Clinical Update: January 2023

NOVEL PSYCHOACTIVE SUBSTANCES: WHAT IS XYLAZINE?

Substance use can take many forms and often involves many unknowns. One of the most important aspects of illicit substance use, especially for the end user, is actually knowing what drugs are contained in a product—especially if it is planned to be injected intravenously. Despite many illicit drugs having unique street names, the contents of the substance often will be unknown to the user. Many of the currently circulating street drugs contain substances that are called New or Novel Psychoactive Substances (NPS). NPS are defined by the United Nations Office on Drugs and Crime, as "substances of abuse, either in pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat."[1] NPS compounds often are designed to avoid traditional drug regulations/scheduling, and many are not necessarily new. NPS compounds may have been discovered or first synthesized decades prior but never became available on the traditional prescription drug market. For example, some compounds may not have been deemed safe enough for public use or were thought to be too addictive to receive marketing approval. Thus, many NPS compounds can be viewed as research chemicals because safety, efficacy, or even dosing information in humans may not be available.

The global availability of illicit drugs poses a significant risk to public health, especially with the increase in NPS compounds seen in the global drug market.[1] Drug control regulations and chemical availability differs all over the world, leading to synthesis and production of various NPS compounds that can be distributed all over the world using social media or internet applications. One NPS drug that has unfortunately been gaining increased attention is xylazine. In this month's Clinical Update, we delve into what xylazine is, how it is showing up in the illicit drug supply, and considerations for healthcare professionals who manage patients at risk for substance use. The nature of NPS drug compounds is that they seem to be constantly changing. Unfortunately, xylazine is a NPS compound that does not seem to be going away.

Xylazine: Drug Information

The only FDA-approved indications for xylazine use are in animals. There are several branded xylazine-containing products (i.e., Rompun®, Anased®, Sedazine®, Chanazine®) approved for veterinary indications for use in dogs, cats, horses, fallow deer, mule deer, sika deer, white-tailed deer, and elk.[2] No product is approved for use in humans. Xylazine's chemical structure resembles clonidine, tricyclic antidepressants, and phenothiazines (Figure 1) and has activity as a potent α_2-adrenergic agonist.[2] This binding to α_2-adrenergic receptors decreases the release of dopamine and norepinephrine in the central nervous system (CNS) resulting in sedation, muscle relaxation, and decreased perception of pain. There are other postulated mechanisms of action for xylazine that may involve serotonergic, dopaminergic, cholinergic, α1-adrenergic, or opioid mechanisms. Adverse effects in animals include hypotension, respiratory depression, and transient hypertension.

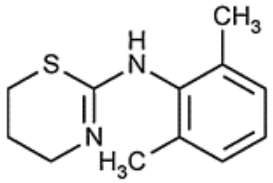

Figure 1: Xylazine Chemical Structure

Administration in animals is by injection, either intravenous (IV), intramuscular, or subcutaneous. The aforementioned branded products are all available as solutions (20, 100, and 300 mg/ml), whereas xylazine that is adulterated in illicit drugs is likely to be in a solid form. The approved labeled doses in animals are weight-based, ranging from 0.25 mg/lb- 4 mg/lb, with an onset within 3-5 minutes after IV administration, and typically provide analgesia for 15-30 minutes while the sedative effects may last for a few hours.[3] In horses and *Cervidae* (deer) sedated with xylazine, their respiratory rate is decreased much like during sleep, and the heart rate is also decreased. Other side effects reported include slight muscle tremors, partial AV heart block, sweating, and salivation. In clinical trials with *Cervidae*, capture-associated mortality was reported up to 3.5% with xylazine, showing the potential miscalculation of the animal's weight, and the dangerous effects of this compound.[3]

Xylazine was first synthesized in 1962 by the Bayer Company for use as an antihypertensive agent in humans. Xylazine was also studied in humans for use as an analgesic, anesthetic, or hypnotic.[5,6] However, these clinical trials in humans were terminated early due to safety concerns. An unacceptable amount of severe hypotension and central nervous system depression was observed in these trials and xylazine was deemed not safe to use in humans. Unfortunately, many individuals may unknowingly use xylazine and report or display unexpected symptoms from its use. Signs of acute xylazine toxicity may include respiratory and CNS depression, hypotension, bradycardia, hypothermia, miosis, or hyperglycemia.[5] Many of these symptoms are similar to what opioids can cause, and xylazine has often been found with several illicit opioids, such as fentanyl or heroin. However, because xylazine is not an opioid, use of naloxone is not expected to reverse its effects. Another adverse effect of xylazine is that repeated exposure may result in dependence and withdrawal. Symptoms of withdrawal from xylazine include agitation and anxiety, and because xylazine is often contained with opioids, patients may struggle to find relief from traditional opioid use disorder treatments. Thus, it may be important for providers to have non-traditional toxicology data about recent substance use, especially if a substance like xylazine or another NPS substance has been consumed, to help guide further patient management.

Why Add Xylazine to Illicit Drugs?

There has been an unusual increase in the adulteration of illicit drugs with highly harmful substances, particularly those that are not even approved for human use.[2,5] It is often not fully understood why or when illicit drugs are adulterated with other substances but it has been suspected that these substances are added for a multitude of reasons, such as prolonging the duration of effect of the traditional illicit drug (i.e. heroin, fentanyl), using them as a cutting agent, or increasing the ease of availability of the base drug. In 2006, xylazine was detected in 36% of street heroin samples in Puerto Rico and was identified in a syringe as an adulterant of speedball (heroin and cocaine) in 2008.[2] Users of this triple drug combination reported that the combination of heroin and xylazine would give a better high, but that the sedative effects of the combination was too strong, necessitating the addition of cocaine.[2] The mechanism of action of these drugs differs so it is possible to have additive or synergistic effects from the combination. Healthcare providers managing patients potentially exposed to illicit drugs should be mindful that the patient may have also been exposed to xylazine, especially in overdose situations, or if the patient begins to experience non-traditional withdrawal symptoms.

Unexpected Side Effect: Xylazine-Associated Ulcers

Individuals who inject IV drugs are at higher risk for infections simply by giving microbes access directly into their body and bloodstream. Blood-based infections can become catastrophic medical problems resulting in sepsis, osteomyelitis, myocarditis, and/or soft tissue necrosis. A strange and not well understood adverse effect of xylazine use has been the repeated cases of skin ulcers, necrotic tissue, and abscesses.[7,8] Figure 2 shows an example of xylazine-induced leg ulcers and cellulitis (in both legs) from a 37-year-old female who had a history of injecting 8-10 bags of "dope" every day.[7] This dope substance was actually a combination of fentanyl and xylazine, which the individual admitted to injecting in her hands or leg veins.

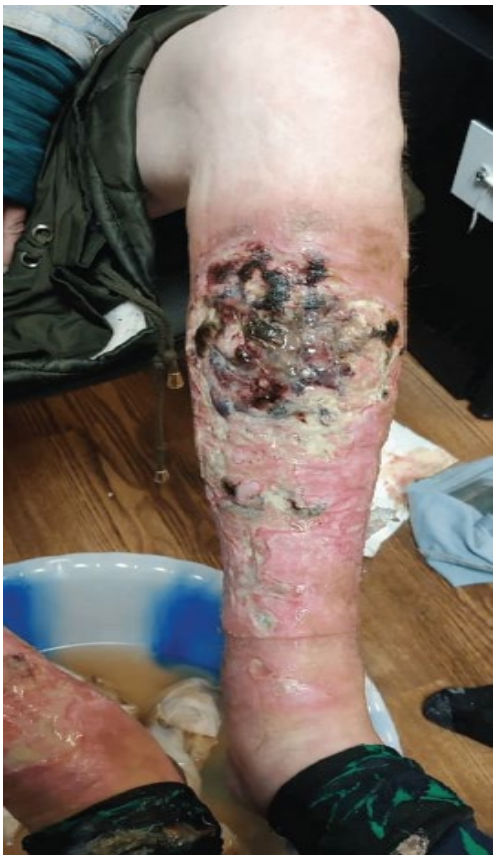

Figure 2: Xylazine-induced leg skin ulcers, cellulitis, and osteomyelitis[7]

The ulcers were reported to be foul-smelling with excessive drainage and extending into the bone in some spots while the patient's vital signs were relatively stable (Temp 99.8F, BP 100/48, HR 92). This patient had a significant history of opioid use disorder, prior skin/soft tissue infections/bacteremia's secondary to IV substance use and was homeless.[7] The patient reported injecting usually in her hands but sometimes in her legs, and when she missed the vein in her legs, she noticed the areas around the injection site were ulcerated.

The mechanism for which xylazine may cause skin ulcers is not clearly understood. It is possible that an excipient contained with the substance causes an allergic type of reaction, or xylazine's effect on the vasculature causes ischemia and necrosis. Peripherally, xylazine causes vasoconstriction and decreased tissue perfusion.[7,8] Ischemia and tissue infection may therefore result from chronic injections of xylazine. Xylazine-associated skin ulcers have also been reported to be very painful, which may lead to further injections of xylazine since it does have anesthetic properties.[9] Xylazine-associated ulcers have been reported since the early 2000's which makes it less likely for an excipient or inactive ingredient from an adulterant to be the cause, considering xylazine ulcers have continuously occurred in many different areas since that time.[7,8] While not confirmed, the vasoactive effects of the drug and lack of appropriate dilution are plausible causes of xylazine-associated skin ulcers.

How to Test for Xylazine and Aegis Xylazine Positivity Rates

Testing for xylazine is not included in basic drug testing methods such as 12-panel rapid quick cups. Point-of-care test cups that many providers may use to screen for substance use often do not include the capability to test for NPS compounds such as xylazine. Even high-complexity laboratories with definitive testing methods and sophisticated laboratory equipment may not test for xylazine. A robust testing methodology must be developed

and implemented to test for NPS compounds, including xylazine. Aegis offers definitive testing for xylazine and, while not every client has the need to test for NPS drugs, testing for xylazine has increased markedly through 2022. Unfortunately, the positivity rate also increased from 0.90% in Q1 2022 to 1.9% in Q4 2022 (data through 12/15/22).

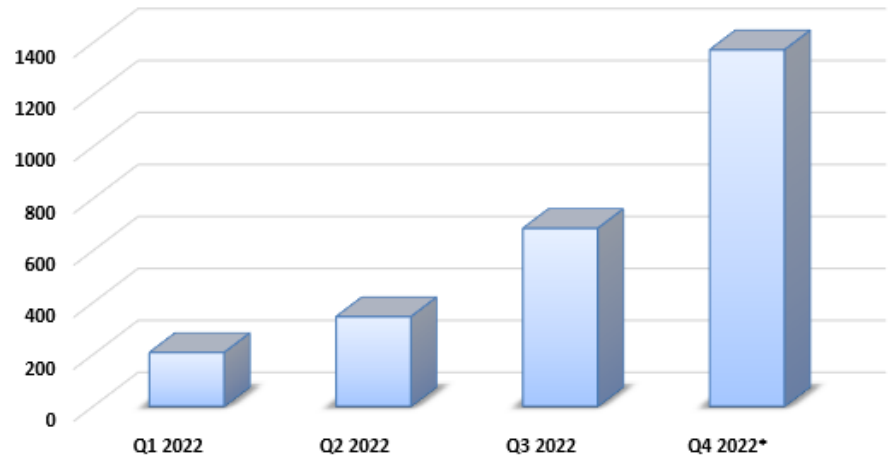

Figure 3: 2022 Xylazine Detection
**Q4 through 12/15/22*

The number of positive xylazine samples by quarter in 2022 is shown in Figure 3. This increased trend in positive samples is likely the result of both an increase in testing, as well as an indicator that xylazine in well-dispersed in illicit drug supplies across the country.

Xylazine is rarely detected alone. Figure 4 shows the most commonly detected co-positive substances in 2022. Fentanyl, fluorofentanyl, and methamphetamine were the top 3 most commonly co-detected substances with xylazine throughout 2022 although their rankings varied by quarter slightly. The 4th most commonly co-detected substance was cotinine (nicotine metabolite), buprenorphine, cocaine, and methadone, for Q1, Q2, Q3, and Q4, respectively. This data suggests that individuals who are exposed to xylazine also may be struggling with polysubstance use.

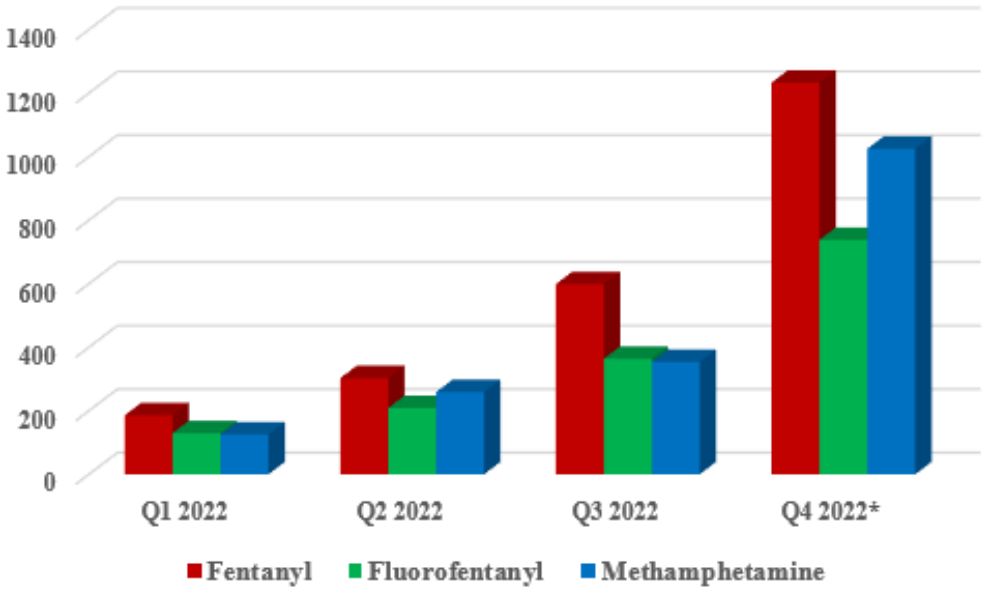

Figure 4: Most Frequently Detected Co-Positive Substances with Xylazine
**Q4 through 12/15/22*

The illicit drug supply has seen a remarkable increase in new NPS compounds over the last few years. Our data suggests xylazine use in particular is widespread across the United States, having been detected in most states where testing was ordered, with certain areas having higher frequencies of positive samples, likely due to test ordering patterns or a portion of testing from higher-risk individuals. Despite these limitations, xylazine positivity appears to be rising in prevalence in Aegis' toxicology testing, highlighting the need for broader awareness of NPS like xylazine, as well as healthcare provider education about the effects and adverse events resulting from NPS use.

NOTICE: The information above is intended as a resource for health care providers. Providers should use their independent medical judgment based on the clinical needs of the patient when making determinations of who to test, what medications to test, testing frequency, and the type of testing to conduct.

References:

1. Early Warning Advisory on New Psychoactive Substances. United Nations Office on Drugs and Crime. Accessed December 28, 2022. https://www.unodc.org/LSS/Page/NPS
2. Ruiz-Colón K, Chavez-Arias C, Díaz-Alcalá JE, et al. Xylazine intoxication in humans and its importance as an emerging adulterant in abused drugs: a comprehensive review of the literature. *Forensic Sci Int* 2014; 240:1–8.
3. Rompun (xylazine) [package insert]. Overland Park, KS: Dechra Veterinary Products; 2022.
4. Xylazine February 2021. Drug Enforcement Administration. Accessed December 22, 2022. https://www.deadiversion.usdoj.gov/drug_chem_info/Xylazine.pdf
5. FDA warns about the risk of xylazine exposure in humans November 8, 2022. Food and Drug Administration. Accessed December 22, 2022. https://www.fda.gov/media/162981/download
6. Greene SA and Thurmon JC. Xylazine—a review of its pharmacology and use in veterinary medicine. *J. Vet Pharmacol Ther* 1988; 11: 295-313.
7. Malayala SV, Papudesi B, Bobb R, et al. Xylazine-Induced Skin Ulcers in a Person Who Injects Drugs in Philadelphia, Pennsylvania, USA. Cureus 2022; 14: 1-6.
8. McNinch, JR; Maguire, M; Wallace, L. A Case of Skin Necrosis Caused by Intravenous Xylazine Abuse. Abstract published at SHM Converge 2021. Abstract 559 Journal of Hospital Medicine. https://shmabstracts.org/abstract/a-case-of-skin-necrosis-caused-by-intravenous-xylazine-abuse/. December 12th, 2022.
9. Torruella RA. Xylazine (veterinary sedative) use in Puerto Rico. *Subst Abuse Treat Prev Policy* 2011; 6:7.