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To: North Carolina Health Care Providers
From: Kimberly McDonald, MD, MPH, Medical Director, NC DPH Chronic Disease and Injury
Subj: Xylazine Update for North Carolina Clinicians

This correspondence updates the [May 2023 Xylazine Exposure Guidance](#) and offers new insights with immediate implications for clinical practice and frontline public health. [Source article.](#)

Brief Overview of Emergence and Prevalence

- Xylazine, a veterinary anesthetic, has been intermittently reported in human exposure cases in Spain, Germany, Canada, and the United States since the 1970s.
- Sustained use of xylazine for euphoric effects began in Puerto Rico around 2001, with sporadic detection in street drugs in the U.S. since 2006, particularly on the East Coast and California.
- In October 2022, the FDA posted a [communication to health care providers](#) about the risks to patients who may be exposed to Xylazine
- The federal government designated “fentanyl adulterated or associated with xylazine” as an emerging drug threat in April 2023.
- Street names include, Tranq, AnaSed, Rompún, Horse tranquilizer, Anestesia de caballo
- According to the [UNC Street Drug Analysis Lab](#) xylazine is regularly detected in drug samples tested in NC. It has been found mostly mixed with fentanyl and heroin.
- While xylazine is often present in toxicology results from overdose deaths, there is insufficient evidence that xylazine alone causes fatal overdose or is a contributing factor when combined with other drugs. Fentanyl is usually indicated as the cause of fatality.
- The use of xylazine may lead to serious skin wounds regardless of intake route. People who have never injected can manifest xylazine wounds.
- The prevalence of xylazine in NC underscores the importance of clinician awareness about local trends in the street drug supply.

Pharmacological Profile

- Xylazine is a veterinary sedative with no FDA approved human uses.
- Xylazine is usually smoked, snorted, or injected along with fentanyl (and other substances).
- Xylazine acts both on alpha-2-adrenergic receptors ($\alpha 2$ -AR) and, contrary to previous assumptions, also shows activity as a [full agonist at kappa opioid receptors \(\$\kappa\$ OR\)](#), a potential mechanism for its naloxone sensitivity. In pharmacological studies, the κ OR activity is stronger than $\alpha 2$ -AR activity.
- It has complex pharmacological interactions with other receptors, including potential crosstalk between adrenergic and opioid, dopamine, and sigma receptor systems.
- Stimulation of alpha-2 adrenergic receptors in the CNS can cause decreased pain perception, drowsiness, muscle relaxation, bradypnea, bradycardia, hypotension, and glucose abnormalities. In veterinary practice, anemia (blood iron deficiency) has also been noted with xylazine, and clinical case reports in humans have enough credence to suggest monitoring patients using xylazine-fentanyl for hemoglobin. [Hyperglycemia](#) has also been reported in the clinical veterinary literature.

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AN EQUAL OPPORTUNITY / AFFIRMATIVE ACTION EMPLOYER

- Onset of drug effect is rapid (1-2 min), with a duration of 4-6 hours depending on dose, route, and whether mixed with other drugs. Potential intensification of other drug effects can complicate overdose presentation and treatment.
- The physiological metabolites of xylazine are also active. Unlike fentanyl, these manifest as a return of sedation 1-2 hours after the initial immediate sedation wears off. People using xylazine-fentanyl may not be expecting this second wave of heavy sedation and may be caught unaware in the midst of other activities.

Clinical and Public Health Challenges

- Management of xylazine exposure is complicated by severe skin ulcers, agitated withdrawal syndrome, and lack of approved antidotes or withdrawal support medications.
- Naloxone precipitates withdrawal from xylazine and fentanyl/xylazine coadministration.
- A recent [study](#) suggests naloxone can be effective in xylazine-related cases and should be administered in suspected opioid overdose.
- Heavy sedation for extended periods in awkward positions can cause painful muscle pains and radial nerve damage (“[Saturday Night Palsy](#)”).
- Heavy sedation in unsecured environments can also make people vulnerable for theft of belongings and assault.
- Xylazine is reliably detectable in urine testing for 24 hours after use. Beyond that time, level of consumption, body mass composition, metabolic factors may change clearance rates and detectability.

Wound Care

- There is no universally accepted protocol for xylazine wound management. The scientific literature describes many different management techniques, but the general approach is debridement and pain management, followed by hydrating dressing and wrapping. Wound healing may take 2-4 months if further exposure can be avoided. Conceptually, the wounds heal like burns, not abscesses.
- Follow-up care can be conducted at home. In some parts of North Carolina, community EMS and home care nurses do weekly house calls to help with wound care and dressing changes. Harm reduction programs distribute at-home wound care kits of [differing composition](#).
- Unnecessary limb amputations have been reported in North Carolina during the early days of xylazine emergence in our state. Wound care clinics and burn units should be considered for consultations before major surgical intervention.
- Xylazine wounds diagnosed at early stages have quicker healing times, provided reduced or no further exposure to xylazine. For patients who may be using xylazine-fentanyl, asking “Do you have small wounds/bites/cuts that aren’t healing?” is an effective conversation starter. Educating patients on *early stage* xylazine wound appearance is critical to encourage earlier clinical presentation ([fact sheet](#) with illustrations).

Withdrawal and Overdose Management - supportive care is key; treat what you see, not the drug you think it might be.

- Administer naloxone and call 911 - the endpoint of naloxone success is not awakening; it's breathing,
 - If O₂ is at a safe level and breathing unlabored do not administer more than 2 doses (each 3-4 mg nasal, or 1mL of 0.4 mg/mL IM) naloxone (to avoid severe withdrawal, vomiting/aspiration, and rapid return to opioid use). Consult literature for suggestions for IV infusion rates.
 - If respiratory status stable, continue monitoring for airway monitoring. Full reanimation may not occur for 45min to 2h.
 - Evaluate and manage respiratory status related to concomitant presence of fentanyl or other opioids. Also consider concurrent benzodiazepine toxicity and/or withdrawal, as bromazolam and other potent benzodiazepines may be mixed in with xylazine-fentanyl. (See also [case report of xylazine masking benzodiazepine withdrawal](#) from Duke).

- **NOTE:** Take home Naloxone kits are likely to remain effective beyond the expiration date or if stored in non-standard conditions for up to 28 days (e.g. hot cars). However, do emphasize importance of proper storage.
- Blood pressure should be monitored and managed if it becomes unstable. Xylazine was originally investigated as a blood pressure reducing medication, and other α 2-AR agonists lower blood pressure.
- Counterintuitively, overdoses involving xylazine-fentanyl may be [less severe](#) (e.g., less intervention, CPR, etc.) than fentanyl alone.
- Xylazine has been shown to [reduce fentanyl consumption](#) in animal models. Human ethnographic studies suggest that xylazine-fentanyl is cheaper *per day* (not per bag) because people use less.
- Notes about reversal
 - There is not currently an approved xylazine reversal agent for use in humans xylazine. Yohimbine and atipamezole are not clinical indicated at this time but reports of off-label use by community members has been reported.
 - Be aware that the person may breathe normally after receiving naloxone, but still be sedated from the xylazine and more naloxone may not be needed.
 - Patients should be educated about use of naloxone in the presence of potential xylazine adulteration to avoid incorrectly attributing these incidents to “naloxone-resistant fentanyl” or “naloxone-resistant opioids.”
 - Xylazine withdrawal symptoms include heightened anxiety, agitation, and paranoia, like those observed with withdrawal from κ OR agonist pentazocine.
 - For MAT inductions, the naloxone component of buprenorphine-naloxone may exacerbate xylazine withdrawal, as the naloxone is not fully sequestered in all patients.
 - Patients should be educated to use naloxone even in the presence of potential xylazine.

Understanding the Local Drug Supply

- You can keep a pulse on substance trends in the street drug supply by checking UNC Street Drug Analysis Lab [NC Xylazine Report](#) and [NC overdoses](#).
- Ratios of xylazine: fentanyl can vary 3-fold in either direction.

Xylazine Associated Adverse Event Reporting

- Health care professionals and patients are encouraged to report adverse events from possible xylazine exposure. This can be done via any one of the following:
 - [County Local Health Department](#)
 - [NC Poison Control](#) website or call **Fast Help** 1-800-222-1222. Toxicologists are available 24/7
 - American Association of Poison Control Centers 1-800-222-1222
 - Online FDA [MedWatch Adverse Event reporting](#)

Xylazine Patient Education

- Consider sharing this [Xylazine Quick Guide](#) with patients who use drugs or are involved with persons at risk. It contains basic information on xylazine along with important harm reduction messages and recommendations.
- Xylazine test strips are available to detect the presence of xylazine within their personal drug supply. However, a negative result does not rule out the possibility of xylazine presence in the drug sample.
- Xylazine test strips can be purchased online and may be available for reduced or no cost at local health departments or harm reduction coalitions.

Wound care

- Health care professionals who see patients with severe, necrotic skin ulcerations should consider repeated xylazine exposure as part of the differential diagnosis”.

- We recommend reviewing this brief [Xylazine Wound Care Guide](#) for specific management recommendations.

Additional Resources

- [CDC Stop Overdose](#)
- [National Harm Reduction Coalition](#)
- [FDA xylazine health alert](#)
- [NASTAD Wound Care & Medical Triage for People Who Use Drugs](#)
- [NASTAD Webinar: Beyond the Alerts: Practical Guidance for Responding to Xylazine](#)
- [NC Harm Reduction Coalition](#)
- [NC Survivors Union](#)
- [NC Syringe Service Program Directory](#)
- [UNC Street Drug Analysis Lab](#)
- [Growing Threat of Xylazine and its Mixture with Illicit Drugs](#)

Best in Health,

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