FAQ: What Every Pharmacist Should Know About Xylazine
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Contact:
ASHP Section of Ambulatory Care Practitioners
sections@ashp.org

Introduction:

The CDC reported during January 2021–June 2022 that xylazine was detected in a higher percentage of illicitly manufactured fentanyl (IMF) involved overdose deaths in the Northeastern U.S. The presence of xylazine in substances tested in labs has increased in every region of the U.S. from 2020-2021, with the largest increase found in the South. The DEA has already seized xylazine and fentanyl mixtures in 48 of 50 states. It is commonly found in combination with fentanyl but has also been detected in mixtures containing methamphetamine, cocaine, heroin, and a variety of other drugs in an effort to lengthen their euphoric effects.

The purpose of this FAQ is to provide information on the effects of xylazine and emphasize harm reduction interventions for individuals who may encounter xylazine in the illicit drug supply.

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1. What is xylazine?

Xylazine (also known as “tranq”) is an alpha-2 adrenergic agonist approved by the Food and Drug Administration (FDA) for procedural sedation in veterinary medicine. Xylazine is a commonly used sedative for veterinary medicine, and it is not FDA-approved for use in people due to severe central nervous system (CNS) depression and sedation in humans.

The chemical structure of xylazine is similar to the class of compounds known as phenothiazines. Xylazine is in the same drug class as clonidine and acts on the alpha-2 adrenoreceptors found in the presynaptic and postsynaptic neurons of the central and peripheral nervous systems. Xylazine has a high affinity for presynaptic alpha-2 receptors. When the presynaptic receptors are activated, the release of norepinephrine and subsequent binding onto the alpha-1 receptor in the postsynaptic neuron is inhibited due to a negative feedback mechanism. This decreases the release of norepinephrine in the central nervous system and results in sympatholytic effects like hypotension, bradycardia, sedation, analgesia, and muscle relaxation.

2. What are the effects of xylazine?

Xylazine has a sedative effect on the brain. Depending on the route of administration, it can put someone into deep sleep for 20-30 minutes. It has been reported to put a person into a deep sedative state for several hours when found mixed with other substances. Xylazine can also cause severe CNS depression which can contribute to muscle relaxation of the tongue. This can lead to a blocked airway and prevent a person from breathing. Due to its similar mechanism of action to clonidine, xylazine can also dangerously lower blood pressure and slow the heart rate. Substances that contain both fentanyl and xylazine have a high risk for a potential overdose due to their combined ability to cause sedation, respiratory depression, and CNS depression.

3. What are the potential health impacts of xylazine?

Withdrawal Symptoms:

Potential withdrawal symptoms can occur when someone decreases or stops using xylazine. Symptoms of withdrawal may include anxiety, high blood pressure, increased heart rate, sweating, restlessness, agitation, and irritability. The report of withdrawal symptoms is common in chronic xylazine use. There is still minimal literature regarding xylazine withdrawal symptom management. While no medication is FDA-approved for xylazine withdrawal, the Philadelphia Department of Public Health (https://hip.phila.gov/document/3154/PDPH-HAN_Update_13_Xylazine_12.08.2022.pdf) has released recommendations that could be helpful in patients experiencing xylazine withdrawal including replacement therapy with other alpha-2 adrenergic agonists such as clonidine, dexmedetomidine, tizanidine, and guanfacine.

Withdrawal Symptoms Management:

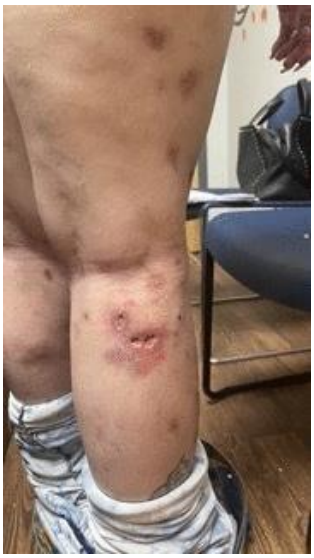
Replacement therapy with another alpha-2 adrenergic agonist like clonidine, dexmedetomidine, tizanidine, or guanfacine can help manage "rebound" symptoms characterized by sympathetic overactivity like hypertension, anxiety, and jitteriness.

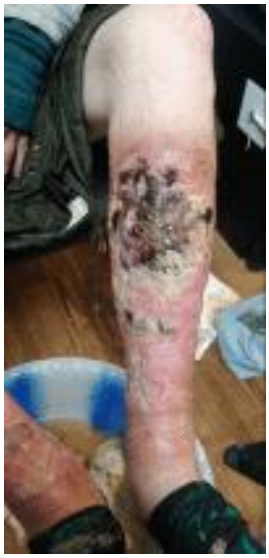
Symptom management for pain includes using short acting opioids, ketamine, gabapentin, ketorolac, acetaminophen, or NSAIDs. If a person is experiencing insomnia, a trial of trazadone, quetiapine, or mirtazapine is recommended. Anxiety can also be managed with hydroxyzine or benzodiazepines.

Opioid use disorder and opioid withdrawal is managed based on the patient's history. If a patient is on opioid agonist therapy, then split dosing can increase analgesic effect and improve pain control. If a patient is undergoing induction, then micro dosing buprenorphine allows for concurrent use of short acting opioids that can improve pain control.

Xylazine-Related Skin Wounds:

Xylazine is thought to cause skin wounds through a direct vasoconstriction effect and subsequent decrease in skin perfusion locally. Wounds can appear both in people who inject and people who don't inject drugs. For people who inject, it is common to see a wound appear at the injection site. The wound could also develop on the forearms and lower legs. It often appears as small bumps with a white or purple center with a dark red fluid. The lesions can quickly merge to form large, full-thickness wounds that move through the skin, fat, and muscle layer. The wounds tend to have necrotic tissue, drainage, a dried black crust, and have an odor. If left untreated, it can become infected with bacteria.





Images from Papudesi BN, Malayala SV, Regina AC. Xylazine Toxicity. In: StatPearls. Treasure Island (FL): StatPearls Publishing; July 17, 2023.

Wound Care:

Patients are to be referred to wound care for managing xylazine-related wounds. Early and consistent wound care is important to avoid further complications. Cleanse the wound with normal saline or clean water and avoid harsh cleansers like peroxide, bleach, or alcohol. Cover it with nonadherent gauze or dry dressing. Remember to wash hands and use gloves when caring for the wound. In severe cases, debridement may be necessary when nonviable tissue covers the ulcer bed. Antibiotic coverage for a secondary infection must cover methicillin-resistant *Staphylococcus aureus* and antibiotic coverage for group A *streptococci* should be considered.

4. What are other potential drug to drug interactions with xylazine?

Taking xylazine with other CNS depressants like alcohol, benzodiazepines, gabapentin, and opioids increases the risk of life-threatening overdose. There is currently no reversal agent for xylazine. Therefore, it is important to test for xylazine in the illicit drug supply and avoid use when possible, to prevent additive harm and the risk of a fatal overdose.

5. What to do in a xylazine overdose?

Naloxone should be given in the event of a xylazine overdose due to it often being mixed with fentanyl and other illicitly manufactured opioids. However, naloxone will not reverse the effects of xylazine. Therefore, it is important to begin rescue breathing until Emergency Medical Services (EMS) arrive if a person does not respond to 1-2 doses of naloxone. In addition to rescue breathing, check for a pulse. If the person has no pulse, it is recommended to perform chest compressions or full CPR.

6. What should patients do to reduce potential harm of xylazine?

The following are harm-reduction strategies that patients can use to help reduce the risk of an overdose.

- Never Use Alone: Call the Never Use Alone Hotline at 800-484-3731 to receive non-judgmental support over a phone or video call, and to help alert emergency services if the caller becomes unresponsive.
- Carry Naloxone: Xylazine is often found mixed with opioids like fentanyl. In the event of an opioid overdose, naloxone can help reverse any possible opioid effects.
- Provide Rescue Breathing: Xylazine can slow down breathing. Therefore, learning how to provide rescue breathing can be helpful in a xylazine overdose.

- Testing for Xylazine: Know what is going into the body by testing the drug for xylazine. There are commercially available test strips that can be used to check for xylazine before using.
- Safe Supplies: For people who might inject, it is important to utilize unused needles and syringes to avoid infectious disease transmission or the formation of skin abscesses.

Contributing Authors:

Jordan Wulz, Pharm.D., MPH, BC-ADM
Associate Professor of Pharmacy Practice
Concordia University Wisconsin, School of Pharmacy

Salena Yang, Pharm.D. and MPH Candidate (2024)
Concordia University Wisconsin, School of Pharmacy

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