Xylazine: The Drug Taking the World By Storm

What You Need to Know

ABSTRACT

Xylazine has taken the world by storm and proactive strategies are urgently needed to combat its negative impacts on population health. Xylazine is an unscheduled non-opioid indicated as a veterinary tranquilizer, also known as "Tranq." This drug is commonly used in combination with other drugs, such as heroin, fentanyl, and cocaine. Xylazine can be used orally, intranasally, sniffed, smoked, and injected, but is mostly used intravenously. Adverse effects of xylazine are secondary to central nervous system (CNS), cardiovascular, and respiratory function depression. When alpha-2-receptors in the cardiovascular and respiratory systems are stimulated, physiological effects include bradycardia, hypotension, and respiratory and CNS depression. There are currently no U.S. Food and Drug Administration–approved medications for the treatment of xylazine withdrawal or reversal of its overdose. Therefore, it is imperative that health care providers are trained to recognize these signs and symptoms and intervene proactively. [*Journal of Psychosocial Nursing and Mental Health Services, 61*(12), 7-10.]

On April 12, 2023, the Biden–Harris administration officially designated fentanyl combined with xylazine as an emerging threat to the United States (The White House, 2023) due to its growing role in the increase of opioid overdose deaths across the nation (Kariisa et al., 2021). Xylazine has been found in almost all states and is greatly implicated in overdose deaths nationally (U.S. Drug Enforcement Administration [DEA], 2022). The southern and western regions of the United States are most affected, with reported increases in overdose deaths involving xylazine of 1,127% and 750%, respectively (DEA, 2022). On July 11, 2023, the White House Office of National Drug Control Policy (ONDCP; 2023) released the Xylazine National Response Plan to address the deleterious effects of the combination of xylazine and other drugs. This plan includes the development and implementation of testing, treatment, and supportive care protocols; use of comprehensive data systems that allow early detection and response; multilevel strategies to interrupt and reduce the supply of xylazine from markets; and rapid research—from basic to applied—to better understand the implications of xylazine on the human condition (ONDCP, 2023).

Xylazine is an unscheduled non-opioid indicated as a veterinary tranquilizer, also known as "Tranq" (Centers for Disease Control and Prevention [CDC],

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2023). This drug is commonly co-administered with other drugs due to its affordability and ability to increase profit margins through diluting other substances (Papudesi et al., 2023). Xylazine is commonly used in combination with other drugs, such as heroin, fentanyl, and cocaine, as well as benzodiazepines and alcohol (National Institute on Drug Abuse [NIDA], n.d.). Mixing xylazine with other central nervous system (CNS) depressants significantly increases the risk of overdose, which is why this drug is now considered an emerging threat to public health in the United States (NIDA, n.d.).

PSYCHOPHARMACOLOGY OF XYLAZINE

Mechanism of Action and Routes of Administration

Xylazine is a centrally acting alpha-2-receptor agonist that achieves its clinical effects by activating alpha-2-receptors. Historically, xylazine was researched as an antihypertensive medication but was never approved by the U.S. Food and Drug Administration (FDA) for human use due to its adverse effect of severe respiratory depression. Xylazine has been FDA approved as a sedative medication to be used only in veterinary medicine since 1972 (Giovannitti et al., 2015; Gupta et al., 2023). Xylazine can be used orally, intranasally, sniffed, smoked, and injected, but it is mostly used intravenously (CDC, 2023). It has been reported that xylazine has a strong gasoline smell and can range in color from whitish-brown to pinkish-purple (Gupta et al., 2023; Thompson, 2023).

Onset and Duration of Action

According to FDA–approved product labeling for veterinary use, xylazine has an onset of action of 10 to 15 minutes after intramuscular injection with a sleep-like state maintained for 1 to 2 hours. During this time, analgesia usually lasts 15 to 30 minutes (FDA, 2022). When xylazine is added to other sedative medications, such as opioids, these times are enhanced and can last for several hours (DEA, 2023; FDA, 2022; McAward, 2021). Dependency can occur with repeated use of xylazine, resulting in significant cravings and life-threatening withdrawal symptoms (U.S. Department of Justice & DEA, 2022). Despite its increasing use, xylazine has been found to be unsafe for humans because it contributes to many secondary conditions, such as nerve damage, from prolonged misaligned posturing and muscle injuries, particularly from intravenous drug use (Papudesi et al., 2023).

Therapeutic Uses and Adverse Effects

As mentioned above, therapeutic effects of xylazine include sedation, analgesia, and muscle relaxation in veterinary medicine. Sedation is achieved when the medication binds centrally with alpha-2-receptors in the brain stem preventing the release of norepinephrine and dopamine, which are essential for wakefulness and arousal. Analgesia and muscle relaxation are achieved by centrally binding to pain receptors and interneuron-level receptors mainly along the spinal cord (DEA, 2023; Giovannitti et al., 2015; Gupta et al., 2023). Adverse effects of xylazine are secondary to CNS, cardiovascular, and respiratory function depression. When alpha-2-receptors in the cardiovascular system and respiratory system are stimulated, physiological effects include bradycardia, hypotension, and respiratory and CNS depression. In addition, when there is less norepinephrine in the CNS, there is less sympathetic response, resulting in decreased heart rate (Giovannitti et al., 2015; Gupta et al., 2023; Sinclair, 2003). These depressed conditions, when not proactively managed, can lead to death.

Withdrawal, Acute Toxicity, and Overdose

It is known that repeated use or exposure to xylazine, either unknowingly or knowingly, can lead to the development of dependence and severe withdrawal symptoms. Withdrawal symptoms include irritability, anxiety, and dysphoria. Because xylazine is also a clonidine analog, it depresses the CNS and can cause drowsiness, hyporeflexia, amnesia, bradycardia, and hypotension. In some cases, xylazine can cause hypoglycemia, dysrhythmias, and even coma (CDC, 2023). Atropine has been used successfully to reverse bradycardia and hypotension caused by xylazine in some cases (Papudesi et al., 2023). However, there are currently no FDA–approved medications for the treatment of xylazine withdrawal or reversal of its overdose. Therefore, it is imperative that health care providers are trained to recognize these signs and symptoms and intervene proactively.

IMPLICATIONS FOR NURSING

Xylazine toxicity and overdose are increasingly being linked to overdose deaths and the nationwide opioid overdose crisis (CDC, 2022). Because xylazine is not identified by routine toxicology screening methods, it is imperative that clinicians are aware of the signs and symptoms (e.g., sedation, difficulty breathing, low blood pressure, slow heart rate, unresponsiveness, death) with a heightened level of suspicion in individuals who present with opioid-like toxicity and overdose symptoms, specifically those who are poor responders to opioid reversal agents, such as naloxone (FDA, 2022; Gupta et al., 2023).

The most common effect of xylazine is profound sedation and respiratory depression that is irreversible by readily available opioid reversal agents, such as naloxone. Moreover, the sedating effects of xylazine when used in combination with other drugs can last longer than what is traditionally seen with illicit substances when used alone (U.S. Department of Justice & DEA, 2022). There is no approved antidote or reversal agent for xylazine overdose in humans and the mainstay of treatment remains supportive care. It is noteworthy that atipamezole is an alpha-2-antagonist that is used as a reversal agent for alpha-2-agonist toxicity in animals but is currently not FDA–approved for human use. However, studies have shown its effectiveness in

reversing sedative and cardiovascular effects of alpha-2-agonists in human trials (CDC, 2023; McAward, 2021).

Because xylazine is usually used in combination with opioids, naloxone should always be given as an initial treatment in all cases (CDC, 2023; Friedman et al., 2022). However, naloxone does not reverse the effects of xylazine or alpha-2-receptor agonist. Therefore, it is crucial to ensure continued reassessment of respiratory status after giving naloxone as the person could begin breathing again but still remain unconscious (NIDA, n.d.). Additional supportive care measures should be implemented, including maintaining a patent airway, administering supplemental oxygen, performing rescue breathing when indicated, and treating hypotension as needed. Sometimes in cases of cardiac arrest, cardiopulmonary resuscitation may be necessary. Bradycardia and hypotension can also be treated with atropine, pacing, intravenous fluids, and vasopressors as deemed clinically appropriate (American Pharmacists Association, 2023; CDC, 2023; McAward, 2021).

As earlier stated, xylazine withdrawal symptoms include irritability, anxiety, feeling uneasy, tachycardia, hypertension, seizures, and angina (Papudesi et al., 2023). However, there are no data available on its effects on human pregnancy and embryo development. Notwithstanding, it is known that xylazine reduces uterine blood flow, can delay oxygen delivery to the fetus, and may lead to potential fetal loss (Papudesi et al., 2023). Toxicity and overdose complications can cause biventricular failure, pulmonary edema, cardiac necrosis, valvular dysfunction, and insulin-dependent diabetes mellitus (Papudesi et al., 2023). Therefore, nurses and other health care providers should be vigilant in recognizing and treating these life-threatening side effects to mitigate the negative impacts of this dangerous drug.

Similarly, education is vital for harm reduction for patients with substance use disorders. For individuals with xylazine intravenous drug use, attention should be paid to potential for non-healing skin lesions and wounds, often located on the forearms and lower legs, which may inadvertently lead to infections if not properly managed. It is important to be proactive and ensure that nurses and other providers are adequately trained to assess the patient's knowledge while educating them of the possible risk of developing wounds and skin infections (Ayub et al., 2023). Early intervention in wound identification and management is crucial. The wounds can become malodorous and necrotic with eschar. Wound care can be managed in an outpatient setting. Surgical debridement and/or amputation may be required in some cases prior to outpatient management being approved (Papudesi et al., 2023). If wounds develop, the patient should be referred to their primary care provider for wound management.

Patients should also be trained with evidence-based wound cleaning and dressing techniques to avoid worsening of the skin lesions. Furthermore, patient education may include aspects such as encouraging patients not to inject xylazine into their wounds when avoidable; implementing clean techniques to avoid further contamination; and education on the importance of avoiding picking at skin and avoiding the use of irritants, such as alcohol-based products, bleach, and peroxide. Using specialty bandages is not encouraged to reduce possible damage to healthy tissue (Ayub et al., 2023; Papudesi et al., 2023). Patients should also be educated on other harm reduction strategies, such as avoiding sharing needles, using needle exchange programs when available, administering naloxone to reverse opioid overdose, and using fentanyl testing strips to increase their understanding of what specific drugs they are consuming.

CONCLUSION

Xylazine has taken the world by storm and proactive strategies are urgently needed to combat its negative impacts on population health. This approach requires multipronged, multisectoral collaborations, including patient-centered treatment approaches. Patient-centered treatment is earning the trust of the patient and ensuring that they are equipped with information to make an informed decision. Building trust and rapport is critical to successful patient management, especially in substance use treatment and management, where stigma often serves as a barrier to accessing and using available treatment services. Using a nonjudgmental approach is best to assist patients with the disclosure of wounds and other negative consequences of their drug use or misuse. Reluctance may be noted when embarrassment, fear of the unknown, concern for hospitalization, or concern for amputation ensues. Thus, nurses and health care providers need to provide empathetic and culturally responsive care to improve patient outcomes.

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