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Perspective

Xylazine — Medical and Public Health Imperatives

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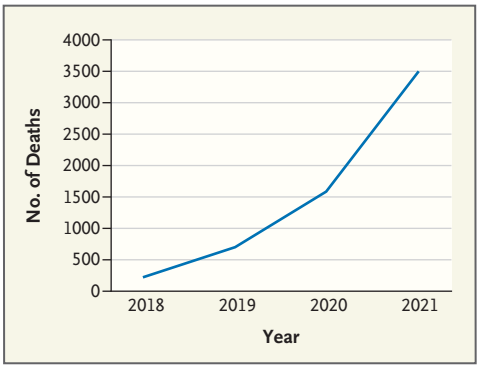
Increasing use of xylazine, most often in combination with other drugs such as fentanyl, is a rapidly growing threat to human health in the United States. Xylazine is an α_2-agonist in the same drug class as clonidine, lofexidine, and dexmedetomidine. It was initially studied for use in humans as an antihypertensive agent, but development for human use was discontinued because of adverse effects. Xylazine was approved by the Food and Drug Administration for use as a sedative in veterinary medicine in 1972 but isn't approved for use in humans.

Centrally acting α_2-agonist medications inhibit the release of norepinephrine and epinephrine. The effects on the central nervous system include sedation, analgesia, and euphoria. Reduced sympathetic outflow from the central nervous system causes decreased peripheral vascular resistance, heart rate, and blood pressure. Some α_2-agonists are approved for use in humans as antihypertensive agents, for sedation, and for mitigation of opioid-withdrawal symptoms to facilitate abrupt opioid discontinuation. This class of drugs is not regulated under the federal Controlled Substances Act and historically has been thought to be associated with a low risk of illicit use. People who use xylazine, however, may develop physiological dependence, have symptoms consistent with a xylazine-related substance use disorder, and have severe withdrawal symptoms (e.g., irritability, anxiety, and dysphoria) after abrupt discontinuation. Xylazine-withdrawal symptoms are not alleviated by the administration of opioids. The severity of such symptoms, combined with uncertainty about effective treatment options, may compel people to continue to use xylazine, since discontinuation without assistance often isn't feasible.

Xylazine appears to have entered the illicit drug supply in the northeastern United States as an additive to fentanyl. It can be consumed orally or by smoking, snorting, or intramuscular, subcutaneous, or intravenous injection. The drug's reported duration of effect is longer than that of fentanyl; adulteration of fentanyl with xylazine therefore probably enhances the euphoria and analgesia induced by fentanyl and reduces the frequency of injections.

The first illicit use of xylazine was reported in Puerto Rico around 2001. Xylazine was initially used in combination with a polydrug mixture, commonly referred to as a speedball, containing a stimulant (e.g., cocaine or amphetamine) and an opioid (e.g., heroin, morphine, or fentanyl). Xylazine was identified intermit-



Estimated Xylazine-Involved Drug-Poisoning Deaths in the United States, 2018–2021.

Data are from the Centers for Disease Control and Prevention WONDER data set and include drug-poisoning cases with codes T42.7 or T46.5 in the *International Classification of Diseases*, 10th revision.

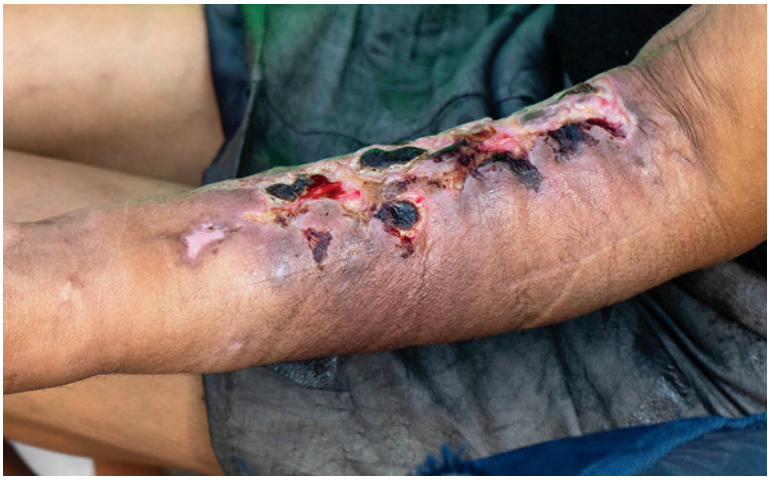
tently in drug samples collected in the continental United States between 2006 and 2018. Philadelphia and Connecticut appear to have been the epicenters of xylazine use in the continental United States, but use is rapidly spreading throughout the country.[1] The drug is known as "anesthesia de caballo" in Puerto Rico and "tranq" in Philadelphia (or "tranq dope" when combined with opioids, most often fentanyl). Xylazine was found in more than 90% of illicit drug samples tested in Philadelphia in 2021[2] and was identified in forensic toxicology samples from 36 of 49 states that were tested in June 2021.[3] As of March 2023, fentanyl mixed with xylazine had been found in drug seizures in 48 states. According to data from the Centers for Disease Control and Prevention, the estimated number of drug-poisoning deaths in the United States involving xylazine grew from 260 in 2018 to 3480 in 2021, an increase of 1238% (see graph), with the highest numbers of such deaths during that period reported in Pennsylvania, Maryland, New York, and Connecticut.

Patients presenting with xylazine intoxication may have central nervous system depression, hypotension, and bradycardia. Clinicians may not recognize the contribution of xylazine to a person's symptoms, since many aren't aware of growing use and rapid point-of-care testing for xylazine isn't widely available. Respiratory depression has been reported in people using xylazine, probably because the drug increases the risk of opioid-induced respiratory depression. Naloxone can reverse opioid-induced respiratory depression but doesn't reverse the effects of xylazine. Although naloxone administration remains a vital treatment for any overdose that may involve opioids, additional supportive care may therefore be necessary in the treatment of xylazine overdose. Such care may include maintaining a patent airway, administering supplemental oxygen, performing rescue breathing when indicated, and treating hypotension as needed. There is no xylazine-reversal agent currently approved for use in humans.

Limited data are available to guide clinical decision making related to the treatment of xylazine withdrawal in inpatient settings. Some institutions are exploring the use of dexmedetomidine infusions for xylazine-withdrawal symptoms in the intensive care unit,[4] whereas others are exploring the use of clonidine and lofexidine in inpatient units. As compared with clonidine, lofexidine may be associated with a lower incidence of adverse effects, including hypotension, when used to treat symptoms of withdrawal. Although tapering these medications over 5 to 7 days may be appropriate, there are limited data to guide clinical decision making regarding treatment duration.

In addition to its acute effects, xylazine is associated with severe necrotic skin ulcerations (see photo).[5] Patients who use xylazine may present to the emergency department seeking care for these wounds. Such wounds are different from the wounds commonly seen in people who inject drugs; tissue injury may occur at or remote from an injection site and irrespective of the mode of use. The pathophysiology of tissue injury is unclear and probably multifactorial. Patients may seek care late in the progression of such injuries because of fear that clinicians will be unable to effectively diagnose and treat the symptoms associated with xylazine withdrawal. Once engaged in care, patients may also leave care prematurely because of severe withdrawal symptoms or the fear of such symptoms. Such challenges may ultimately result in further progression of tissue injury.

Concurrent use of xylazine and fentanyl and other opioids can complicate addiction treatment. Treatment programs may not include xylazine testing in their testing protocols and therefore may not identify concurrent xylazine use. In addition, programs may not be prepared to treat xylazine withdrawal when it occurs. The presence of xylazine-associated wounds requiring care that is not commonly available in outpatient or residential addiction treatment programs may make access to addiction treatment difficult. As has been observed in patients taking multiple substances, patients taking opioids and xylazine may require more intensive treatment than those taking opioids alone to increase the like-



Xylazine-Associated Skin Injury.

Photograph courtesy of Sarah Laurel, the founder of Savage Sisters, a Philadelphia-based organization that provides support services, including wound care, to people with active substance use disorder.

lihood of a successful outcome.

Xylazine poses a threat to public health, and the people being harmed by this drug deserve rapid, comprehensive, and high-quality health care. The White House Office of National Drug Control Policy (where we work) declared xylazine, particularly the use of fentanyl adulterated or associated with xylazine (FAAX), an emerging threat on April 12, 2023. This first-of-its-kind declaration triggered the development of an emerging threat response plan, which will be published within 90 days after the emerging threat designation, as required by the SUPPORT (Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities) Act, and will include content focused on 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. We expect that this designation will trigger a vigorous national response with targeted actions that will save lives.

Addressing use of FAAX will present critical challenges. Collection and dissemination of comprehensive data on xylazine use, including on the harm caused by such use and potential disparities in outcomes based on race, ethnicity, and socioeconomic status, are needed. Similarly, basic science and clinical research are necessary to better understand the effects of xylazine in humans, including the pharmacokinetics of xylazine and the mechanisms of injury associated with its use. There is an urgent need for more robust evidence on treatment options for acute xylazine intoxication, management of withdrawal symptoms, wound care, and long-term management of xylazine-related substance use disorder. It will also be important to support rapid development and distribution of reliable point-of-care tests for both biologic specimens and drug products, as well as widespread implementation of hospital- and community-based xylazine testing. Education for the public and clinicians will be needed as additional data are collected on the consequences of xylazine use and treatment options. Finally, as more is learned about the sources and supply of xylazine used by humans, effective strategies for disrupting and reducing this supply will be necessary.

FAAX is associated with increasing harm to people living in the United States. Our goal is for the designation of xylazine as an emerging threat and subsequent actions to begin to address this threat before it worsens and undermines efforts to reduce illicit fentanyl use in the United States.

Disclosure forms provided by the authors are available at NEJM.org.

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