Editorials

The Role of Xylazine in the Overdose Crisis

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Xylazine (street name tranq or tranq dope when combined with opioids) is a centrally acting alpha-2 adrenergic agonist. It is similar to clonidine and dexmedetomidine, which are widely used in veterinary practices as a sedative and anesthetic for large animals. Xylazine has been increasingly used as an adulterant mixed with recreational drugs such as fentanyl and heroin to intensify and prolong the euphoria induced by these opioids.[1] It has a variable duration of action in humans (8 to 72 hours), depending on the dose, route of administration, and drugs with which it is mixed.[1,2] Currently, there is no approved reversal agent for xylazine in humans.

Xylazine is typically dried into a powder to facilitate its addition to opioids, making it difficult to identify by its physical properties and increasing the risk of a fatal overdose. Xylazine can exacerbate typical opioid adverse effects (e.g., bradypnea, apnea, bradycardia, hypotension) and, with repeated use, can lead to xylazine dependence and associated withdrawal symptoms (e.g., irritability, anxiety, dysphoria). Xylazine overdose should be suspected in cases of apparent opioid overdose that do not respond to naloxone. Xylazine use is also associated with disfiguring skin and soft tissue infections, which were recently described in the *AFP* Community Blog.[3,4]

The combination of opioids and xylazine was first identified in the drug supply in Puerto Rico around 2001 and has been found in postmortem toxicology tests and drugs seized by the U.S. Drug Enforcement Administration in the continental United States since 2006.[5-10] The highest prevalence has historically been in Philadelphia, Maryland, and Connecticut, with recent increases in xylazine-related overdose deaths in the southern and western United States.[11,12]

In 2022, the U.S. Drug Enforcement Administration issued a public safety alert regarding the emerging threat of fentanyl mixed with xylazine.[9] Previously, the U.S. Food and Drug Administration released a warning to health care professionals regarding the harms associated with xylazine exposure, including delayed diagnosis and management of polysubstance overdose; severe, necrotic skin ulcerations; and interference with treatment of opioid use disorder (OUD).[13] The rapid rise and widespread geographic distribution of fentanyl adulterated with xylazine, and related morbidity and mortality, led the Office of National Drug Control Policy to name xylazine as an emerging threat.[14] This designation allocates new federal funds for "testing, treatment, harm reduction, comprehensive data collection and analysis, source identification and supply reduction, possible regulatory actions, and rapid conduct of basic and applied research."[15]

What can family physicians do? Although evidence is limited regarding best practices,[15] family physicians should have an awareness of the drug supply and understand the potential implications of xylazine to provide comprehensive and holistic care. This approach can be summarized with the HOPE mnemonic (harm reduction, OUD treatment if applicable, physical and emotional supports).

Harm reduction should include discussions about the unpredictable and inconsistent nature of street drugs, the risks of xylazine, overdose education, naloxone education, and safer use (i.e., not using drugs when you are alone, staggering use with other individuals to ensure someone is more alert, identifying access to sterile supplies, and skin monitoring).[16] Although it is important to discuss alternating injection sites, wounds can occur anywhere, not only at injection sites.

OUD treatment, including pharmacologic therapy (buprenorphine, methadone, and naltrexone) and aftercare recovery support, is an important public health service that family physicians can offer to individuals who have had a xylazine overdose (which in the United States typically occurs in the context of OUD). Pharmacologic interventions do not treat xylazine overdose or withdrawal specifically, but they are effective in treating OUD in isolation or in combination with xylazine exposure.

Physical and emotional supports for individuals with complications from xylazine use include managing intoxication and withdrawal concurrent with opioid withdrawal. Treatment can be challenging because anxiety and symptoms from incompletely treated opioid or xylazine withdrawal may cause individuals to leave the acute care setting. Treatment for xylazine intoxication is mainly supportive. Although other alpha-2 adrenergic agents (clonidine, tizanidine, guanfacine [Intuniv]) can assist with withdrawal,[17] the doses needed can exacerbate adverse effects of xylazine, such as bradycardia and hypotension. Benzodiazepines may be more effective for these individuals. Although clinician hesitancy to prescribe benzodiazepines is understandable, concerns can be allayed within a controlled acute care setting. Benzodiazepines may be appropriate in ambulatory settings, as well as selective serotonin reuptake inhibitors and other anxiety medications. Treatment of wound infections and wound debridement are important. Healing typically occurs over weeks to months, with the most effective treatment component being removal of the causative source (xylazine) whenever possible.

Although more research is needed to understand best practices around management of xylazine use, the foundation of our approach must be to ensure we are delivering nonstigmatizing, trauma-informed, person-centered care for patients and communities.

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