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

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“Tranq Dope”—The Heroin Combo That’s Been Putting Philly to Sleep

By Christopher Monholt / April 3, 2018

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

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

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.
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
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 → sedation
  • **CNS DEPRESSION** - No effect on respiratory rate, blunted response to airway occlusion similar to other sedatives, synergistic effect with opioids
    • Major clinical effect is profound sedation
    • Imidazoline receptor activity → hypotension/bradycardia

• Similar effects to imidazoline compounds such as clonidine, dexmedetomidine, oxymetazoline, tetrahydrazoline, tizanidine, and lofexidine

• 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
NORMAL PHYSIOLOGY

Central Nervous System

Presynaptic Neuron

Negative feedback

Norepinephrine

α<sub>1</sub> receptor

Postsynaptic Neuron

Alertness, blood pressure, heart rate
Central Nervous System

XYLAZINE EFFECT

Excessive inhibition of sympathetic outflow causes sedation

Norepinephrine

α₁ receptor

Presynaptic Neuron

Stimulation at the α₂ receptor triggers the negative feedback signal

Xylazine and other α₂ receptor agonists

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

While no polydrug seizures contained xylazine between 2010 and 2013, 5% contained xylazine in 2015, 9% in 2017, and 25% in 2019
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.
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

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

Overview: Traditionally, drugs (e.g., heroin, fentanyl, cocaine, methamphetamine) are commonly identified among drug samples in cities across the United States, albeit at varying periods 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 related 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.

Objectives: 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 presentation of this report. The results reported herein may not represent the entirety of the drug supply.

Acknowledgments: This report was prepared by Alex J. Kostaklis, Ph.D. (CFSRE), MD, Jeffrey Son, MD, MPH, Sara Z. Walker, MD, and Barry R. Logan, MD, MPH, FASHP. The authors acknowledge CFSRE and PDPH personnel for their involvement. Funding for this study was provided internally by the Founders Fund of PDPH. 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@phila.gov or visit cfsrephiladelphia.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 the only opioid (without fentanyl or heroin)
- Two "heroin" samples were found to contain fentanyl & stimulants

Counterfeit "Xanax" found to contain an NPS benzodiazepine

Other: cocaine and fentanyl/methamphetamine samples noted. "Pure heroin" samples not observed. Philadelphia City Council recently admitted there was confusion with listing the location in the report.
**Drug Checking Report: Q1 2022**

**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 panel sizes 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 continually 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 (CFSE) 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, holistic, and multi-faceted approach. A careful analysis of drug testing results from samples obtained within the city were compiled to facilitate the preparation of this report. The results reported herein may not represent the entirety of the drug supply.

**Acknowledgments:** This report was prepared by John S. Kornacki, Ph.D., Marc Shrikhande, M.D., Jeffrey Born, M.D., ASHP, Jerzy F. Wałęza, M.D., and Berenice Lagana, Ph.D., B.A.D.E.T. The authors acknowledge CFSE and PDPH personnel for their contributions and involvement. This work was funded by a federal grant in part, in accordance with the HHSOPH.

**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-Flurofenacetyl continues increasing in prevalence, being identified as the primary opioid in some “heroin” samples.
- A counterfeit tablet was found to contain an NPS benzodiazepine.

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### Drug Identification

<table>
<thead>
<tr>
<th>Drug</th>
<th>Primary</th>
<th>Secondary</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin</td>
<td>Fentanyl (n=27)</td>
<td>-</td>
<td>-</td>
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<tr>
<td></td>
<td>Xylazine (n=15), Caffeine (n=1)</td>
<td>M/A</td>
<td>-</td>
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<tr>
<td></td>
<td>Methamphetamine (n=1), Klonopin (n=1)</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Cocaine</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Dextromethorphan (n=1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Alprazolam (n=1), Xylazine (n=1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Methylamphetamine (n=1), Fluoxetine (n=1)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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### Other Drugs

- “Crack” (n=2)
- “Coke” (n=1)

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### Drugs and Substances

- Cocaine & Lidocaine
- Cocaine
- Flurazepam, Heron & Xylazine
- GBL
- Pentamyl, p-TP & Xylazine
- Pills / Tablets (e.g., Oxycodone, Xanax, Lintazone)
- Alprazolam
- Xylazine
- Methamphetamine
- Methylamphetamine
- Xylazine
- Ketamine
- Flurazepam
- Alprazolam
- Oxycodeone
- Xanax
- Lintazone
- Methamphetamine
- Methylamphetamine
- Xylazine
- Ketamine
- Flurazepam
- Alprazolam
- Oxycodeone
- Xanax
- Lintazone
States/Jurisdictions Reporting Xylazine

Courtesy of: Jewell Johnson
• 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

33% 85% 92% 100% 100% 100%
67% 15% 8% 0%

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
Significance of the imidazoline receptors in toxicology
J. A. Lowry & J. T. Brown

RVLM: rostral ventrolateral medulla
NTS: nucleus tractus solitarii
Drug-facilitated assault with tetrahydrazoline

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

By Jeffrey A. Johnson j.johnson@postregister.com

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.

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.

By Christine Hauer

Jan. 17, 2020
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?
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

Naloxone (Narcan Nasal Spray)

• Indication for use
  • Apnea or cyanosis and decreased mental status in suspected opioid overdose (respiratory rate <8 bpm and POx <92%)

• 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

Test Code 4815B/U
Method LC-MS/MS
Specimen Type Blood or urine
Turnaround Time 8 days
### Xylazine: Pharmacology Review and Prevalence and Drug Combinations in Forensic Toxicology Casework

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- 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 dexmedetomidine, 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

Introduction
We investigated the incidence, symptoms and risk factors for withdrawal associated with prolonged dexmedetomidine use. Dexmedetomidine is an α₂-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 and role of clonidine 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 μg/kg/hour with a median cumulative dose of 87 μg/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

*Implications for buprenorphine induction*
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
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.

“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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