

# Wounds, Withdrawal, and Overdose: What to Expect from Xylazine Drug Supply Adulteration

Panel Presentation and Discussion

ASAM 54<sup>th</sup> Annual Conference, April 2023



# Disclosure Information

## Moderator

- ◆ **Lewis S. Nelson, MD, MBA**
  - ◆ Professor and Chair, Department of Emergency Medicine, Rutgers New Jersey Medical School
  - ◆ No Disclosures

## Panel

- ◆ **Joseph D'Orazio, MD, FAAEM, FACMT, FASAM, FCPP**
  - ◆ Associate Professor of Clinical Emergency Medicine, Director, Division of Medical Toxicology & Addiction Medicine, Lewis Katz School of Medicine at Temple University
  - ◆ No Disclosures
- ◆ **Rachel S. Wightman, MD, FACMT**
  - ◆ Assistant Professor of Emergency Medicine and Epidemiology, Alpert Medical School of Brown University
  - ◆ No Disclosures
- ◆ **Evan S. Schwarz, MD, FASAM**
  - ◆ Associate Professor of Emergency Medicine, Medical Toxicology Fellowship Director, Emergency Medicine, University of California Los Angeles
  - ◆ No Disclosures
- ◆ **Jeanmarie Perrone, MD**
  - ◆ Director, Center for Addiction Medicine and Policy, Emergency Medicine, University of Pennsylvania
  - ◆ No Disclosures
- ◆ **JoAn Laes, MD, DFASAM, FACMT**
  - ◆ Addiction Medicine Physician, Division of Addiction Medicine, Allina Health
  - ◆ No Disclosures
- ◆ **Rachel Haroz, MD**
  - ◆ Associate Professor of Emergency Medicine, Emergency Medicine, Cooper University Healthcare
  - ◆ No Disclosures

# Learning Objectives

- ◆ Describe adulteration practices, current trends in drug adulteration, and a look back at historical clusters of adulterants (what's old is new again!)
- ◆ Describe the pharmacology, toxicology, diagnostic testing, and epidemiology of xylazine in exposures
- ◆ Describe common adverse effects of xylazine exposure including overdose, withdrawal, and wound development

# Cutting Agents/Adulterants

- ◆ Why would substances be added to drugs?
  - ◆ Bulk or dilute the drug
  - ◆ Complement or enhance the effects
  - ◆ Facilitate use of the drug
- ◆ Cocaine
  - ◆ Phenacetin, levamisole, caffeine, procaine/lidocaine, diphenhydramine
- ◆ Heroin
  - ◆ Fentanyl, caffeine, quinine, acetaminophen, scopolamine, clenbuterol

# Historical Events

- ◆ Parkinsonism due to MPTP exposure in meperidine analog (Demerol) synthesis, Northern California (1983, 1984)
- ◆ China White (3-methyl-fentanyl) contaminated heroin, Allegheny County (1988)
- ◆ Scopolamine poisoning in heroin, NYC, Newark, Philadelphia, and Baltimore (1995, 1996)
- ◆ Clenbuterol contamination of heroin, North Carolina (2007)
- ◆ Fentanyl contaminated cocaine, New Haven CT (2016)
- ◆ Manganese encephalopathy caused by homemade methcathinone, Poland (2011, 2012)
- ◆ Synthetic cannabinoid-associated coagulopathy linked to Vit K Antagonist Brodifacoum, Illinois (2018)

# Xylazine Background

- ◆ Developed in 1962 by Bayer pharmaceuticals as an antihypertensive
  - ◆ Trials in humans stopped due to hypotension and CNS depression
- ◆ FDA approved for veterinary use as a sedative, analgesic, and muscle relaxant
  - ◆ Available in liquid solutions at 20, 100, and 300 mg/mL
  - ◆ Used alone or in combo (e.g. with ketamine, barbiturates)



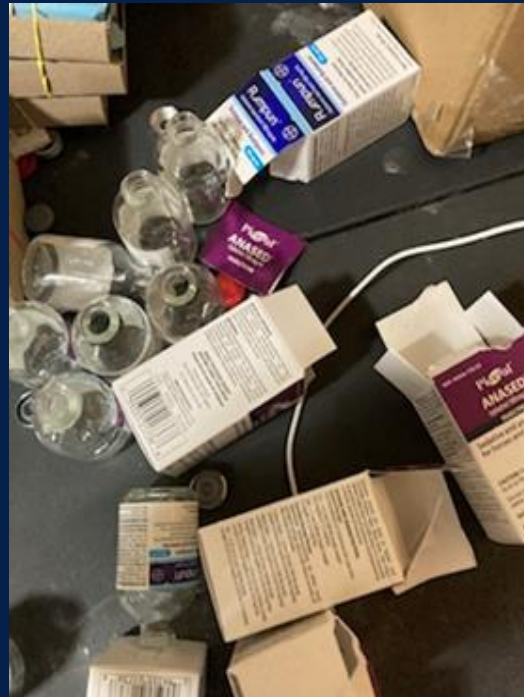
# Xylazine in Puerto Rico

- ◆ Marketed as an adulterant to heroin prepackaged for the consumer to control the ratio and later in pre-mixed form
- ◆ “I shot the anesthesia [...] and I felt asleep face first and when I opened my eyes five hours had gone by and I was laying on the floor. [...] I don’t remember anything. I don’t remember anything! I fell down and I was gone. And I said: What the hell is this?! Oh, and I woke up sick [withdrawing]!”



# Xylazine Adulteration

- ◆ Found in combo with xylazine in bags of heroin/fentanyl
- ◆ Pharmaceutical grade adulteration of heroin/fentanyl supply
  - ◆ Added locally
  - ◆ Salting of liquid
- ◆ Powder xylazine from China supply



Source: Drug Enforcement Administration Philadelphia Division



**USA Xylazine**  
USP BP, 99% Pure  
WHATSAPP: +86-18145728414  
WICKR: wendy6888

USA Market, 99% Pure White Crystal  
**Xylazine/Xylazina/Xylazin/Zylazine/Zylazina/Xilazine/Xil...**  
US\$ 540-720 / kg (FOB Price)  
1 kg (MOQ)  
CAS No. : 23076-35-9      Formula : C12h17cln2s  
EINECS : 245-417-0      Type : Pharmaceutical Inte... [More](#)

Guangzhou Teng yue Chemical Co., Ltd. > [❤](#) [🇺🇸](#) [🇨🇳](#)

[✉ Contact Now](#) [🛒](#) [🌐](#)

---

100% no customs issues  
**Xylazine**  
2c22.3.4  
99% pure  
MOQ 1kg

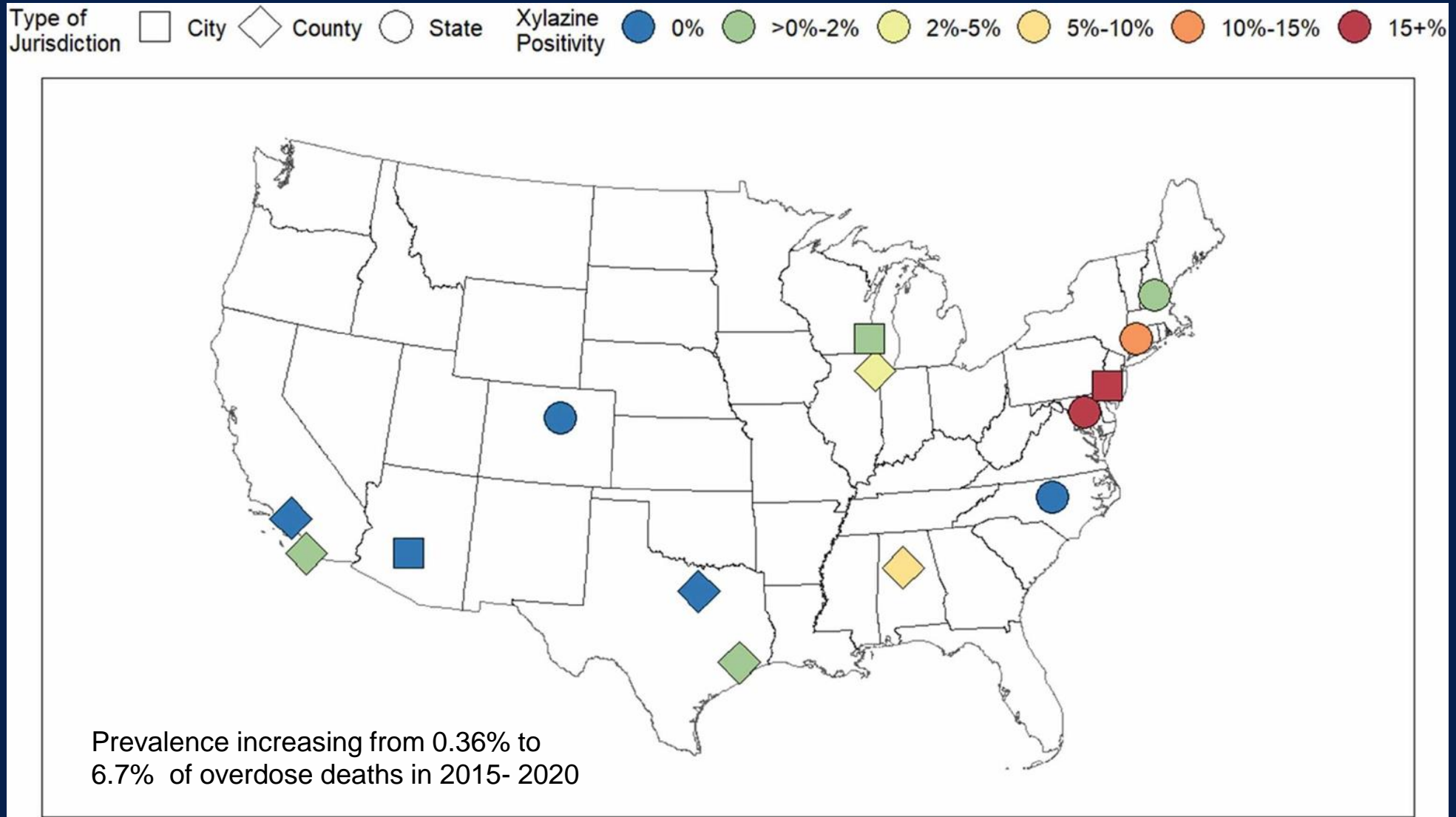
USA Market USP Bp 99% Purity **Xylazine/Zylazine HCl**  
**Powder Security Clearance**  
US\$ 630-750 / kg (FOB Price)  
1 kg (MOQ)  
CAS No. : 23076-35-9      Formula : C12h17cln2s  
EINECS : 245-417-0      Type : Pharmaceutical Inte... [More](#)

Guangzhou Hongtu Chemical Co., Ltd. > [❤](#) [🇺🇸](#) [🇨🇳](#)

[✉ Contact Now](#) [🛒](#) [🌐](#)



# Xylazine prevalence is highest in the East



# Regional Prevalence



(U) Figure 1. DEA Forensic Laboratory Identifications of Xylazine by Region

Region	2020	2021	Percent Increase
Northeast	346	556	61%
South	198	580	193%
Midwest	110	118	7%
West	77	163	112%

Source: DEA

(U) Figure 2. Number of Xylazine-Positive Overdose Deaths by Region

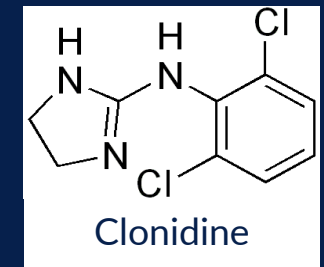
Region	2020	2021	Percent Increase
Northeast	631	1,281	103%
South	116	1,423	1,127%
Midwest	57	351	516%
West	4	34	750%

Source: DEA



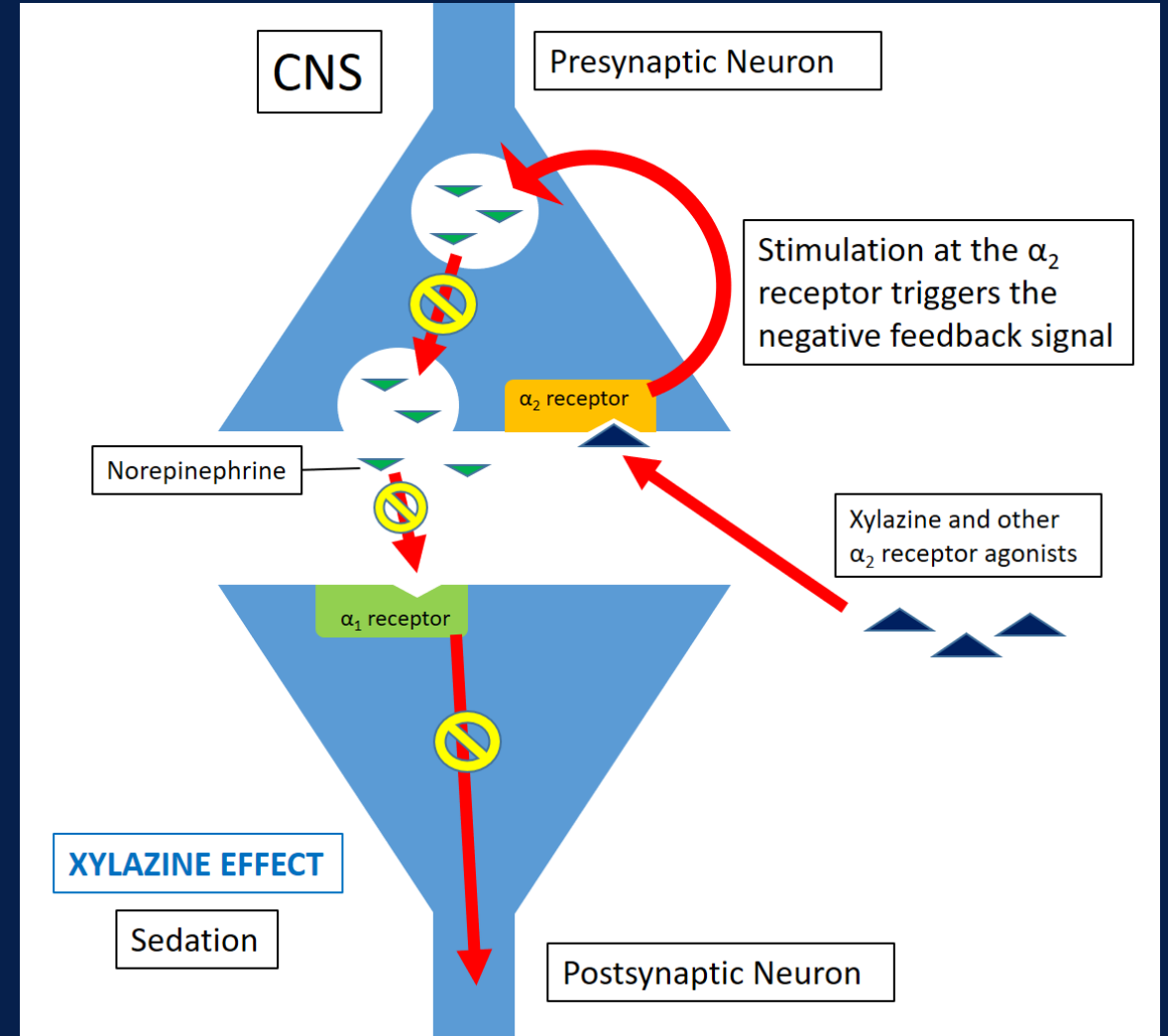
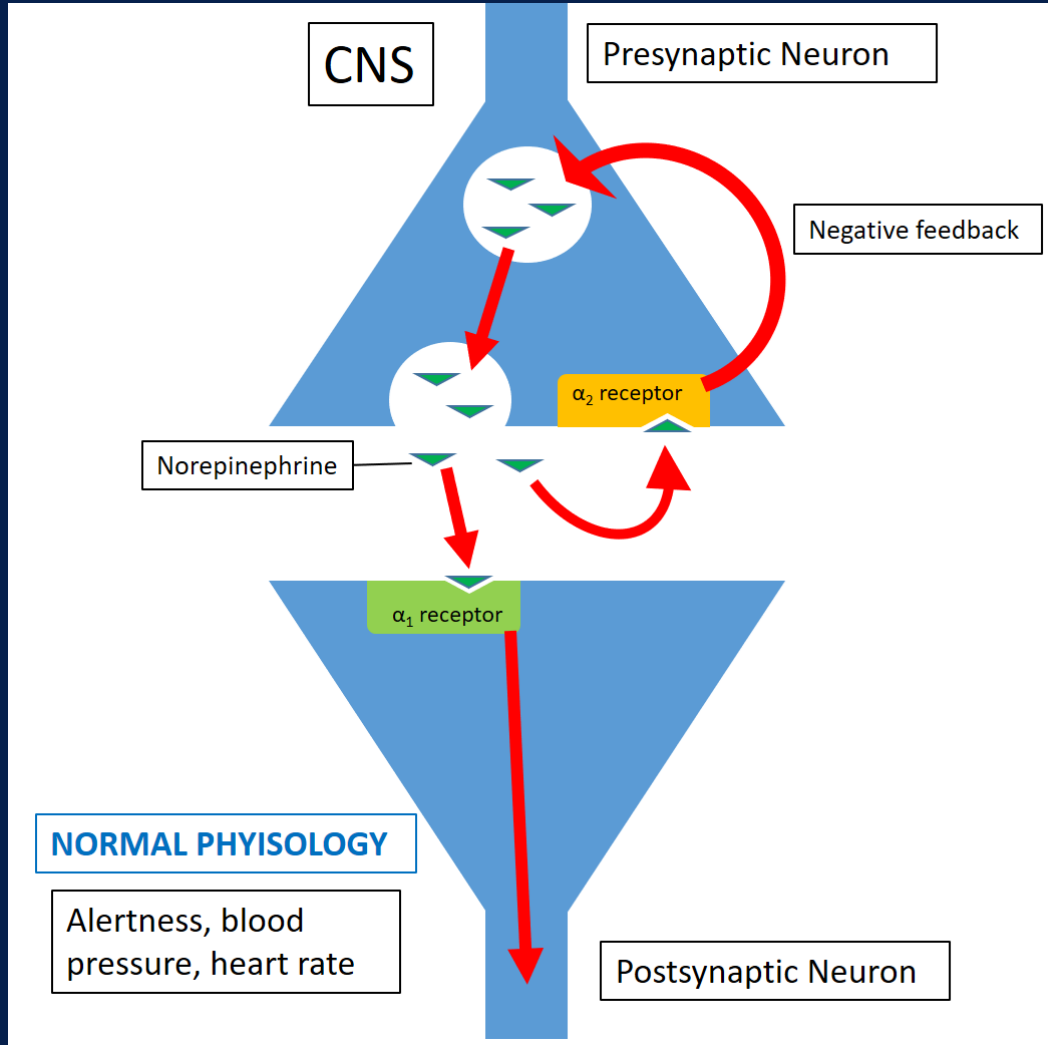
# Xylazine – Pharmacology/Toxicology

- ◆ Alpha-2 adrenergic agonist that stimulates central alpha-2 receptors:
  - ◆ Decreases sympathetic outflow → sedation
  - ◆ Naloxone does not reverse the effects of xylazine
- ◆ Similar to imidazoline compounds
  - ◆ Clonidine, dexmedetomidine, oxymetazoline, tetrahydrozoline, tizanidine, lofexidine
- ◆ Pharmacokinetics
  - ◆ Time to effect is 1-2 minutes with IV administration (Other routes described include IM, SC, PO, IN, IH)
  - ◆ Duration of effect up to 4 hours



Xylazine and clonidine are structurally similar and have some similar effects

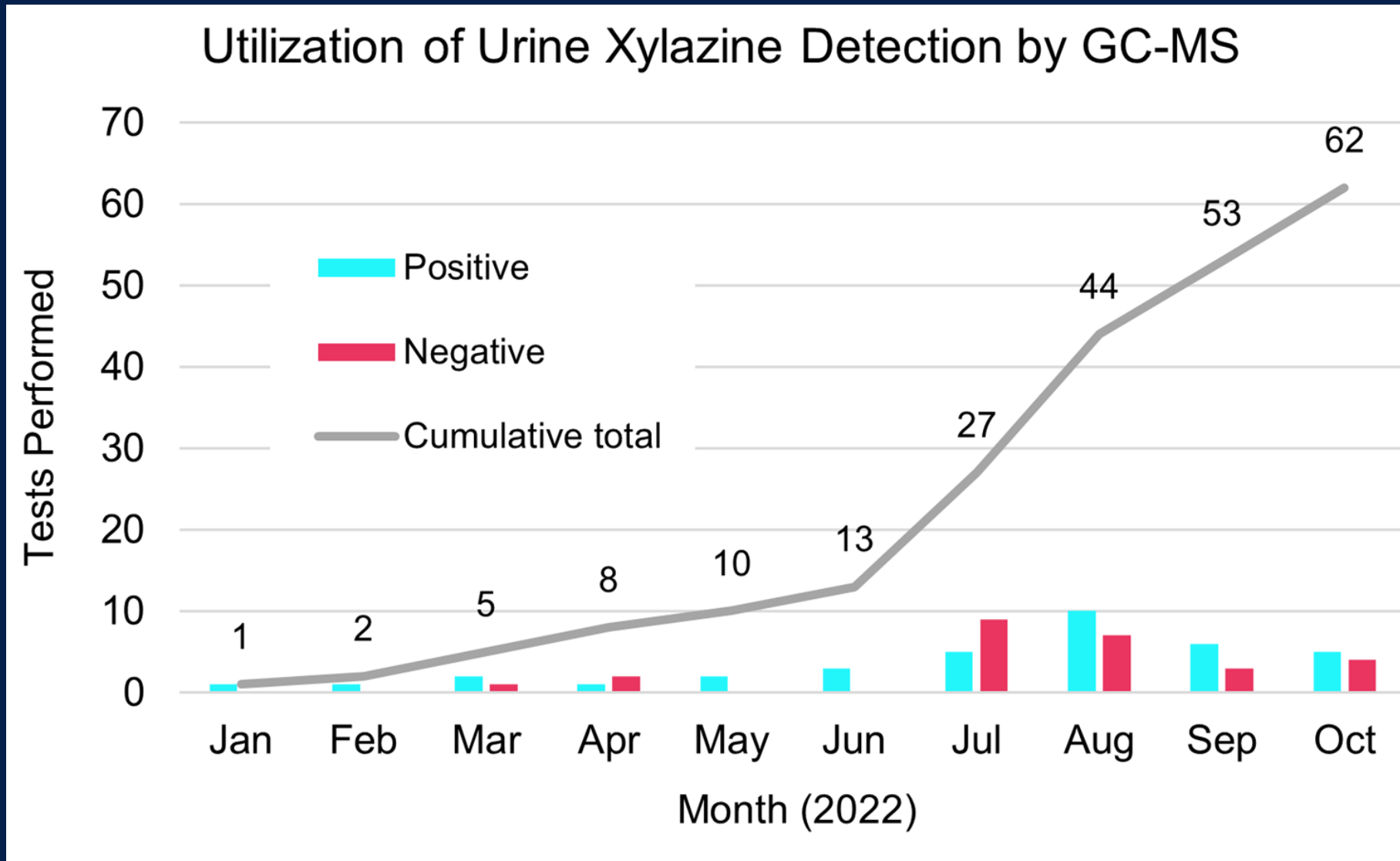
# Pharmacology/Toxicology of Xylazine



# Diagnostic Testing

- ◆ Techniques
- ◆ Availability
- ◆ Utility
  - ◆ Positive/Negative vs Quantitative
  - ◆ False negative – time to negative test?
  - ◆ Urine vs serum testing
- ◆ Does it affect medical examiner data
  - ◆ Quantitative

# In Hospital Testing Data - Philadelphia



# Xylazine testing in hospital

- ◆ 87 GC-MS urine xylazine tests performed between Jan-Oct 2022, 46 (52.9%) detected xylazine
  - ◆ 24 (27.6%) female
  - ◆ 56 (64.4%) White
  - ◆ 28 (31.2%) Black
  - ◆ 4 (4.6%) Hispanic/Latinx
- ◆ Initial median COWS score was higher among xylazine positive vs. negative patients (6 (IQR 2-10.3) vs. 4 (IQR 2- 7))
- ◆ Among xylazine positive patients: 16 (34.8%) vs. 7 (17.0%) left as patient-directed (against medical advice or “AMA”) discharges (difference, 17.8%,  $p=0.06$ )

# Toxicosurveillance from social media: “Listening” to xylazine chatter on Reddit

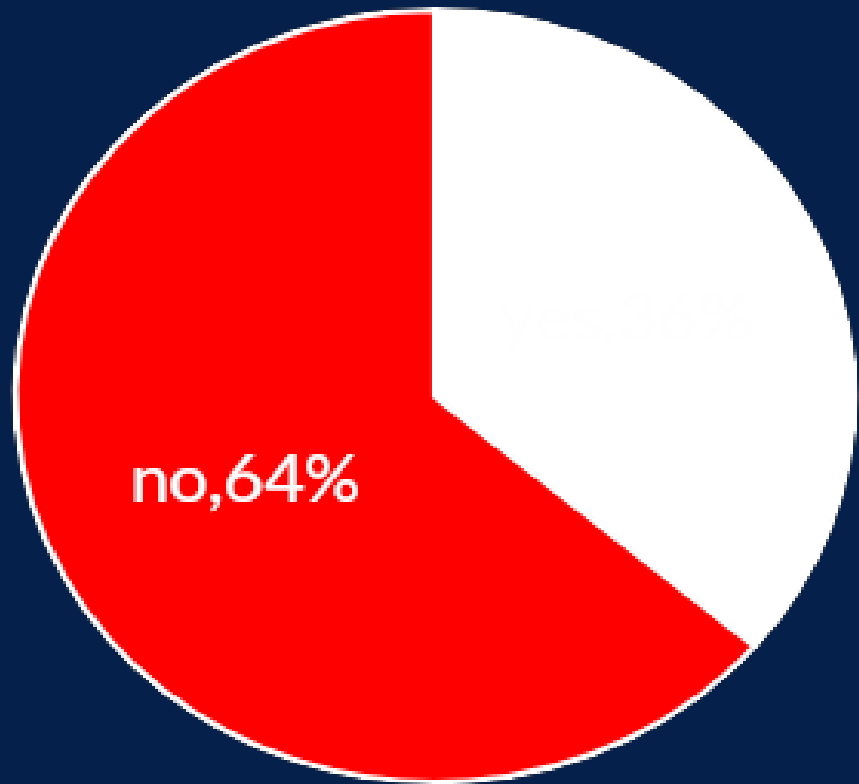
Utilizing NLP, we reviewed thousands of posts on opioid-related sub-Reddits and identified a forum w xylazine chatter and posted a survey to describe:

- ◆ Who is describing xylazine use?
- ◆ How does xylazine impact withdrawal symptoms?
- ◆ What complications are people reporting?
- ◆ Posts were qualitatively evaluated for xylazine-related themes.



# Survey Results: Patterns of use

Do you seek out xylazine intentionally?

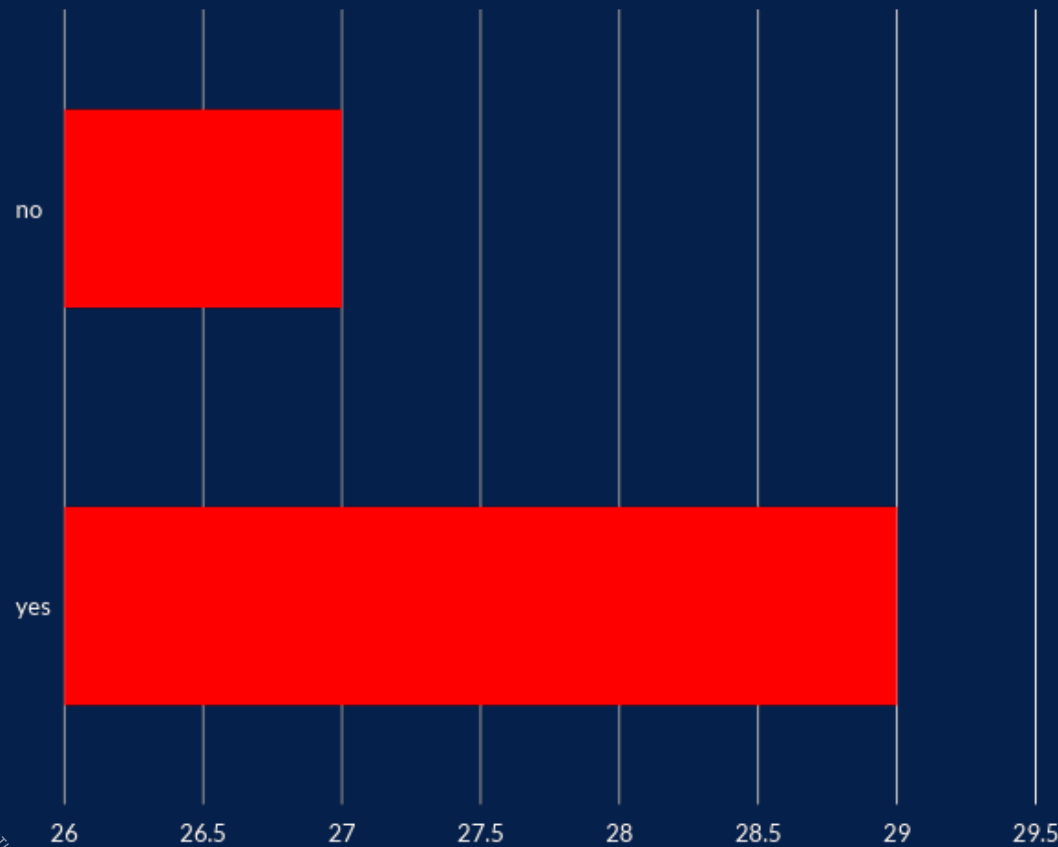


Most Common Routes of Use:

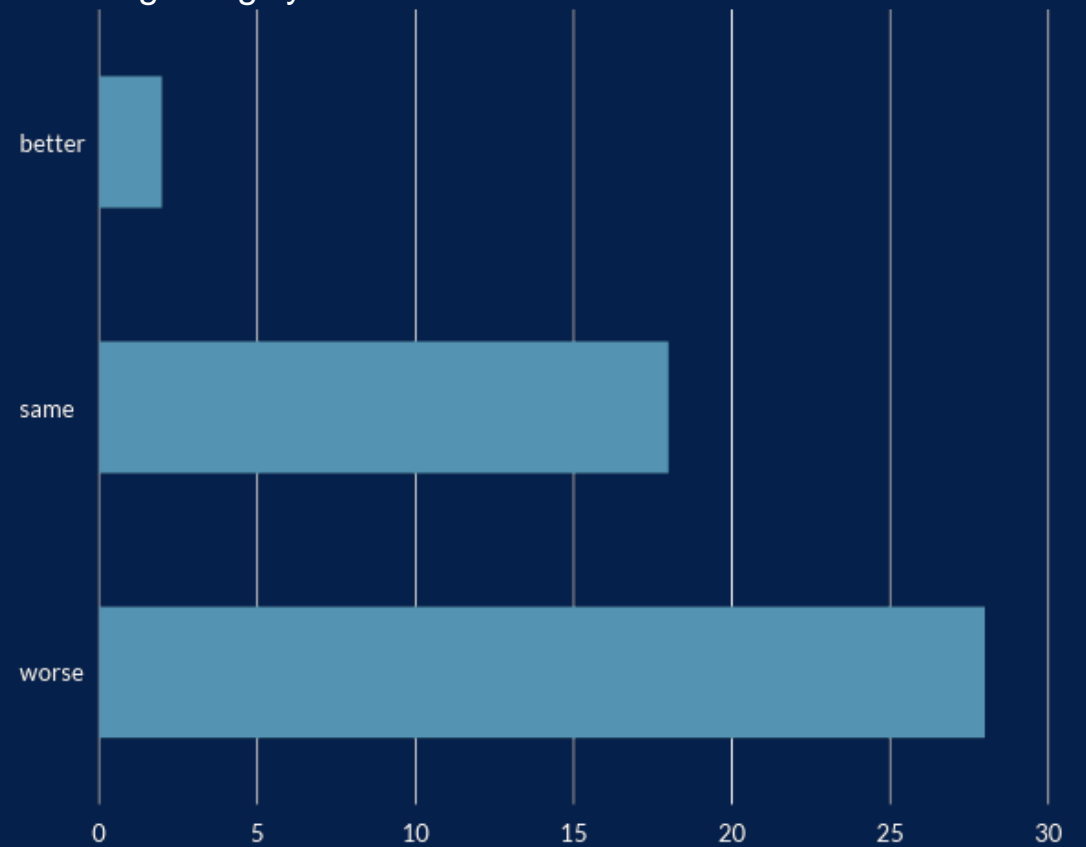
1. Intranasal
2. Injection
3. Inhalation
4. Oral

# Survey Results: Withdrawal

Have you ever experienced withdrawal from xylazine?



How has withdrawing from other drugs changed since you starting using xylazine?



# 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*

- ◆ 29 year old admitted for wound care
- ◆ 25 bags heroin/fentanyl IV per day
- ◆ Withdrawal symptoms:
  - ◆ Anxious and tearful
  - ◆ Restlessness, rigors, and dysphoria
- ◆ Medications utilized:
  - ◆ Buprenorphine microinduction, gabapentin, dexmedetomidine, tizanidine, ketamine, clonidine, phenobarbital, hydromorphone PCA pump,
- ◆ Withdrawal not responsive to typical treatments for opioid withdrawal



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

# Xylazine Withdrawal- Overlapping Symptoms

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

# Xylazine Withdrawal Treatment

## Current Practice

- ◆ Clonidine
- ◆ Benzodiazepines
- ◆ Antipsychotics
- ◆ Phenobarbital
- ◆ Gabapentin

## ICU

- ◆ Dexmedetomidine
- ◆ Ketamine

## Others

- ◆ Ropinirole
- ◆ Tizanidine

# Case Discussion- Overdose

◆ A 27-year-old man presents to the ED after an overdose with heroin. He is deeply sedate, responds to a noxious stimulus, and has no signs of trauma.

## ◆ Vital Signs

◆ Blood pressure: 120/80      Pulse: 82      Temp: afebrile

◆ Resp: 4      Oxygen saturation: 82% on RA

◆ Pupils pinpoint, lungs clear

◆ Naloxone restores breathing and normalizes PO<sub>2</sub>, but patient remains sedate

◆ Two additional doses given with no response. Patient remains sedate

# Xylazine/Fentanyl overdose

- ◆ Multicenter prospective cohort of patients following an opioid overdose from 9 EDs across the US
  - ◆ Included 321 patients testing positive for an illicit opioid or xylazine
  - ◆ 83% of patients received naloxone (median initial dose 2 mg)
  - ◆ Xylazine-negative patients were more likely to develop a coma within 4 hours of ED arrival and suffer a cardiac arrest
  - ◆ Most patients were discharged from the ED (59 [65.5%] xylazine-positive, vs. 147 [63.6%] xylazine-negative patients)

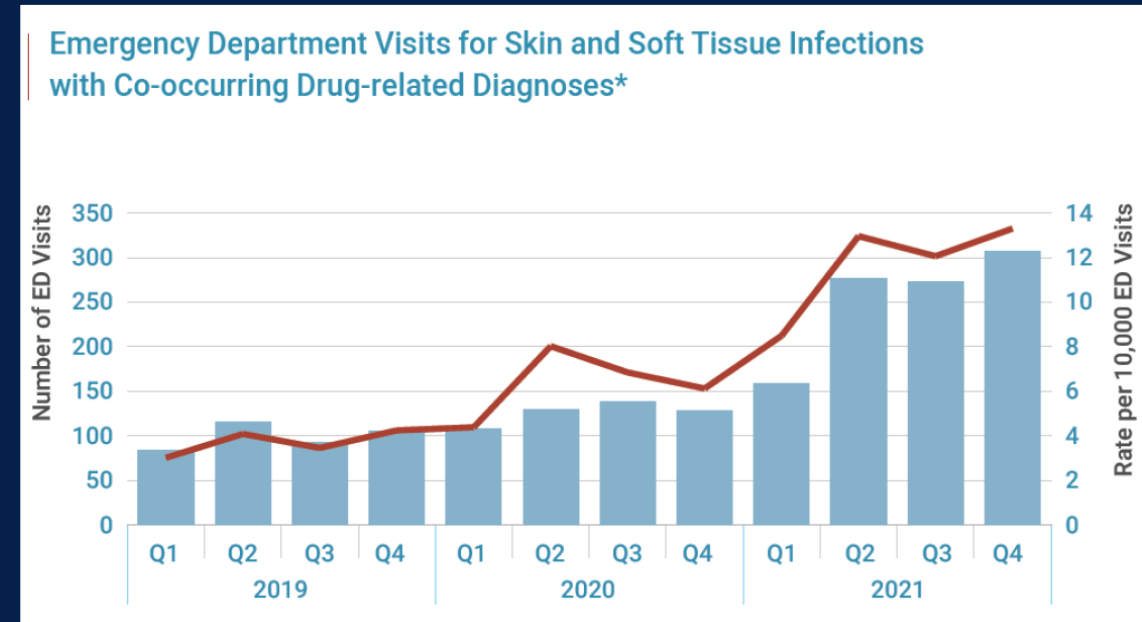
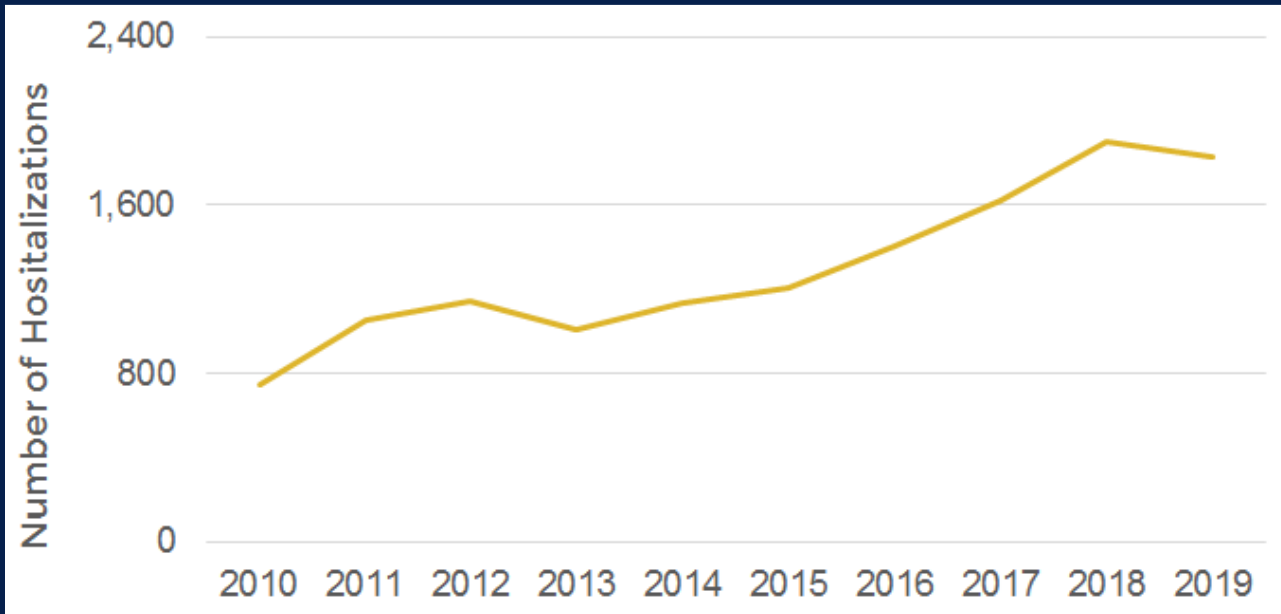
Love JS: et al. Opioid overdoses involving xylazine in emergency department patients: a multicenter study. Clin Toxicol (Phila). 2023 Mar;61:173-180.

# What is the optimal dosing strategy for naloxone?

- ◆ What are the clinical endpoints for reversal?
- ◆ Is there a naloxone resistant overdose?
- ◆ Can “too much” naloxone be administered?
- ◆ Are there alternative agents for reversal?



# Xylazine Associated Wounds



# Xylazine Associated Wounds

Early Stage



# Xylazine Associated Wounds

Late Stage



# Xylazine Associated Wound Pathology

- ◆ Longstanding history of skin ulcers with injection drug use  
Heroin → fentanyl → xylazine

## Potential Causes of Wounds from Injection Drug Use:

- ◆ Increased frequency of injection behavior
- ◆ Obliterative vasculitis from repetitive injection (“shooter’s patch”)
- ◆ Cytotoxic effect of drug or contaminants
- ◆ Skin picking behavior causing excoriations and ulcers
- ◆ Infectious
- ◆ Compression ulcers
- ◆ Poor wound healing (various causes)

# Wound Treatments

Cessation of injection

Clean with soap/water, chlorhexidine, Dakin's Half Strength Solution, or 1% acetic acid

Debridement (enzymatic > surgical)

Antimicrobial coverage (Silver sulfadiazine cream, bacitracin ointment)

Non-adherent (petroleum gauze or other additive to promote moist wound environment) and absorptive dressing



Biodegradable Temporizing Matrix (BTM), skin grafting, epithelialization/complete closure

# Areas of study: Research Agenda

- ◆ Characterize the incidence and clinical spectrum of xylazine withdrawal phenomenon
- ◆ Explore medication strategies to prevent progression of withdrawal and to optimize treatment of opioid and xylazine co-withdrawal
- ◆ Identify the pathophysiology of wound injury and risk factors for development of progressive non healing wounds
- ◆ Assess effective wound treatment strategies
- ◆ Rapid and scalable interventions needed to provide co-located OUD treatment with xylazine withdrawal and wound management
- ◆ Laboratory testing and/or expanded patient/provider education to enhance awareness

# Final Takeaways/Summary

- ◆ Xylazine is an alpha-2 agonist found in increasing frequency as an additive to bags of heroin/fentanyl especially in the Northeast
- ◆ Although sedation is common, naloxone should be considered first line therapy due to nearly ubiquitous fentanyl co-use
- ◆ Repeated use causes a withdrawal syndrome typically described as anxiety and dysphoria but not associated with seizures
- ◆ Benzodiazepines are first-line agent for acute withdrawal
- ◆ No point-of-care testing/urine immunoassay for diagnostics
- ◆ Chronic xylazine injection is associated with necrotic wound development

# References

- Greene SA, Thurmon JC. Xylazine--a review of its pharmacology and use in veterinary medicine. *J Vet Pharmacol Ther.* 1988 Dec;11(4):295-313. doi: 10.1111/j.1365-2885.1988.tb00189.x. PMID: 3062194.
- Spoerke DG, Hall AH, Grimes MJ, Honea BN, 3rd, Rumack BH. Human overdose with the veterinary tranquilizer xylazine. *The American journal of emergency medicine.* May 1986;4(3):222-4. doi:10.1016/0735-6757(86)90070-7
- Torruella RA. Xylazine (veterinary sedative) use in Puerto Rico. *Subst Abuse Treat Prev Policy.* Apr 11 2011;6:7. doi:10.1186/1747-597x-6-7
- <https://preventoverdoseri.org/local-drug-supply/>
- National Center for Biotechnology Information. PubChem Compound Summary for CID 5707, Xylazine. <https://pubchem.ncbi.nlm.nih.gov/compound/Xylazine>.
- Lowry JA, Brown JT. Significance of the imidazoline receptors in toxicology. *Clin Toxicol (Phila).* 2014 Jun;52(5):454-69
- [https://www.deadiversion.usdoj.gov/drug\\_chem\\_info/Xylazine.pdf](https://www.deadiversion.usdoj.gov/drug_chem_info/Xylazine.pdf) Nov 2022
- Kacinko SL, Mohr ALA, Logan BK, Barbieri EJ. Xylazine: Pharmacology Review and Prevalence and Drug Combinations in Forensic Toxicology Casework. *J Anal Toxicol.* 2022 Oct 14;46(8):911-917
- Friedman J, Montero F, Bourgois P, Wahbi R, Dye D, Goodman-Meza D, Shover C. Xylazine spreads across the US: A growing component of the increasingly synthetic and polysubstance overdose crisis. *Drug Alcohol Depend.* 2022 Apr 1;233:109380
- Johnson, J., et al. (2021) *Inj Prev* 27(4): 395-398.
- Warner M, Paulozzi LJ, Nolte KB, Davis GG, Nelson LS. State Variation in Certifying Manner of Death and Drugs Involved in Drug Intoxication Deaths. *Academic Forensic Pathology.* 2013;3(2):231-237.
- Ehrman-Dupre et al. *J Addict Med* 2022;16:595-8.
- Love JS: et al. Opioid overdoses involving xylazine in emergency department patients: a multicenter study. *Clin Toxicol (Phila).* 2023 Mar;61:173-180.