Illinois Xylazine Best Practices for Health Care Providers*

Xylazine, a non-opioid sedative commonly used in veterinary medicine, has become increasingly prevalent in the unregulated drug supply in the United States. According to the October 2022 Drug Enforcement Administration (DEA) Joint Intelligence Report, xylazine was first noted as an adulterant in Puerto Rico in the early 2000s through DEA reporting and laboratory analysis. Around a decade later, xylazine was documented as a drug of abuse on its own, which has continued to present.[1] While the presence of xylazine use is underreported likely both in its geographic distribution and in its contribution to overdose deaths, available data indicate xylazine use is widespread and impacting overdose mortality throughout the country.[2-4] Xylazine was detected in 45 Illinois overdose deaths in 2020 and has been detected in more than 200 overdose deaths in the state in 2022 (Illinois Department of Public Health, Vital Records).

Although found in combination with other substances, xylazine is commonly mixed with illicitly manufactured fentanyl. [5] In licit sales for veterinary use, xylazine is available in liquid form and sold in vials or preloaded syringes. These solutions are prepared at a concentration appropriate for administration by injection based on the general size and weight of the species. It is legitimately sold directly through pharmaceutical distributors and internet sites catering to veterinarians. However, xylazine is also readily available for purchase on other internet sites in liquid and powder form, often with no association to the veterinary profession nor requirements to prove legitimate need. A kilogram of xylazine powder can be purchased online from suppliers in China with common prices ranging from $6-$20 per kilogram. At this low price, its use as an adulterant may increase the profit for illicit drug traffickers, as its psychoactive effects allows them to reduce the amount of fentanyl or heroin used in a mixture. It may also attract individuals looking for a longer high since xylazine is described as having many of the same effects for users as opioids, but with a longer-lasting effect than fentanyl alone. Some users intentionally seek out heroin or fentanyl mixed with xylazine, while many are completely unaware it is included as an adulterant. Conversely, there are also users who try to avoid opioids mixed with xylazine, stating that it reduces the euphoria experienced with heroin or a heroin-fentanyl mix or that they fear its added effects.[1] Because xylazine is approved by the U.S. Food and Drug Administration (FDA) for use in veterinary medicine only, it is not classified as a controlled substance under the U.S. Controlled Substances Act.

As the prevalence of xylazine has increased in the unregulated drug supply, there have been subsequent increases in the number of hospitalizations for skin wounds associated with substance use.[6] Xylazine can cause skin wounds that are not associated with environmental factors (such as living unhoused and/or lacking access to hygiene facilities), but rather with use of the substance itself.[7-8] <u>These complex wounds often occur at skin sites associated with injection, but they can occur at skin sites that are not associated with injection and in individuals who don't inject substances.</u>[9] Early intervention in treating xylazine-related skin wounds can prevent them from progressing into severe necrotic skin ulcerations. For more information, see **Appendix A**.

People who use drugs (PWUD) may be interested in testing their substances for xylazine prior to using them.[10] Immunoassay drug checking technology, like fentanyl and xylazine test strips, are available commercially. [11-12]

Surveillance and point-of-care drug checking programs are available in Chicago with drug-checking programs expanding into new counties. Current drug-checking data from Illinois are showing that xylazine has been detected in 32% of opioid samples in 2023 (drugdata.org).

Xylazine-Involved Overdose Deaths

Xylazine's presence in the unregulated drug supply and its contribution to overdose deaths is widespread and

***Adapted from NYS OASAS Medical Advisory Panel (MAP) Xylazine Guidance**

increasing.[4] Xylazine is an alpha-2 adrenergic agonist that causes profound sedation and central nervous system (CNS) depression. This can contribute to a blunted response to airway occlusion much like the effects from other sedatives, such as benzodiazepines and barbiturates. Because of xylazine's co-occurrence with fentanyl, the sedation that it causes has synergistic effects with the respiratory depression caused by opioids, which contributes to increases in overdose mortality.[13]

Xylazine likely is highly underrecognized in most overdose situations. Because it is not an opioid, xylazine overdose is not responsive to naloxone. Naloxone has become the standard and often the only response to overdoses. However, most overdoses involve multiple substances, making polysubstance overdose recognition and response an important strategy to reduce overdose deaths.[14-15] Xylazine often is mixed in with fentanyl, therefore naloxone administration still is the first recommended step in responding to an overdose; however, it should be followed by other lifesaving interventions, such as rescue breathing. See **Appendix A** for more information on xylazine overdose recognition and response. Because drug checking is not available in most jurisdictions, and xylazine is not included routinely on toxicology tests in health care settings, much of the available data on xylazine is from postmortem forensic testing of overdose deaths. The existing research indicates almost all overdose deaths that involved xylazine also involved fentanyl.[4,16,17] In 2021, 12.2% of the fentanyl-related deaths in Cook County and 6.1% of all fentanyl-related deaths statewide, involved xylazine.[18]

While xylazine can be detected in post-mortem testing, it may not be included routinely on the death certificate. However, the available data indicate xylazine is widespread, increasing in prevalence, and contributing significantly to overdose mortality.

Nationally, xylazine was present in 1.8% of all overdose deaths in 2019 with fentanyl present in more than 98% of xylazine-involved overdose deaths.[3] Provisional data from the U.S. Centers for Disease Control and Prevention (CDC) indicate xylazine was present in 5.6% of opioid-involved overdose deaths in 2022.[19] This has prompted national attention to increase the awareness about xylazine among PWUD, substance use disorder treatment and harm reduction providers, law enforcement, and the wider medical community and to align stakeholders for the development of best practices to address xylazine.[9,20-22]

See **Appendix B** for frequently asked questions about xylazine.

Appendix A: Nascent Best Practices for Xylazine

1. **Harm Reduction Strategies for Xylazine**

Harm reduction strategies for people who may be using xylazine need to be tailored to address the profound sedating effects that occur from this substance, especially in the first 20-30 minutes after use.[5,23-25] When using substances that contain xylazine, a person can be immobilized for hours,[24-25] putting them at risk for physical and sexual assault, and physical health complications, such as compartment syndrome, pressure ulcers, and blood clots. Because of these potentially life-threatening risks, in addition to existing harm reduction practices, there are specific strategies to support persons who use substances that may contain xylazine.

Xylazine-focused harm reduction strategies:[26,27]

- Have someone with you when using or use the Never Use Alone Hotline (800-484-3731).
- Start low and go slow.
- Try to avoid mixing substances.
- Test your substances.
    - Use fentanyl test strips to test substances for the presence of fentanyl prior to using them.
    - Use xylazine test strips to test substances for the presence of xylazine prior to using them.
- Since the persons who are using substances may become deeply sedated up to eight hours:[24-25]
    - Try to use it in a safe location, with belongings securely stored.
    - Try to be in a comfortable seated position.
        - It is important to be in a position that doesn't cut off circulation to the arms or legs.
        - If injecting substances, use a flexible tourniquet that can be removed easily.
    - Individuals deeply sedated who cannot move themselves easily should be moved (repositioned) every two hours:
        - Roll the individual to the opposite side.
        - Smooth out the skin.
        - Gently massage/rub areas that appear red or swollen.
        - Keep skin as clean as possible and flex (bend) the joints.
    - When the person awakens, exercise the limbs to improve the circulation and prevent blood clots.
        - Monitor for signs of a blood clot over the next 48 hours or more.
            - ◊ Signs of a blot clot usually include new-onset redness, swelling, and/or pain in one lower extremity but may be asymptomatic and have no visible abnormalities.
- Connect PWUD with a drug checking program so they can be aware of the substances present in the unregulated drug supply in their community, including xylazine.
    - Surveillance drug checking is available through The Chicago Recovery Alliance. Visit their website for schedules.
- Learn how to perform rescue breathing and keep naloxone nearby so someone can administer it to persons using substances if they experience an overdose.
    - In the event of a suspected overdose, emergency medical services (EMS) should be activated (e.g., call 911).
    - Xylazine most frequently is mixed in with fentanyl.
        - Naloxone will reverse an opioid-related overdose and should be administered first, followed by rescue breathing.
            - ◊ Once the first dose of naloxone is administered, the responder should wait two minutes before giving an additional naloxone dose.

- Because xylazine is not an opioid, rescue breathing is a critical part of xylazine-involved overdose response.
  - Include face shields in naloxone kits to perform mouth-to-mouth resuscitation more safely.
  - To open the airway, maneuvers such as a head tilt and chin lift may be necessary.
  - Use an oral or nasal airway, bag valve mask (e.g., Ambu bag), supplemental oxygen, and pulse oximetry, if available.

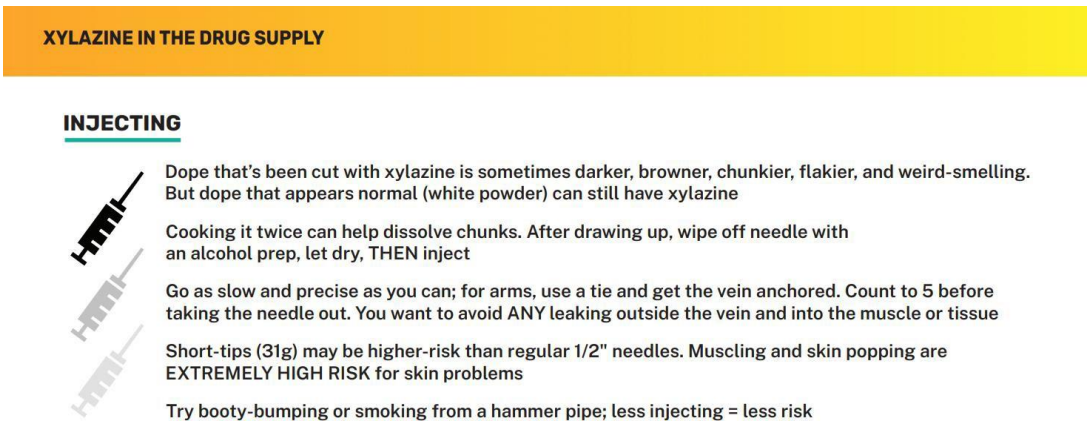
2. Preventing, Recognizing, and Addressing Xylazine-Related Skin Wounds

Preventing Xylazine Wounds

Safer injection education and wound care are important for persons who use substances with or without xylazine present. There is an increased risk for developing skin wounds when injecting substances that contain xylazine. See below for general safer injecting practices, including specific strategies to stay safer when using substances that may contain xylazine. For more information on safer injection, visit the National Harm Reduction Coalition (NHRC), NASTAD, and Bevel Up.

See **Figure 1** for xylazine safer injection practices found in the Xylazine in the Drug Supply guide developed by the National Harm Reduction Coalition (NHRC) based on advice from people who use/have used xylazine.[27] Because xylazine is an emerging and novel substance, these are nascent practices shared within communities of PWUD to reduce the harms from xylazine. It is possible that cooking a substance twice to dissolve all chunks may ensure there is an even distribution to prevent one specific part of the skin and/or body from receiving a disproportionate amount of the substance, thereby potentially reducing the risk for developing wounds.

Figure 1. Xylazine Safer Injection[27]

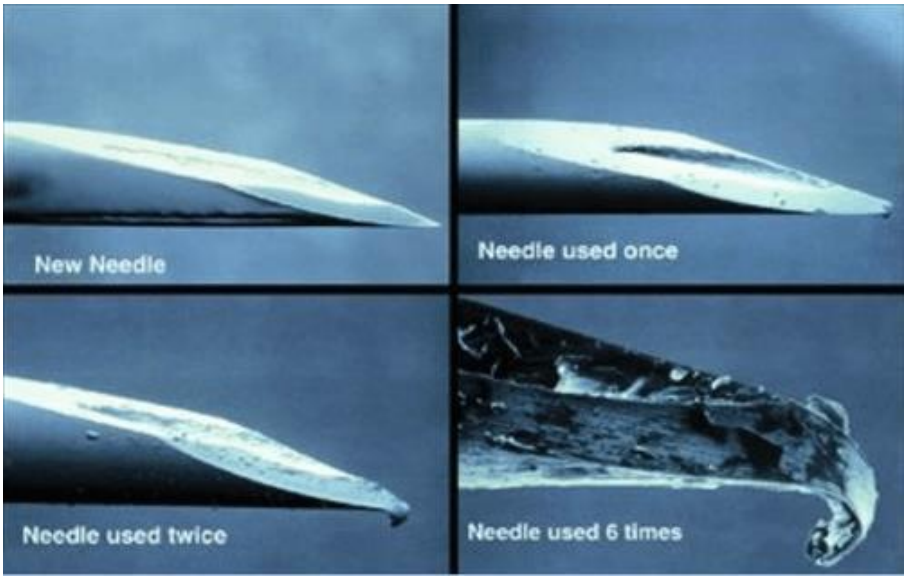


In addition to the risk of developing injection-related skin wounds, insufflation of substances that contain xylazine can contribute to damage inside the nose resulting in blood and tissue discharge from the nostril.[28] Engagement around trying other ways to use substances besides injection, such as ingestion, rectal insertion (booty bumping), smoking, or insufflation with an atomizer, may help reduce some of the risk for developing xylazine wounds and/or nasal damage.[27-28] However, xylazine wounds can occur at skin sites that are not associated with injection and in individuals who don't inject substances;[9] therefore, xylazine skin wounds still may occur despite using these alternative routes of administration. See the ***Recognizing and Addressing Xylazine Wounds*** section for more information on caring for xylazine wounds.

General and xylazine-specific safer injection practices:[30-33]

- Access to safer injection kits that include:[33]
    - Clean syringes
        - It is important that people who inject substances have access to a new syringe every time they inject **(see Figure 2).**
    - Cookers (aluminum caps)
        - It is important that people who inject substances have access to their own cooker and do not share cookers.
    - Cottons (filters)
        - It is important that people who inject substances have access to their own cottons and do not share cottons.
    - Fentanyl Test strips
    - Xylazine Test strips
    - Alcohol pads
    - Sterile water vials
    - Gauze
    - Soap or hand sanitizer (to keep hands clean)
    - Tourniquets
- Keep the injection site clean and dry.
    - Before injecting, clean the site with an alcohol pad.
        - When using an alcohol pad, clean the site by wiping in the same direction.
    - Avoid picking at the skin around the site of injection or other areas of the body.
- Do a test shot and wait to see the effects.
- Rotate injection sites frequently.
    - Avoid injecting at the site of a wound or infection.
- Cut back on or stop xylazine use (if feasible).
- Visit your local harm reduction program to access safer injection education and supplies.
    - Find a harm reduction program.

Figure 2. Needle Tip Wear Over Time[32]



Recognizing and Addressing Xylazine Wounds

Xylazine wounds are underrecognized by medical providers and have an unknown etiology. These wounds can occur at skin sites that are not associated with injections and in individuals who don't inject substances.[9] Xylazine wounds often begin as small superficial lesions with a white or purple center with a dark red fluid discharge. These wounds initially appear innocuous but will become more severe if left untreated. The basic tenets of wound care are to keep the wound moist, free of debris, absorb excess drainage, manage necrotic tissue, and cover with an appropriate dressing.[34]

If a wound begins to develop[34-37]

- Wash hands before tending to wounds.
- When possible, keep the wound clean with soap and sterile water or saline.
    - It is recommended to avoid cleaning wounds with alcohol, hydrogen peroxide, or hand sanitizer because they damage healing wound tissue.
- Apply barrier ointment to peri-wound skin with gauze or with a gloved or clean hand. Protecting the skin around a wound from drainage will prevent erosion of healthy tissue and moisture associated maceration. Some recommended ointments suitable for barrier ointment include:
    - Vaseline
    - Petrolatum
    - Diaper cream/ointment with zinc oxide
    - Medical grade incontinence/barrier ointments
- Manage necrotic tissue in the wound through a mode of debridement, such as conservative sharp, enzymatic, autolytic, or referral for surgical debridement as indicated. [34-37]
    - Autolytic debridement through moist wound healing and careful dressing selection is a slow but less painful option readily employable in the office setting.
    - Medical grade honey and hydrogel can be used to rehydrate dry necrotic tissue. Attempt to remove loosely adhered necrotic tissue during wound irrigation with gauze.
    - Collagenase (Santyl) is the only FDA approved enzymatic debridement agent. It can be cost prohibitive in under resourced populations and requires prior authorization in Illinois Medicaid patients.
    - Avoid application of topical antibiotics to the wound as this can contribute to resistant bacteria. All wounds are colonized with bacteria but not all wounds are infected and require antibiotics.
    - Povidone iodine 10% can be applied to heavily colonized wounds to disrupt biofilm. Application with saline soaked gauze for a minimum of 15 seconds is required with subsequent irrigation. Povidone iodine is the broadest spectrum and least cytotoxic wound antiseptic. Avoid use in those with underlying thyroid disorders.
- Cover a wound bed with a wound contact layer to prevent absorbent dressings from adhering followed by an absorbent pad or non-adherent dressing to absorb secretions from the wound.[36]
    - Recommended wound contact layer: Acetate mesh impregnated with petrolatum (non-adhering dressing, Adaptic™ or similar).
    - Avoid use of xeroform or petroleum gauze which are occlusive dressings. Recommended absorbent dressings are ABD pads or nonadherent pads.
    - Secure dressings with stretch gauze or elastic bandages as tape may damage wound margins.
    - Avoid wrapping the wound too tightly or too loosely.
    - Change dressing daily, if possible.
- Continue to check the wound for possible infection.
    - While xylazine wounds are not themselves infectious, they can become infected secondarily with bacteria.
    - Wound infections can manifest as cellulitis spreading from wound margins.
    - Additionally, wound infections can contribute to osteomyelitis and sepsis.

- Symptoms of a secondary bacterial infection include:
  - Redness
  - Swelling
  - Worsening pain
  - Fever
  - Tiredness
  - Increased drainage (pus or fluid)
  - Drainage that is yellow/tan/green
  - Odor/smell from the wound
  - Wound feels hot to the touch
  - Wound increases in size with a black, yellow, or tan color
- Seek medical attention if any symptoms of infection begin to develop.
  - Debridement in the emergency department, an outpatient setting, or a surgical setting may be required to effectively treat xylazine wounds that have progressed.
  - If left untreated, xylazine-caused wounds may require significant treatment, including skin grafting or amputation as a last resort.

Motivational interviewing to address self-care is important when engaging around wound care.[28] It is also important that wound care strategies are individualized to the needs and environment of the person who will be caring for their wounds.[33] More information on xylazine-caused wound care can be found at NASTAD and The Harm Reduction Nurses Association.

3. Xylazine-Involved Overdose Recognition and Response

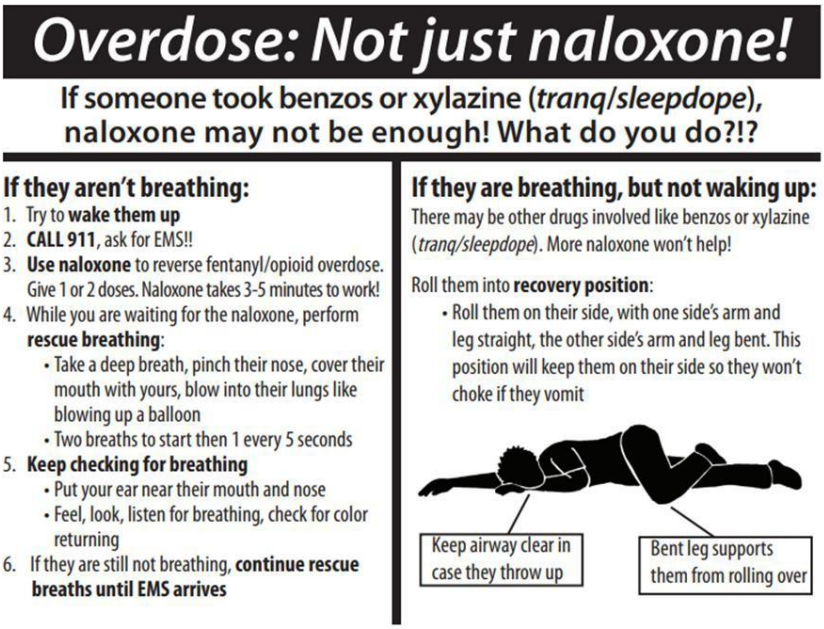
Because xylazine is often found mixed with fentanyl (an opioid) in the unregulated drug supply, when responding to an overdose, assume an opioid is involved and administer naloxone. Once administered, the responder should wait two minutes before giving an additional naloxone dose. However, if an individual is not responding to 1-2 doses of naloxone, suspect that it is a polysubstance overdose with possible xylazine involvement.[38] See **Figure 3** for a fact sheet on recognizing and responding to polysubstance overdoses.

If responding to a known or suspected xylazine-involved overdose, the response should include rescue breathing, placing the person in the recovery position, and ensuring an open airway.[32,38] Overdose reversals that have xylazine involvement may not present the same as overdose reversals without xylazine involvement.[28] After administering naloxone and performing rescue breathing, a person who is experiencing an overdose from both opioids and xylazine may begin breathing again but remain sedated.[28] Appropriately recognizing and responding to a polysubstance overdose also will prevent over administration of naloxone that can cause severe precipitated opioid withdrawal.

In addition to checking for breathing, check for a pulse. If there is no pulse, the recommendation is to perform chest compressions or full cardiopulmonary resuscitation (CPR), if trained to do so. If not trained to perform CPR, activate EMS immediately.

Having a low threshold for activating EMS when responding to a suspected xylazine-involved overdose is recommended. When EMS respond to a suspected xylazine-involved overdose, continuous pulse oximetry and airway monitoring/control using bag valve masks (e.g., Ambu bags), oral and nasal airways, or intubation and ventilator support may be needed.[32] There currently are no medications approved for use in humans that will reverse xylazine's effects in the event of an overdose.

Figure 3. Polysubstance Overdose Recognition and Response[39]



4. Xylazine Clinical Recognition and Supportive Care

The effects of xylazine are similar to other alpha-2 agonists, such as clonidine, dexmedetomidine, oxymetazoline, tetrahydrazoline, tizanidine, and lofexidine. Xylazine causes profound sedation, but it does not act on the imidazoline receptors, so it does not cause hypotension or bradycardia.[5,40] Xylazine is lipophilic, diffuses widely in the body, and has good bioavailability.[13] Depending on the route of administration, xylazine takes effect in 1-2 minutes and the duration of effect lasts between 3 and 4 hours, on average, but can last up to eight hours.[24-25] See **Table 1** for clinical findings and supportive care considerations for xylazine.

Table 1. Xylazine Clinical Findings and Supportive Care Considerations[24-25]

Possible Clinical Findings (especially with polysubstance use)	Supportive Care Considerations
Blood pressure instability	Avoid CNS depressants
Heart rate instability	Give oxygen
Heavy sedation, unconsciousness, coma	Consider IV fluids
Respiratory depression or arrest	Consider IV atropine (no clear data to support this)
Hyperglycemia (with rebound hypoglycemia)	Ventilator assistance, possible intubation
Cardiac arrythmias	Consider IV insulin
Miosis	Consider ECG continuous monitoring
Hyporeflexia	Consider pulse oximetry continuous monitoring
CNS depression	Consider replacement of potassium and magnesium
Enuresis (urinary incontinence)	Hemodialysis is not effective at removing xylazine due to its lipophilicity

There is an under recognition of xylazine withdrawal by clinicians that negatively impacts PWUD and their ability to receive quality care.[41-43] While there are no current evidence-based recommendations for the management of xylazine withdrawal syndrome, it is important to recognize and sufficiently treat xylazine withdrawal symptoms. Because xylazine often is mixed in with fentanyl in the unregulated drug supply, xylazine withdrawal symptoms can occur simultaneously with and appear similar to opioid withdrawal syndrome (OWS). If a person is not experiencing relief from OWS management, consider xylazine involvement and modify the treatment to address both OWS and xylazine withdrawal. See **Table 2** for the comparisons between xylazine and opioid withdrawal syndromes.

Although xylazine withdrawal is not a well-defined syndrome, non-specific anxiety is the primary symptom.[9,44,45] Other symptoms of xylazine withdrawal can appear much like the symptoms associated with clonidine and dexmedetomidine withdrawal.[5] There are typically no significant vital sign abnormalities or seizures associated with xylazine withdrawal. The duration of xylazine withdrawal typically lasts several days but it can be protracted, lasting for several weeks.

Table 2. Comparisons Between Xylazine and Opioid Withdrawal Syndromes

Opioid Withdrawal Syndrome[46]	**Xylazine Withdrawal Syndrome [9,44,45]**
Myalgias Hypertension Tachycardia Diaphoresis Tachypnea Pupillary dilation Hyperreflexia Hyperthermia Photophobia Diarrhea Nausea/vomiting Insomnia Piloerection “goose flesh” Lacrimation or rhinorrhea	Non-specific anxiety (primary symptom) Hypertension Tachycardia Diaphoresis Restlessness Agitation Irritability

People are more likely to remain in treatment for their substance use disorder, skin wounds, or other health needs if all their withdrawal symptoms are managed adequately and they are comfortable. Negative experiences with poorly managed or untreated withdrawal symptoms can result in future health care avoidance, later presentations of medical problems, more complicated care, and worse medical outcomes. Case reports suggest there are benefits to using other alpha-2 agonists like clonidine, tizanidine, and dexmedetomidine for managing xylazine withdrawal symptoms.[5,9,25, 44,45]

The Illinois Department of Public Health, based on the recommendations of local addiction medicine and toxicology experts, recommends considering the following medications for the inpatient management of xylazine withdrawal:

- Clonidine (dose limited secondary to side effects of hypotension and bradycardia)
- Tizanidine (dose limited secondary to side effects of hypotension and bradycardia)
- Dexmedetomidine
- Guanfacine
- Ketamine

- Gabapentin
- Pentobarbital
- Antipsychotic medications
- Lofexidine (dose limited secondary to side effects of hypotension and bradycardia)

Depending on the severity of the symptoms and concomitant other withdrawal syndromes, it may be possible to manage xylazine withdrawal in medically managed/medically supervised withdrawal and stabilization programs, inpatient rehabilitation programs, or outpatient/office-based settings. It is important, especially for clinicians, to recognize and to manage xylazine withdrawal while providing acute medical care for PWUD, such as wound care.[42]

Appendix B: Frequently Asked Questions on Xylazine

Why is xylazine showing up in the unregulated drug supply?

There appears to be an ecological connection between xylazine and fentanyl in the unregulated drug supply.[3] Ethnographic data describe xylazine as giving fentanyl "legs," meaning xylazine extends the duration of fentanyl's effect. Historically, the unregulated drug supply has shifted towards more potent substances in response to the prohibition of other substances.[47] These shifts lead to greater risk for harm and overdose[48] as currently seen with xylazine.

Are xylazine test strips available?

Xylazine test strips (XTS) recently became available commercially in the United States. Two recent studies on the validity and utility of XTS found they are effective in their sensitivity (100%), specificity (85%), and precision (91%) to detect xylazine.[11,12]

This research determined xylazine can be detected with the test strips by diluting a small sample of the substance in water in a similar way as done with fentanyl test strips. Like fentanyl test strips, there also is a risk for false positives in samples that have high concentrations of certain substances. A false positive (the measure of specificity) occurs when a test strip indicates xylazine is present in the substance when it isn't. False positives are more common when diphenhydramine, lidocaine, levamisole, MDMA (e.g., Molly or ecstasy), or methamphetamine are present in the substance.[11,12] Future research is needed to determine the dilution instructions for using XTS to test samples with those substances present. To learn more about the research on XTS, visit CFSRE here and here.

How can I know what substances are present in the community where I live?

Drug checking programs are becoming more widely available in Illinois to help both communities and PWUD test local drug supplies. Connecting PWUD with a harm reduction program that has either surveillance or point-of-care drug checking technologies available can help them stay informed about the substances that are present in the unregulated drug supply in their community. Drug-checking programs are available through The Chicago Recovery Alliance with additional sites in progress. Point-of-care drug checking technologies allow for a sample to be tested rapidly and the results relayed to the person who intends to use it so they can adjust their substance use accordingly.

How do additives like xylazine impact the initiation of medications for opioid use disorder (MOUD)?

The American Society of Addiction Medicine is developing guidance on the initiation of buprenorphine in the setting of frequent exposure to high potency synthetic opioids. This guidance briefly will address other additives, including xylazine, in the unregulated drug supply. For now, recognizing and managing opioid and xylazine withdrawal is important when initiating MOUD and providing wound care in clinical settings.

Do xylazine wounds require hospitalization?

If detected and treated early, xylazine wounds can be managed without requiring hospitalization.[28] PWUD, regardless of how they use substances, should keep an eye out for small white or purple spots that may appear on the skin. Because xylazine-induced wounds can occur in locations not associated with injection and in individuals who don't inject substances, all PWUD should have access to wound care education and supplies.

There are three main tenets to wound care: keeping the wound moist, keeping the temperature of the wound regulated, and keeping the wound covered.[34] If a wound worsens or becomes infected secondarily with bacteria, it is important to seek care as soon as possible. Street outreach teams are an important resource for providing PWUD with education and supplies to prevent wounds, support and supplies for wound care, and warm handoffs to medical providers when needed. When providing wound care support, health care professionals also should monitor the person actively and treat any prolonged withdrawal symptoms that aren't relieved by medications used to manage opioid withdrawal

symptoms.

Does naloxone work on xylazine?

Because xylazine is not an opioid, naloxone (an opioid receptor antagonist) will not reverse xylazine overdoses. However, because xylazine frequently is mixed in with fentanyl in the unregulated drug supply[3] it is still recommended that naloxone is administered for any suspected overdose. If a person is not responding after 1-2 doses of naloxone, suspect that it is a polysubstance overdose with possible xylazine or other sedative involvement. When responding to a suspected overdose, EMS should be called. Polysubstance overdose response should include rescue breathing, placing the person in the recovery position, and ensuring an open airway.[38] Administering more doses of naloxone in the event of a polysubstance overdose will not help reverse the non-opioid contributions to the overdose and may cause the person to go into severe precipitated opioid withdrawal.

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