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Toxicology Rounds: Crazy Cases

Gabrielle Procopio, PharmD, BCPS

Clinical Pharmacy Specialist, Emergency Medicine
PGY2 EM Pharmacy Residency Program Director
Hackensack University Medical Center

Associate Professor, Department of Emergency Medicine
Hackensack Meridian School of Medicine

Disclosures

- **Nothing to disclose**

Objectives

- Describe patient evaluation with toxic ingestions and the treatment of a patient with a toxic ingestion

Patient Presentation

AZ is a 55 year old male presenting to the ED today after he was found down at the local 7-11. He stated he used heroin.

Police were called and naloxone 2mg IN was administered. Per EMS, when they received the patient he was more alert than what police described prior to the naloxone administration. He is currently somnolent and slightly arousable to painful stimuli.

BP: 78/54 mmHg **HR: 52 bpm** **Temp: 98.6 F**

RR: 7 bpm **O2 sat: 93% RA**

Patient Presentation

What would you do next?

BP: 78/54 mmHg

HR: 52 bpm

Temp: 98.6 F

RR: 7 bpm

O2 sat: 93% RA

Patient Presentation

It is 4 hours later, after fluids and several repeat naloxone doses, he is still somnolent

BP: 96/62 mmHg **Temp: 98.6 F**

RR: 9 bpm

Now what?

Image accessed from: <https://stock.adobe.com/search/images?k=confused+doctor> April 2, 2023

Xylazine

Xylazine

- Sedative, anesthetic, muscle relaxant and analgesic utilized in veterinary settings
- Frequently found in fentanyl and heroin in areas in the north east
  - Commonly referred to as “tranq”, “tanq dope”, “zombie drug”, “sleep-cut”, “Philly dope”
  - Thought to prolong euphoric effects
  - Patient experiences are mixed

Image accessed from: <https://harmreduction.org/issues/xylazine/> April 10, 2023.
Image accessed from: <https://www.reddit.com/r/photoshopbattles/comments/67a2k8/psbattle_surprised_bunny/> April 10, 2023.
FDA. FDA warns about the risk of xylazine exposure in humans. Nov 8, 2022. <https://www.fda.gov/media/162981/download>
Hoffman J. Tranq Dope: Animal Sedative Mixed with Fentanyl Brings Fresh Horror to US Drug Zones. Jan 7, 2023. <https://www.nytimes.com/2023/01/07/health/fentanyl-xylazine-drug.html>

Xylazine Mechanism of Action and Pharmacokinetics

- **Mechanism of action**
  - **Synthetic alpha-2 adrenergic agonist**
  - **Similar properties to clonidine and dexmedetomidine**

Onset	Within minutes
Half-life	23-50 min (animal data)
Duration	Clinical effects may last > 8 hours (animal data)
Elimination	Rapid

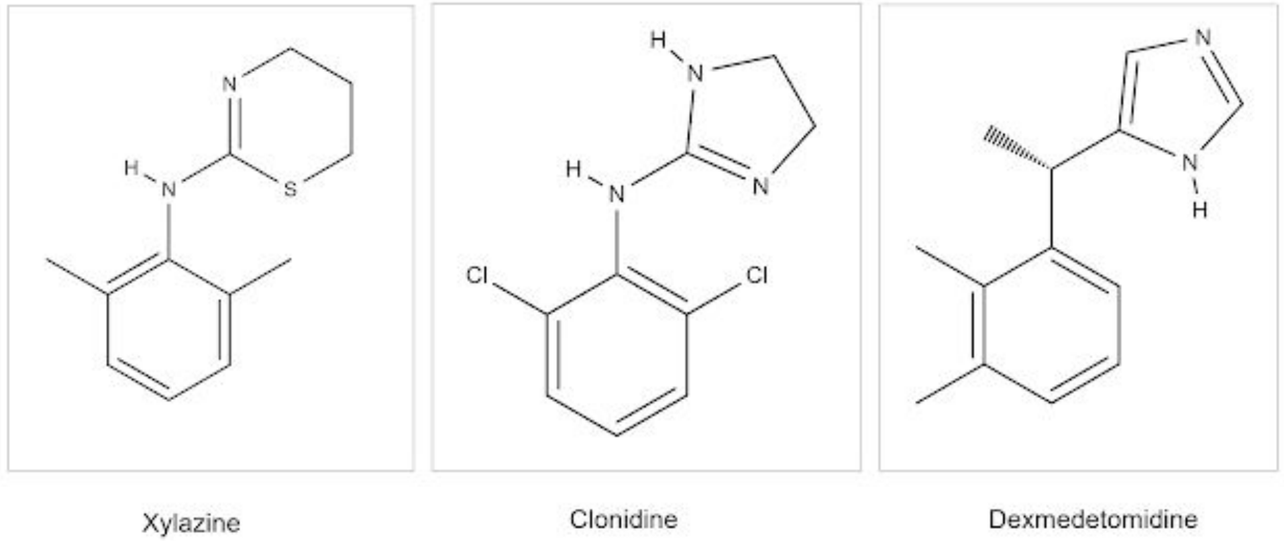
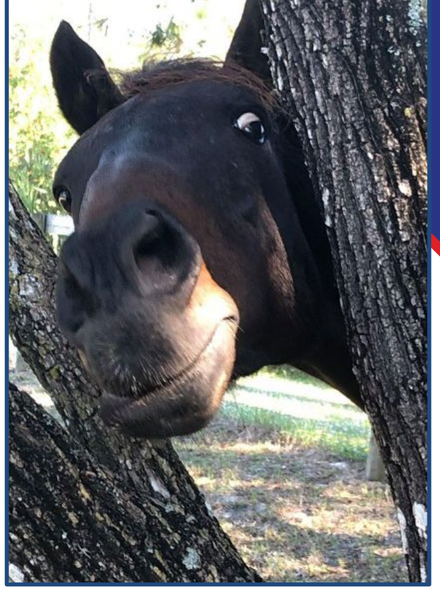


Image accessed from: <https://real-psychiatry.blogspot.com/2022/04/xylazine-another-dangerous-street-drug.html> April, 10, 2023.

Xylazine Timeline



1962 xylazine developed
(human trials stopped due to CNS effects)

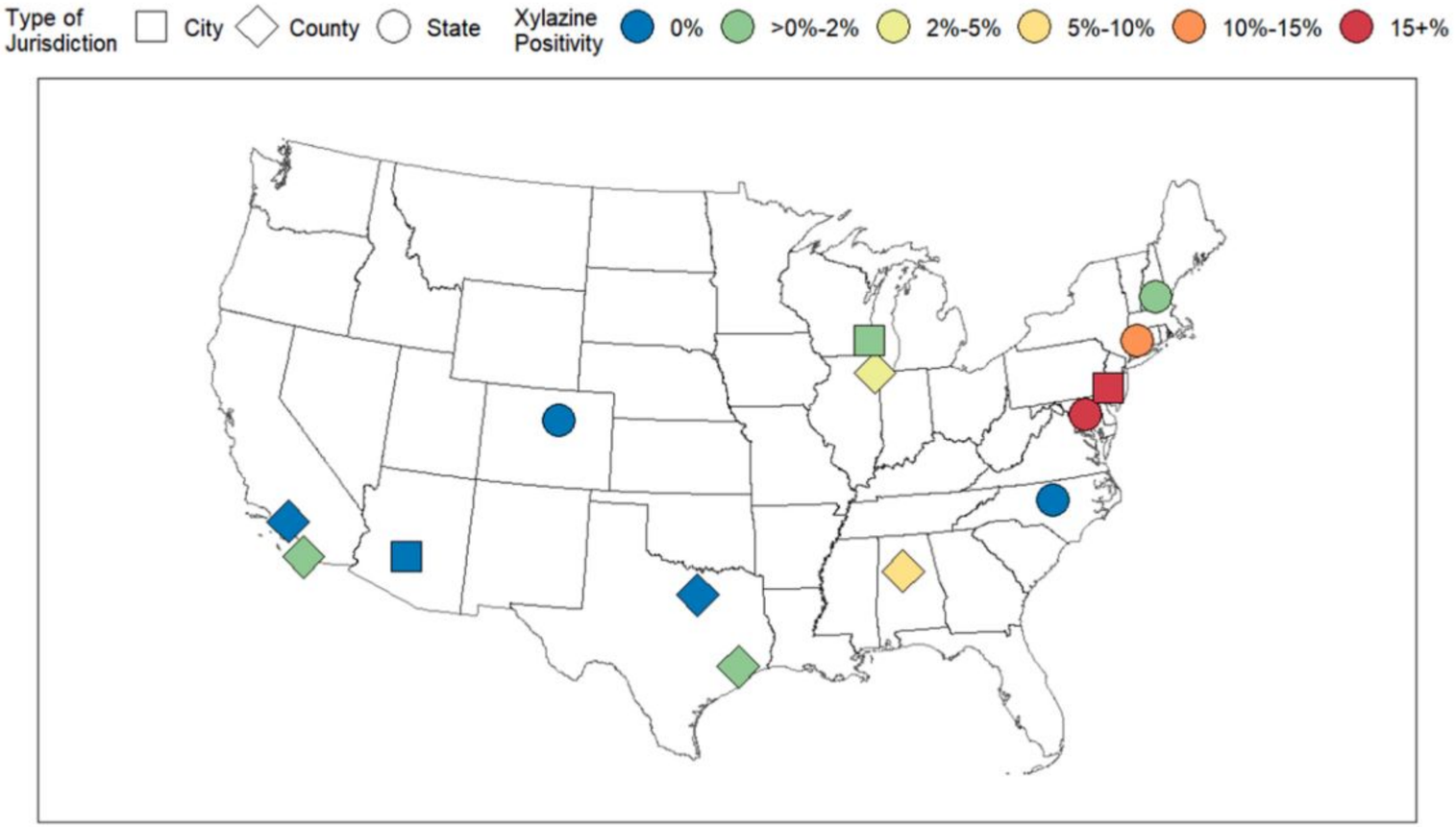
Early 2000's - begins long standing presence in opioids in Puerto Rico

2006-2018 increasing presence in Philadelphia noted

2021 xylazine in 90% of drug samples in Philadelphia

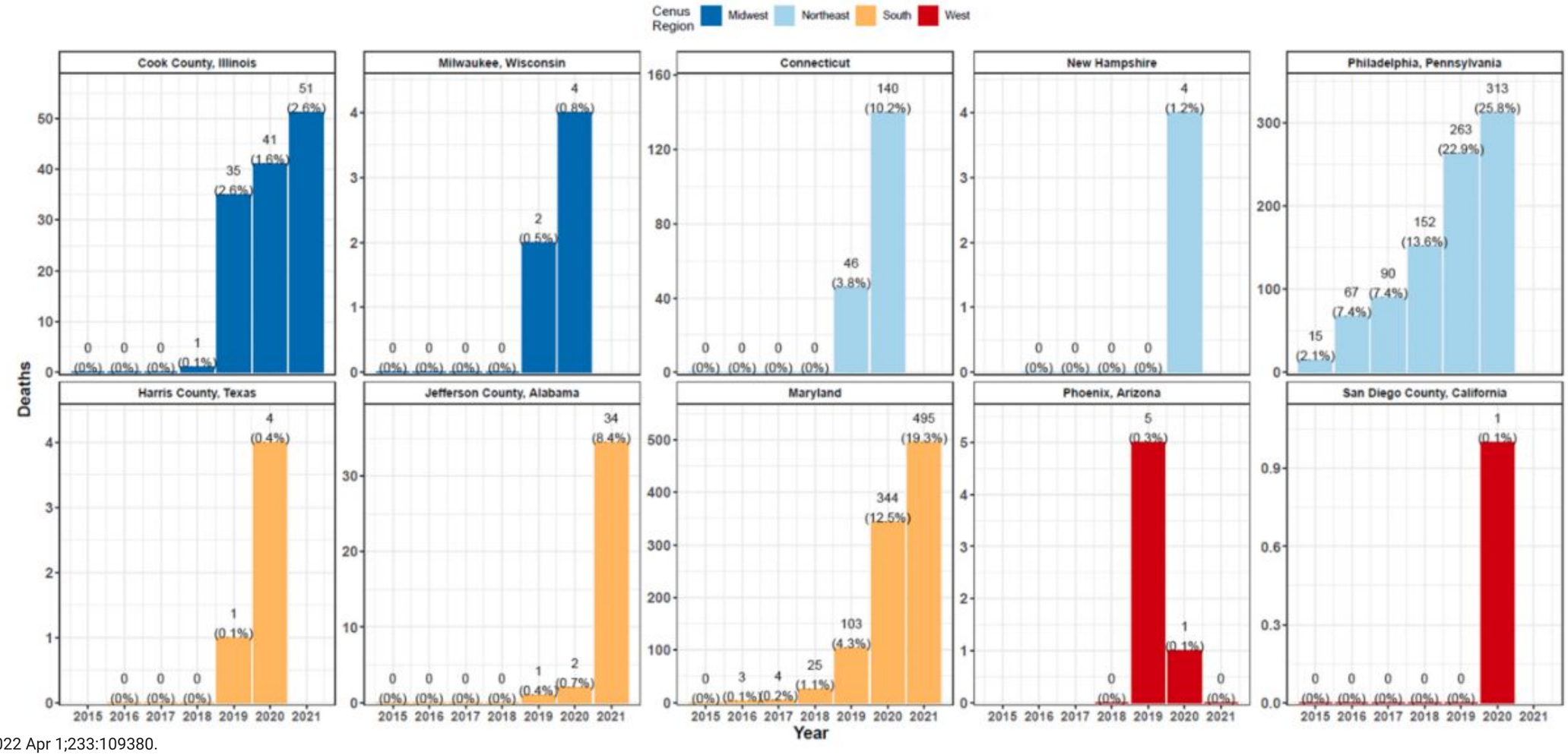
Image accessed from:<https://www.horsenation.com/2019/11/21/reader-photo-challenge-14-surprised-horses/> April 12, 2023
Hoffman J. Tranq Dope: Animal Sedative Mixed with Fentanyl Brings Fresh Horror to US Drug Zones. Jan 7, 2023. <https://www.nytimes.com/2023/01/07/health/fentanyl-xylazine-drug.html>

Xylazine Positivity in Overdose Deaths



Friedman J, et al. 2022 Apr 1;233:109380.

Xylazine-Present Overdose Deaths by Jurisdiction/Year



Friedman J, et al. 2022 Apr 1;233:109380.

FDA alerts health care professionals of risks to patients exposed to xylazine in illicit drugs

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[11-8-2022] Health care professionals should be cautious of possible xylazine inclusion in fentanyl, heroin, and other illicit drug overdoses, as naloxone may not be able to reverse its effects. FDA is aware of increasing reports of serious side effects from individuals exposed to fentanyl, heroin, and other illicit drugs contaminated with xylazine.

CNN health | Life, But Better | Fitness | Food | Sleep | Mindfulness | Relationships

Congress moves to make xylazine a controlled substance

By Janelle Chavez, CNN
Updated 4:16 PM EDT, Fri March 31, 2023

FDA NEWS RELEASE

FDA Takes Action to Restrict Unlawful Import of Xylazine

Agency Aims to Maintain Availability for Legitimate Use in Animals while Preventing Importation for Illicit Purposes

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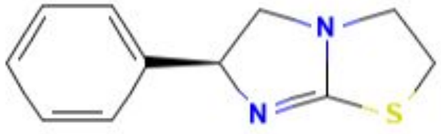
For Immediate Release: February 28, 2023

Xylazine Clinical Presentation

- Sedation, bradypnea, bradycardia, hypotension
- Skin and soft tissue wounds
  - Range of skin soft tissue infections
    - Cellulitis, abscesses
    - Skin necrosis, osteomyelitis
  - May occur independently of injection site
    - Legs and arms



Levamisole

Xylazine

Malayala SV, et al. Cureus. 2022 Aug 19;14(8):e28160.
New York State Department of Health. Xylazine: What Clinicians Need to Know. <https://www.health.ny.gov/publications/12044.pdf>
Image accessed from: <https://shmabstracts.org/abstract/a-case-of-skin-necrosis-caused-by-intravenous-xylazine-abuse/> April 10, 2023.

Has anyone received feedback from patients on their experiences?

medRxiv. 2023 Mar 14;2023.03.13.23287215. doi: 10.1101/2023.03.13.23287215. Preprint

Self-reported Xylazine Experiences: A Mixed Methods Study of Reddit Subscribers

Anthony Spadaro, Karen O'Connor, Sahithi Lakamana, Abeed Sarker, Rachel Wightman, Jennifer S Love, Jeanmarie Perrone

PMID: 36993695 PMCID: PMC10055471 DOI: 10.1101/2023.03.13.23287215

Table 4: Reported Adverse Effects of Xylazine use

Adverse Effects from xylazine use (N=48)	
Increased overdoses/passing out	81%
Skin Wounds or Infections	43%
Increased Emergency Room visits	17%
Have you experienced withdrawal from xylazine? (N=59)	
Yes	53%
What xylazine withdrawal symptoms have you experienced (N=35)	
Body Aches	63%
Cravings	49%
Anxiety	91%
Depressed Mood	74%
How has withdrawing from other drugs changed since you started using xylazine? (N=51)	
Worse	57%
The Same	39%
Better	4%

Table 1: Major themes from Reddit posts about Xylazine

Theme	Definition	Example Quotes	Theme Frequency (% of posts theme appeared in)
Other Drugs used with Xylazine	Posts that discussed xylazine use with other specific drugs	"Around me it's usually fetty/etonitazene analogs mixed with Xylazine which is an animal tranq similar chemically to clonidine, and sometimes ketamine is thrown in too alongside synthetic cannabinoids"	53%
Sentiment about Xylazine	Posts that described a positive or negative experience about using xylazine	"I fucking LOVED xylazine... I loved it. I was so upset if my fetty wasn't cut with it."	24%
Method of Xylazine use	Posts that described how xylazine was used	"Always break the tiniest crumb off to test new batches. Smoking helps cause it hits pretty fast so you can judge"	6%
Geographic Use	Posts that described a geographic area	"It's called xylazine... philly's got that "tranq dope".. puts you out but you get addicted to that along with the fent!"	37%
Dependence on xylazine and other substances	Posts that discuss dependence, addiction, or withdrawal to xylazine and other substances	"12 hours later from my last shot of this fent/trank/ketamine/xylazine shit i started going thrpigh the worst withdraws ever. drank another 115 methadone and within 15 minutes thru it up everywhere. withdraw is ridiculous and methadone doesnt fucking cut it"	11%

Opioid overdose involving xylazine in ED patients - a multicenter study

Table 1. Demographic characteristics of xylazine and control cohorts.

Demographic variables	Xylazine ($n = 90$)	Xylazine absent ($n = 231$)
Male (%)	69 (76.7%)	154 (66.7%)
Age; median (IQR)	41 (32–53)	38 (30–50)
Psychiatric history		
Any	58 (64.4%)	138 (59.7%)
Anxiety	19 (21.1%)	34 (14.7%)
Attention deficit hyperactivity disorder	4 (4.4%)	10 (4.3%)
Bipolar	9 (10%)	25 (10.8%)
Depression	17 (18.9%)	55 (23.9%)
Post-traumatic stress disorder	4 (4.4%)	12 (5.2%)
Schizophrenia	4 (4.4%)	10 (4.3%)
Geographic Region		
East (PA, NY, NJ)	63	127
Central (MI, MO)	26	74
West (CA, OR)	1	30
Naloxone		
Received any naloxone (%)	70 (77.8%)	195 (84.4%)
Initial naloxone dose mg; median (IQR)	2 (0.875–4)	2 (2–4)
Total naloxone dose mg; median (IQR)	3.6 (1.3–4.1)	2.8 (2–4.1)
Number of naloxone doses; median (IQR)	2 (1–3); range 1–5	1 (1–2); range 1–9
Repeat naloxone received (%)*	39 (43.3%)	96 (41.5%)
Initial ED vital signs		
SBP; median (IQR)	132 (114–150)	130 (118–145)
DBP; median (IQR)	84 (68–98)	84 (70–95)
HR ED; median (IQR)	95 (81–108)	98 (84–112)
RR ED; median (IQR)	18 (14–20)	18 (15–20)
Opioid analytes detected **		
Heroin	23 (25.5%)	37 (16%)
Fentanyl	89 (98.9%)	216 (93.5%)
Other fentanyl analogs	29 (32.2%)	32 (13.9%)
Novel synthetic opioids	2 (2.2%)	7 (3.0%)

Abbreviations. IQR, interquartile range; PA, Pennsylvania; NY, New York; NJ, New Jersey; MI, Michigan; MO, Missouri; CA, California; OR, Oregon; ED, emergency department; DBP, diastolic blood pressure; SBP, systolic blood pressure; HR, heart rate; RR, respiratory rate.
*Percentage of entire cohort.
**Samples tested for all potential analytes. Single sample may have multiple analytes and percent totals may exceed 100%.

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 JS, et al. Clin Toxicol (Phila). 2023 Mar;61(3):173-180.

Testing?

Xylazine Testing

- **Not readily available**
- **Rapid elimination (23-50 minutes) may be difficult to obtain samples**

FDA. FDA warns about the risk of xylazine exposure in humans. Nov 8, 2022. <https://www.fda.gov/media/162981/download>

Overall management...

Xylazine Toxicity Management

- Awareness
  - Not “naloxone resistance”
- Naloxone prn respiratory depression for opioid component
- Supportive care
  - Altered mental status
  - Hypotension
- Disposition difficult due to unreliable kinetics in humans and lack of real time testing

Love JS, et al. Clin Toxicol (Phila). 2023 Mar;61(3):173-180.
FDA. FDA warns about the risk of xylazine exposure in humans. Nov 8, 2022. <https://www.fda.gov/media/162981/download>

What about withdrawal?

Xylazine Withdrawal

- Similar to clonidine
  - Hypertension
  - Agitation, anxiety, irritability, restlessness
- Management
  - Co-managing withdrawal syndromes of other agents
  - Benzodiazepines and alpha agonists

Learning Assessment Question

AZ is a 55 year old male presenting to the ED today after he was found down at the local 7-11. He stated he used heroin. Police were called and naloxone 2mg IN was administered. Per EMS, when they received the patient he was more alert than what police described prior to the naloxone administration. He is currently somnolent and slightly arousable to painful stimuli.

BP: 78/54 mmHg HR: 52 bpm Temp: 98.6 F
RR: 7 bpm O2 sat: 93% RA

What is the best treatment option at this time?

a. Administer IV fluids only
b. Administer IV fluids and nalxone 2mg IV once
c. Administer IV fluids and naloxone 0.04mg IV titrate to respiratory response
d. Administer IV fluids and naloxone 0.4mg IV titrate to respiratory response

Learning Assessment Question

AZ is a 55 year old male presenting to the ED today after he was found down at the local 7-11. He stated he used heroin. Police were called and naloxone 2mg IN was administered. Per EMS, when they received the patient he was more alert than what police described prior to the naloxone administration. He is currently somnolent and slightly arousable to painful stimuli.

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What is the best treatment option at this time?

c. Administer IV fluids and naloxone 0.04mg IV titrate to respiratory response

Explanation: Administering IV fluids is important for addressing the patient's low blood pressure. However, given the patient's respiratory rate of 7 bpm and low oxygen saturation (93% on room air), additional naloxone administration is necessary to reverse the respiratory depression caused by the overdose. Option (c) suggests administering naloxone 0.04mg IV and titrating it to the patient's respiratory response, which is the appropriate approach. This allows for a more controlled reversal of the respiratory depression. Options (a), (b), and (d) are incorrect because they either do not provide appropriate naloxone dosing for a opioid overdose, or they do not emphasize the importance of titrating naloxone to the patient's respiratory response, which is essential for safe and effective reversal.

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