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
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 + isotonitazene/nitazenes, etc. + flualprazolam + xylazine + brorphine + 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, tetrahydrazoline, 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
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!
- 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!
Xylazine and Skin Ulcers/Wounds

NHRC Xylazine Office Hours, 4/2022
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