on xylazine overdose
- Xylazine and fentanyl are a combination product



- Indication for use
  - Apnea or cyanosis and decreased mental status in suspected opioid overdose (respiratory rate <8 bpm and POx <92%)</li>
- Bystander administration saves lives
  - Recovery position, rescue breathing, give second dose after 2-3 minutes if no improvement in breathing
  - Risk of overshoot and precipitating opioid withdrawal in patients with significant opioid dependence







# **Diagnostic Testing**

- Not available for point-of-care or hospital urine immunoassay
- The detection of xylazine in (serum and urine):
  - Thin layer chromatography (TLC)
  - Gas chromatography mass spectrometry (GC-MS)
  - Liquid chromatography mass spectrometry (LC-MS)
- Rapidly eliminated from blood
  - 70% excreted in urine as major metabolite 2,6 xylidine

	NMS
-	LABS
	When you need to know."

Test Code	
4815B/U	
Method	
LC-MS/MS	
Specimen Type	
Blood or urine	
Turnaround Time	
8 days	



Test Number ∲	Test Name 🔺	Specimen Requirements	Reference Ranges	♦ Stability ♦	Rejection/References	♦ CPT Code ♦
6504	XYLAZINE URINE LCMS	At least 10 ml Urine (plastic urine container)	Cutoff: 5 ng/ml	Room temperature 8 days / Refrigerated 30 days / Frozen 6 months	Leaked in transit, improperly labeled	80375



Journal of Analytical Toxicology, 2022, **00**, 1–7 DOI: https://doi.org/10.1093/jat/bkac049 Advance Access Publication Date: 30 June 2022 **Special Issue** 

#### Xylazine: Pharmacology Review and Prevalence and Drug Combinations in Forensic Toxicology Casework

Sherri L. Kacinko<sup>1,\*</sup>, Amanda L.A. Mohr<sup>2</sup>, Barry K. Logan<sup>1,2</sup> and Edward J. Barbieri<sup>1</sup>

<sup>1</sup>NMS Labs, 200 Welsh Rd, Horsham, PA 19044, USA <sup>2</sup>Center for Forensic Science Research and Education at the Fredric Rieders Family Foundation, 2300 Stratford Ave, Willow Grove, PA 19090, USA

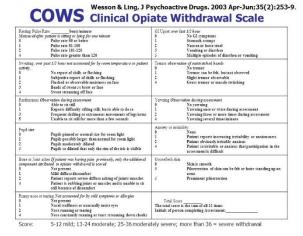
\*Author to whom correspondence should be addressed. Email: sherri.kacinko@nmslabs.com

- Two fatal isolated xylazine intentional overdoses: 9,100 and 11,000 ng/mL
  - 50-year-old male found dead in his truck. A bottle of xylazine and 24-gauge needles were found in the truck along with a suicide note. A femoral blood sample contained 9,100 ng/mL of xylazine
  - 38-year-old female found dead in a hotel room. The decedent worked at a racetrack, which is how she acquired the xylazine
  - Mean concentration was 34 ng/mL for the other 3,077 cases
- 3,074 of the 3,079 medico-legal death investigation cases of xylazine also contained fentanyl or fentanyl metabolites
- In fatal cases with both opioid and xylazine positive, xylazine concentrations ranged 5.0 1,700 ng/mL
- Non-fatal attempted suicide case report (27yo farmer, 1.5g injection), the highest plasma concentration achieved was 4,600 ng/mL
- Even at concentrations in excess of 1,500 ng/mL, xylazine overdose may not be fatal if patients receive prompt medical attention



### Xylazine Withdrawal

- Not a well-defined syndrome
  - Major symptom is anxiety
  - No severe VS abnormality or associated withdrawal seizures
  - Duration few days to a week
- Some corollary to clonidine and dexmedetomidine withdrawal
  - Hypertension, tachycardia, diaphoresis, anxiety, and agitation
- Overlap with opioid withdrawal syndrome anxiety, irritability, restlessness
  - Treat opioid withdrawal
- No data or evidence-based recommendations available for treatment
- Treat like sedative-hypnotic withdrawal (benzo/alcohol)
  - Benzodiazepines are first-line agent, followed by dexmedotomidine, phenobarbital
    - Gabapentin, clonidine, antipsychotics as adjunctive therapies
    - Ketamine?
- Clonidine/Lofexidine/Tizanidine
  - Unlikely to benefit at typical doses recommended for HTN (clonidine 0.1 0.6 mg BID-TID) as sole therapy
  - Major limitation is bradycardia and hypotension as side-effect





### Prolonged dexmedetomidine infusion and drug withdrawal in critically ill children

<u>A Haenecour</u>, <u>A Goodwin</u>, <u>W Seto</u>, <u>C Urbain</u>, <u>P Laussen</u> & <u>C</u> Balit. *Critical Care* v19, Article number: P484 (2015)



#### Introduction

We investigated the incidence, symptoms and risk factors for withdrawal associated with prolonged dexmedetomidine use. Dexmedetomidine is an  $\alpha_2$ -adrenergic receptor agonist, with anxiolytic, analgesic and sedative properties. Intended for short-term use, there is increasing literature describing prolonged use for sedation. However, this raises the potential of withdrawal syndrome and there is no recommendation for the discontinuation of dexmedetomidine. Other goals included determining the hemodynamic effects of discontinuation of dexmedetomidine in patients with prolonged dexmedetomidine use.

#### Methods

A retrospective review of patients admitted to the critical care unit who had exposure to dexmedetomidine for longer than 48 hours, between 1 January 2014 and 15 July 2014. Data included patient demographics, dexmedetomidine exposure (bolus dose, total cumulative dose, duration), other sedative exposure, withdrawal symptoms measured by WAT-1 score, nursing subjective assessment and treatment given for withdrawal. Each potential withdrawal episode was reviewed by two reviewers. Hemodynamic parameters were analyzed to assess hemodynamic changes associated with discontinuation of dexmedetomidine. Descriptive statistics were used with *t* test and chi-square test. Median and interquartile range (IQR) are reported.

#### Results

A total of 53 patients accounted for 69 unique dexmedetomidine treatment courses. Median age at the time of dexmedetomidine infusion was 5 months (range 1 day to 3 years). Dexmedetomidine dose ranged from 0.1 to 2  $\mu$ g/kg/hour with a median cumulative dose of 87  $\mu$ g/kg (IQR 53, 156). Median duration of exposure to dexmedetomidine was 124 hours (IQR 76, 178) with a maximum duration of 466 hours. We identified 24 separate episodes of withdrawal (incidence 35%). Most common symptoms were agitation (100%), fever (67%), vomiting/retching (46%), loose stools (29%) and decreased sleep (20%). Statistical analysis showed that factors significantly associated with withdrawal were cumulative dose (P = 0.01) and duration of use of dexmedetomidine (P = 0.02). Duration of opioids exposure prior to dexmedetomidine wean was also a risk factor for withdrawal (P = 0.01). Use of clonidine as a transition from dexmedetomidine did not protect against withdrawal (P = 0.59).

#### Conclusion

This study showed that withdrawal syndrome is associated with prolonged infusion of dexmedetomidine. Patients with higher cumulative doses and longer duration of exposure were more at risk. Our results suggested that clonidine use is not protective for withdrawal from dexmedetomidine.



# Management of Xylazine Withdrawal

### Inpatient Drug Rehab Treatment

### Similar to benzodiazepine withdrawal management but not as severe

Unlikely to have significant hypertension or tachycardia requiring medical intervention

No evidence of seizures

#### Medications options:

- Benzodiazepines PRN for anxiety
- Benzodiazepine taper
- Phenobarbital taper
- Adjunctive medications including gabapentin, antipsychotics
  - Clonidine/Lofexidine/Tizanidine?

### Office Based Opioid Treatment

Manage similar to benzodiazepine dependence

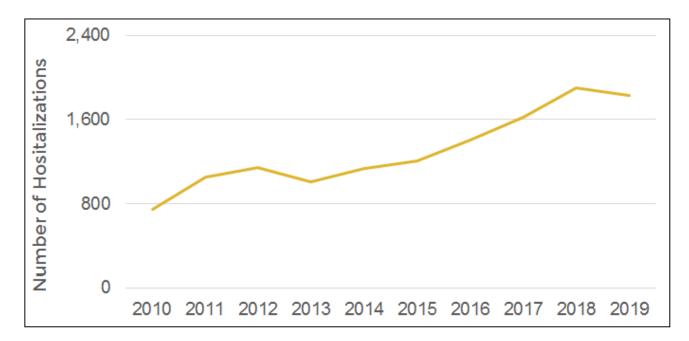
#### Medication options:

- Short course benzodiazepine
- Adjunctive medications including gabapentin, antipsychotics
  - Clonidine/Lofexidine/Tizanidine?
- Detox admission



### Wounds Associated with Xylazine Use

Number of hospitalizations for skin and soft tissue infections associated with drug use, Philadelphia, PA 2010-2019



Courtesy of: Jewell Johnson Data source: Pennsylvania Healthcare Cost Containment Council



#### **TEBNews**

### Drug Users Are Losing Their Fingers and Toes After Shooting 'Tranq Dope'

In Philadelphia, the animal tranquilizer xylazine has infiltrated the opioid supply, and it's been linked to horrific wounds and amputations.

By <u>Manisha Krishnan</u> TORONTO, CA

March 22, 2022, 7:00am 📑 Share 🍯 Tweet 🌲 Snap



#### "It's eating away at my skin."







#### Management of Xylazine Withdrawal in a Hospitalized Patient: A Case Report

Rachel Ehrman-Dupre, MD, Caroline Kaigh, MD, Matt Salzman, MD, Rachel Haroz, MD, Lars-Kristofer Peterson, MD, and Ryan Schmidt, MD





FIGURE 1. Initial examination of patient AB's wounds.





















### Wounds

Longstanding history of skin ulcers with injection drug use
Heroin → fentanyl → krokodil → cocaine → methamphetamine → xylazine

#### Potential Causes of Wounds from Injection Drug Use:

- Obliterative vasculitis from repetitive injection ("shooter's patch")
- Skin picking causing excoriations and ulcers
- Poor wound healing (various causes)
- Infectious
- Local effect from caustic agent extravasation (but wounds not always seen at site of injection)
- Compression ulcers
- Drug effect

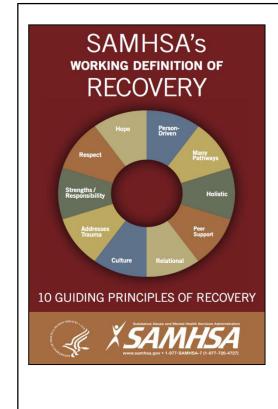




### Wound Treatments

- Cessation of injection
- Debridement (OR, bedside)
- Clean with soap/water, chlorhexidine, Dakin's Half Strength Solution, or 1% acetic acid)
- Silver sulfadiazine cream, bacitracin ointment for antimicrobial coverage
- Non-adherent dressing with an ABD to absorb drainage
- Biodegradable Temporizing Matrix (BTM), skin grafting, epithelialization/complete closure
- Amputation





#### **SAMHSA's Guiding Principles of Recovery**

- Recovery emerges from hope.
- Recovery is person driven.
- Recovery occurs via many pathways.
- Recovery is holistic.
- Recovery is supported by peers and allies.
- Recovery is supported through relationships and social networks.
- Recovery is culturally based and influenced.
- Recovery is supported by addressing trauma.
- Recovery involves individual, family, and community strengths and responsibilities.
- Recovery is based on respect.



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