

If fentanyl was not enough, now we have xylazine!

- “Anestesia de caballo”
- “Tranq and tranq dope”
- Dan Nauts, MD, FASAM
- SUD Task Force, 4/26/2023



Thanks to Joseph D'Orazio

History of xylazine

- Xylazine is a non-opioid used as a sedative, anesthetic, muscle relaxant, and analgesic for animals. It is a strong synthetic alpha-2 adrenergic agonist, synthesized in 1962 in Germany by Bayer as an anti-hypertensive, analgesic, hypnotic, and anesthetic. *It was not approved for human use due to severe CNS depressant effects.*
- A veterinary medication used for procedural sedation in both small and large animals (approved for veterinary use in the US by the FDA)
 - Not a controlled substance; not scheduled in the US as it is not intended for human use
 - When used in combination with opioids, enables use of lower doses of opioids and enhances both sedation and anesthesia
- Initially emerged sporadically in the literature as a substance of use in the 1980s and 1990s, emerged as a substance of widespread misuse in Puerto Rico in the early 2000s and was known as 'anestesia de caballo'
 - Xylazine appears to be added to fentanyl either at source of manufacture, or ?Mexico or ?by distributor. This is uncertain. Diversion from veterinary sources unlikely.
 - Misuse first noted in Philadelphia in 2006



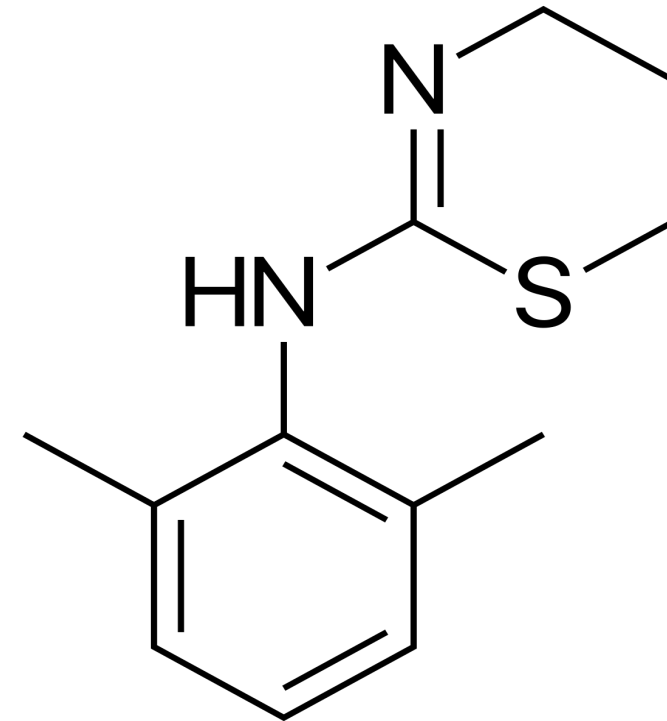
Epidemiology: Xylazine

- Xylazine in the drug supply is following a multi-year progression of appearing increasingly in the unregulated drug supply
- Over the last decade, the number of novel psychoactive substances (NPS) has increased, and they have increasingly replaced the historical heroin supply in parts of the US and Canada
 - heroin->heroin + fentanyl->heroin + fentanyl + carfentanil + etizolam->heroin + etizolam + isotornitazene/nitazenes, etc. + flualprazolam + xylazine + buprenorphine + O-DMST + U-47700
 - ***What does all this mean?***
 - ***npsdiscovery@cfsre.org excellent data as to what is in drug supply.***

Xylazine: Structure, Pharmacology, and Clinical Effects

- Alpha-2 adrenergic agonist that *stimulates central alpha-2 receptors*:
 - Decreases sympathetic nervous system outflow
 - > sedation (decreases the release of NE and dopamine)
 - **CNS DEPRESSION: No effect on respiratory rate, blunted response to airway occlusion (hypoxia) similar to other sedatives (benzodiazepines, barbiturates), synergistic effect with opioids**
- Similar effects to *imidazoline* compounds, such as clonidine, dexmedetomidine, oxymetazoline, tetrahydrozoline, tizanidine, and lofexidine
 - **Major clinical effect is profound sedation**
 - **But NO imidazoline receptor activity, so NO hypotension/bradycardia**
 - Increase in vagal tone is reported in the veterinary literature
 - Acts on alpha-2 receptors in pancreatic beta cells, inhibiting insulin release->hyperglycemia
 - One of xylazine's metabolites, 2,6-xylidine, has been classified as potentially genotoxic and carcinogenic in humans based on animal studies
- Pharmacokinetics:
 - Typical anesthesia dose ranges (0.2-1 mg/kg IM or IV)
 - Time to effect is 1-2 minutes (depending on administration route); lipophilic, diffuses widely, good bioavailability
 - Average duration of substance effect up to 4 hours, but can last longer
 - Routes of Administration: IV, IM, SC, PO, inhalation, insufflation, ocular

Xylazine Structure



Similar chemical structure to phenothiazines, TCAs, and clonidine
Thanks to Joseph D'Orazio, MD

Forensic Sci Int. 2014 Jul;240:1-8

BCCDC Harm Reduction Services, 1/24/22

ToxTalks, Blue Ridge Poison Center, 2/2022

Seeking Xylazine, “gives fentanyl legs”

- NO 64%
- Yes 36%
- Identified in 48/50 states, also identified in cocaine, methamphetamine
- Sedation onset of action in 1-2 minutes, enhances euphoria, and duration of action up to 4 hours
- Hazardous side effects, excess sedation, prolonged immobilization (potential myoglobinuria due to rhabdomyolysis) “can’t move for hours at a time!”
- Synergism with opioids.

Xylazine, alpha 2-agonist decreases sympathetic outflow resulting in sedation.

Sedation Not responsive to Naloxone!

- Goal of naloxone rescue with the presence of xylazine and other sedatives is to establish “**respiration not conversation!**” Don’t keep administering naloxone I
- W/D is not responsive to treatment for opioid withdrawal, veterinary agents are not available for humans.
- **W/D symptoms include, dysphoria, anxiety, restlessness hypertension**

Medications tried for xylazine W/d

- Other alpha-2 agonists such as clonidine, lofexidine, tizanidine, dexmedetomidine (ICU)
- Benzos
- Antipsychotics
- Ketamine(ICU)
- Phenobarbital
- Gabapentin

Toxidrome

acute

- Prolonged sedation, blackouts
- Disorientation
- Drowsy
- Blurred vision
- Slurred speech
- Dry mouth
- Hypotension, bradycardia
- Muscle relaxation, respiratory depression

chronic

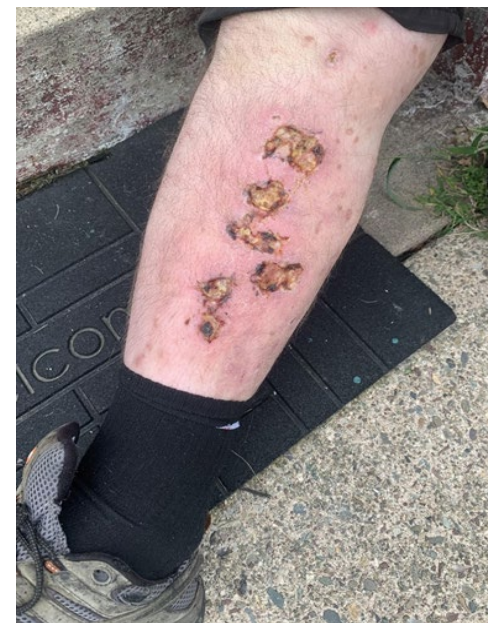
- Severe skin wounds
- Dysglycemia, abnormal blood sugar
- anemia

Warning, the following wounds may be difficult for some if non-medical!

Differential?



Xylazine and Skin Ulcers/Wounds





Xylazine and Skin Ulcers/Wounds

- Severe necrotic skin ulcerations, often necessitating complicated wound care
- Occur at skin sites associated with injection, *but also at skin sites not associated with injection and in individuals who don't inject*
- The pathophysiological mechanism which causes the ulcerations is unclear; they are not infectious, but can become superinfected with bacteria, particularly with skin picking

Harm reduction

- Talk to potential users about xylazine in the supply, advise to seek other batches
- Ask about unusual wounds.
- Educate on “red flag symptoms”; fever, chills, skin turning black or dark
- Rotate sites, and avoid injecting groin and neck
- Wash hands and injection sites with soap and water or use alcohol pads
- Needle angle at 45 degrees, wipe needle with alcohol pad wiping any solution off prior to injection.
- Evaluate for infection ?systemic antibiotics, cleanse wounds, topical ointment, don't scratch, A+D on healthier skin, non-adhesive dressings, debridement? Daily dressing changes.

What can we do?

- Educate
- Continued importance of naloxone
- Pathways for low barrier wound care
- Support and contact local drug checking centers
- Fund test strips when available
- Medical examiners should screen universally for xylazine