

## Zeroing in on Xylazine

**To the Editor:** A recent case report by Robbins-Welty et al<sup>1</sup> involving a patient with a history of polysubstance use illustrated a xylazine masking of benzodiazepine withdrawal, resulting in a withdrawal seizure. This case highlights a public health threat in the United States due to xylazine's infiltration into the illicit drug supply. Xylazine, a veterinary tranquilizer not approved for human use, is an  $\alpha$ -adrenergic agonist used as a bulking agent in drugs such as fentanyl and cocaine, often without the user's knowledge.<sup>2</sup> Bulking agents can increase the dealer's profit margins or enhance or alter effects of the drug, albeit at the expense of increased risks.<sup>3</sup>

In 2023, the White House Office of National Drug Control Policy identified xylazine, especially when combined with fentanyl ("tranq dope"), as an escalating problem in the United States. Philadelphia and Connecticut have emerged as hubs for xylazine use. By March 2023, fentanyl adulterated with xylazine had been detected in 48 states across the nation.<sup>4</sup>

Xylazine is often combined with fentanyl to enhance euphoria and analgesia while reducing the need for frequent injections and delaying the onset of withdrawal symptoms.<sup>4</sup> Notably, there is no established safe, toxic, or fatal dose for xylazine.<sup>5</sup> Typically administered intravenously, often as part of a combination of substances, xylazine contributes to the complexity of addressing polysubstance use.<sup>3</sup>

Symptoms of acute xylazine toxicity/overdose mirror those of clonidine (another  $\alpha_2$ -agonist) and can include respiratory depression, bradycardia, miosis, central nervous system depression, and unstable blood pressure. Hyperglycemia and QT prolongation are unique to xylazine

toxicity.<sup>6</sup> Chronic use leads to necrotic ulceration and tissue damage, which can occur at or remote from point of use regardless of mode of administration.<sup>4</sup>

Urine is the most common sample used to detect xylazine.<sup>7</sup> Analytical methods such as thin-layer chromatography and mass spectrometry are most commonly used for detection, and immunoassay methods have not yet been developed.<sup>5</sup>

Treatment of overdose is mainly supportive and focuses on maintaining respiratory function and blood pressure.<sup>5</sup> Proposed antidote for xylazine, yohimbine, an  $\alpha_2$ -adrenergic antagonist, lacks evidence of efficacy, and naloxone is ineffective in reversing xylazine toxicity.<sup>8,9</sup> However, a review of overdose data found that 98.4% of xylazine-related overdose deaths involved fentanyl, emphasizing the critical importance of timely naloxone administration.<sup>10</sup>

Incorporation of wound care with harm reduction strategies is recommended to increase patient access to basic treatment for xylazine-associated wounds.<sup>2</sup> Measures like adding xylazine to routine toxicology must be considered to assess incidence and provide timely treatment.<sup>8</sup>

Development of standard protocols to manage xylazine overdose and detoxification is overdue. Rescue agents also must be determined. Public health measures such as prohibiting sales of xylazine online, tracking data on how it is being diverted (from veterinary clinics, clandestine laboratories, pharmaceutical companies, or smuggling), and raising xylazine awareness among public and health care professionals are the need of the hour.<sup>11</sup>

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