



What is xylazine?

Xylazine is a veterinary agent, approved in 1972, which is used for sedation, muscle relaxation and analgesia. In veterinary medicine, xylazine can be administered subcutaneously, intramuscularly, or intravenously.

Federal Guidance on Xylazine

The Food and Drug Administration has provided guidance to physicians on the emergence of xylazine through direct alerts and a dear colleague letter which have been provided below for your review with most of the main points also addressed in this communication.

FDA Alert to Health Care Providers

FDA Dear Colleague Letter on the risk of xylazine to Human Subjects

How does xylazine work?

Xylazine is a central α -2 adrenergic receptor agonist and is structurally similar to clonidine and dexmedetomidine (Precedex). Xylazine acts by decreasing the release of norepinephrine and dopamine with resultant sedation, muscle relaxation, and analgesia.

Is xylazine used in humans?

It is not approved for human use. In fact, human trials were discontinued due to adverse effects.

Why do physicians and other healthcare professionals need to know about xylazine?

Xylazine is increasingly being found as an adulterant in the illicit drug supply and has been identified as one of the substances present in some fatal overdoses. It is most commonly found in combination with illicit opioids, such as heroin and fentanyl. However, it has also been found in combination with cocaine and psychostimulants (e.g., methamphetamine) and benzodiazepines. Many people who are using drugs adulterated with xylazine are not seeking it out and are unaware that it has been cut into the drugs they are buying.

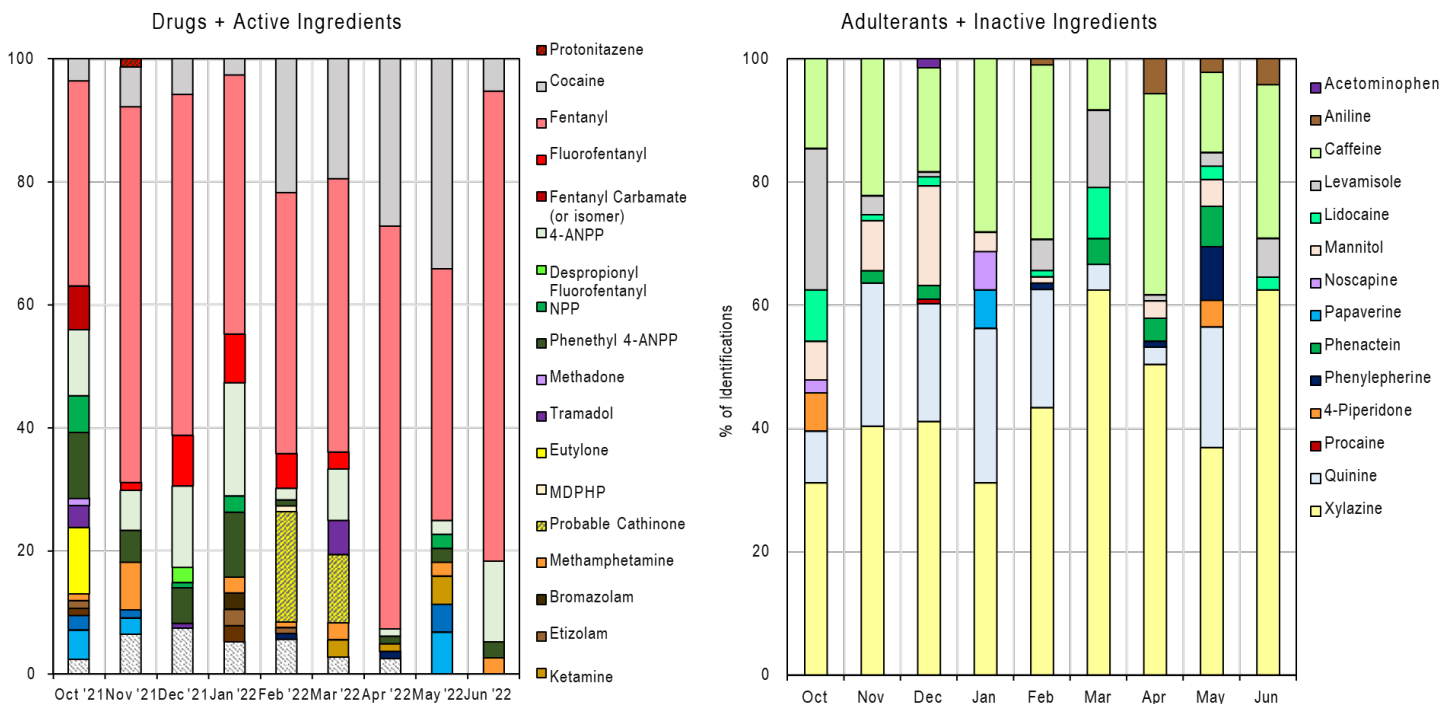
Is xylazine detectable in toxicology screens?

Xylazine is not detected in routine toxicology screens, which are immunoassays. Currently, more advanced toxicology testing, such as chromatography, is required to detect xylazine. However, xylazine has a half-life of about 30 minutes and is rapidly eliminated from the body, which means even with the appropriate testing, it might be missed. Thus, some of the reports of the presence of xylazine in the drug supply are anecdotal and not based on drug testing. However, increasingly states and local jurisdictions are testing for the presence of xylazine in those who have died from an overdose death. In Maryland, the Office of the Chief Medical Examiner has been testing for the presence of xylazine in overdose death decedents and the proportion of overdose deaths in which xylazine was present has increased dramatically since 2017.

Is xylazine here in Maryland?

Yes, Maryland's Office of the Chief Medical Examiner has been testing for xylazine for a number of years. From 2006 through 2018, there were 83 cases that were positive for xylazine. In 2018 alone, there were 56 cases, a 331% increase from the year before.

Additionally, the Maryland Department of Health has implemented an illicit drug surveillance program through the Center for Harm Reduction Services. The **Rapid Analysis of Drugs** program captures samples provided by Syringe Service program participants and has those samples analyzed via mass spectroscopy at the National Institute of Standards and Technology. An analysis of sample results below demonstrates the prevalence of xylazine and fentanyl in current illicit drug samples.



What are the clinical effects of xylazine use in humans?

- Hypotension (↓ blood pressure)
- Bradycardia (↓ heart rate)
- Arrhythmias
- Hyperglycemia
- Skin lesions and necrotic ulceration that are distinctly different from other soft-tissue infections and have been associated with risk for amputation
- Altered level of consciousness: drowsiness → coma
- Death*

*Deaths from xylazine intoxication are rare but have been reported. In these instances, the amount of xylazine present was much higher than what is commonly seen when xylazine is used as an adulterant in the illicit drug supply.

Xylazine-associated wounds

Xylazine has been associated with the development of skin ulceration. These ulcerations are often severe, presenting with necrosis and black eschars. While most commonly seen in persons who inject substances containing xylazine, the lesions may develop in areas distant from the injection site and in some instances occur in persons who have histories of smoking or snorting drugs but deny history of injection drug use.

Again, because of limitations in testing for xylazine, the association with xylazine and the presence of these wounds is often presumptive and not confirmed by toxicology.



Xylazine associated wounds at various stages of development

Management of these wounds is an integral part of the recovery process for these patients as the presence of chronic wounds can be a barrier to entering residential drug treatment program settings. Care for xylazine-associated wounds typically requires debridement, long-term dressings [durable dressings], and an individualized follow-up plan based on access to clean water, housing status, access to medical supplies, comfort accessing healthcare, and comfort with self-care. Individuals with injection drug related wounds can get wound care supplies and preliminary wound care support at syringe service programs **located** throughout the state.

Xylazine and opioids

Xylazine can have effects that are synergistic with opioids.

- Bradycardia
- Hypotension
- Sedation

Thus, xylazine in combination with opioids may increase the risk of sedation and potentially increase the risk of overdose. Yet, because xylazine is not an opioid, its effects cannot be reversed with the opioid antagonist, naloxone (brand name: Narcan).

However, naloxone should always be administered in cases of suspected overdose. Opioids are almost always present in cases of overdose in which xylazine is present and while naloxone will not reverse the effects of xylazine, it will reverse the effects of any opioids that are present and can still be lifesaving.

How should healthcare professionals treat an overdose in which xylazine is suspected?

As opioids are almost always present in cases of overdose in which xylazine is present, naloxone should be administered to reverse the effects of any opioids that may be present. Supportive care is otherwise recommended for the effects of xylazine intoxication. This may include cardiovascular support, respiratory support, and glucose management.

While no medication is FDA approved for xylazine withdrawal, the following approaches are being used:

Replacement therapy with alpha-2-adrenergic agonists:

Clonidine, Dexmedetomidine, Tizanidine, Guanfacine

Symptom management:

- Pain: Consider employing a multi-modal pain management strategy utilizing a combination of short acting opioids, Ketamine, Gabapentin, and NSAIDs
- Insomnia: Trazodone, Quetiapine, Mirtazapine
- Anxiety: Hydroxyzine, Benzodiazepines (judiciously)

Treat opioid use disorder and opioid withdrawal:

- If a patient is on opioid agonist therapy, then split dosing can increase analgesic effect and improve pain control.
- If a patient is initiating buprenorphine maintenance, then starting with small doses of buprenorphine (2mg or less) allows for concurrent use of short acting opioids that can improve pain control.

What happens with chronic xylazine exposure?

Repetitive exposure to xylazine has the potential to result in physiologic dependence resulting in the presence of withdrawal symptoms in the setting of abrupt discontinuation. Potential withdrawal symptoms include:

- Severe anxiety
- Autonomic instability
 - » Rebound hypertension
 - » Tachycardia
- Agitation

There is minimal research to guide management of withdrawal symptoms associated with xylazine. However, physicians have described using the strategies described in the question above to manage the range of associated symptoms.

Reference: Erhman-Dupre, et al. J Addict Med 2022;16