Editorial

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Xylazine in illicit drug mixtures: a growing threat and overlooked danger

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Xylazine, classified as a nonopiate sedative, analgesic, and muscle relaxant, belongs to the drug class of α2-adrenoreceptor agonists alongside medications like clonidine, lofexidine, tizanidine, and dexmedetomidine. Originally formulated by Farbenfabriken Bayer AG in 1962 as an antihypertensive agent[1], its development for human use was halted due to severe adverse events associated with hypotension and central nervous system (CNS) depression[2]. Despite this setback, the U.S. Food and Drug Administration (FDA) approved for veterinary use in 1972[3]. Xylazine has emerged as a concerning factor in the ongoing drug addiction and overdose crisis, with a notable rise in overdose deaths attributed to its presence[4]. As Xylazine has been reported to have many of the same effects on users as opioids but a longer-lasting effect than fentanyl alone, it may draw customers looking for a longer high, according to a joint intelligence report released in 2022 by the Drug Enforcement Administration (DEA) and the Department of Justice[5]. The source of this statement most likely originated from epidemiological reports asserting that people are drawn to Xylazine because it 'prolong[s] the duration of fentanyl injections, in particular, overcoming 'the problem' of the 'short legs' of the ordinarily euphoric effects of fentanyl manufactured illegally'[4]. Individuals, whether knowingly or unknowingly, frequently combine Xylazine with other substances, notably illicit fentanyl, to extend the euphoric effects[4,6–8]. Illicit opioids, including fentanyl, are often adulterated with Xylazine to enhance their impact[6]. Investigations into overdose cases involving Xylazine and fentanyl have revealed the concurrent use of additional substances such as cocaine, heroin, benzodiazepines, alcohol, gabapentin[6], methadone, and prescription opioids[2]. In the Friedman *et al*.[4] study, 98.4% of overdose deaths involving Xylazine contained illicitly made fentanyls, indicating a strong ecological association. Beyond its association with overdose deaths, Xylazine has been misused for various purposes, ranging from a horse doping agent to a substance of abuse and even as a tool for attempted sexual assault. Incidents of accidental or intentional poisoning have also been reported[9]. In Philadelphia, Xylazine is colloquially known as 'tranq', and the term 'tranq dope' refers to heroin and fentanyl mixed with Xylazine on the street.

Xylazine's role in illicit drug combinations

Xylazine, when combined with fentanyl, poses a significant and escalating risk of fatal drug poisoning for users. A comprehensive study conducted in Philadelphia revealed a staggering increase in the percentage of drug overdose deaths involving Xylazine, rising from 2 to 26% between 2015 and 2020[4]. Similarly, in Maryland and Connecticut, Xylazine was identified as a factor in 19 and 10% of drug overdose deaths, respectively[4]. Despite its non-approval for human use and the absence of scheduling as a controlled substance, the lack of human studies on Xylazine makes it challenging to determine crucial factors such as drug-to-drug interactions, lethal doses, or potential reversal protocols. Its easy online accessibility without a prescription further compounds the issue, facilitating access for drug abusers. Street-level drug users are often exposed to Xylazine, either knowingly or unknowingly, as it is frequently mixed with other illicit substances, notably fentanyl. A notable case study conducted by the Philadelphia Medical Examiner's Office in 2006 identified Xylazine and fentanyl in specimens from seven cases. Immunoassay screening and subsequent confirmation by gas chromatography-mass spectrometry revealed positive tests for fentanyl and Xylazine.

Additionally, all seven xylazine-positive cases also tested positive for fentanyl, with six cases indicating the presence of 6-acetylmorphine, a definitive marker for heroin abuse[10]. Regarding the political and cultural background of drug abuse, it is imperative to consider the socio-economic factors contributing to drug abuse in different regions. Socio-economic disparities, lack of access to education and healthcare, unemployment, and societal stigmatization can exacerbate drug abuse issues. Additionally, cultural norms and attitudes towards drug use play a significant role in shaping patterns of substance abuse and addiction within communities. Understanding these contextual factors is essential for developing effective prevention and intervention strategies tailored to the specific needs of each region. Illicit drug adulteration has become a pressing health concern for drug users, as evidenced by U.S. Census statistics on drug overdose mortality. In 2015, Xylazine was detected in 0.36% of such

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deaths, a figure that surged to 6.7% in 2020[11]. However, it is important to note that this percentage is likely an underestimate, given that Xylazine is not routinely included in standard drug testing protocols. A study based on data from a drug detection service in Toronto further highlighted the escalating presence of Xylazine. Initially detected in the Toronto area in September 2020, Xylazine was found in 7.2% of all samples containing fentanyl and 12.5% of samples containing methamphetamine in 2021[12]. This alarming trend emphasizes the urgent need for increased awareness, surveillance, and intervention strategies to address the growing threat posed by Xylazine in illicit drug mixtures.

Exploring the impact

According to a 2008 study by Rodriguez *et al*.[13], evaluating the level of xylazine use in Puerto Rico, Xylazine was detected in 36% of the syringes that were collected, and it was most frequently found in 'speedball preparations', which are mixtures of heroin and cocaine. In the United States, Xylazine was discovered in 2.2% of 357 syringes examined as part of a New York City syringe exchange program, according to a 2020 study by Fiorentin and Logan[14]. Xylazine was detected in 1.5% of the samples examined in a follow-up study by Fiorentin *et al*.[15] that assessed cutting agents in drug-positive confiscated materials ($N = 515$) from Kentucky and Vermont. However, it was most frequently discovered in conjunction with heroin (4.6%), fentanyl (11%), and cocaine (2.6%). There are not any prospective clinical study articles that we are aware of that discuss the effects of fentanyl mixed with Xylazine on human populations. However, several case reports have detailed both clinically significant but nonlethal pathological problems with this combination of drugs[16,17] and clinical symptoms of fatal drug overdoses[18,19]. The rising incidence of this combination of drugs in clinical[20,21] and postmortem[22] populations has recently been reported in several retrospective and prospective forensic medicine studies. The clinical effects of xylazine-laced fentanyl on emergency departments have been confirmed by these reports, leading to several recent commentaries on the immediate threats to healthcare[3], hospitals, community health[23], nursing[24], and emergency care[25]. Fentanyl-xylazine combinations have been designated as a significant public health threat by the U.S. Drug Enforcement Administration and the Centers for Disease Control. Reports about the deadly effects of this combination of drugs on humans have been documented in both lay and scientific[26] publications. The White House Office of National Drug Control Policy has declared Xylazine plus fentanyl an emerging hazard to the United States because of the sharp rise in fatal drug overdoses linked to this combination[27]. No research has measured the interactions between these medicines and lethality despite mounting evidence that Xylazine worsens fentanyl-related morbidity and mortality. All of this highlights the crucial hole in the body of knowledge regarding the impact of fentanyl and Xylazine on human populations. It recognizes the growing use of this medication combination, its significant influence on various healthcare settings, and the lack of prospective clinical trials.

Research urgency on xylazine

The inclusion of Xylazine in illicit drug mixtures poses a profound and concerning impact on the human body. Users report striking parallels between Xylazine and opioids in terms of experience, underscoring the gravity of their effects. The toxicity or overdose of Xylazine can have serious clinical consequences, even death. The effects unique to each human organ system have not received enough research attention. The few human and animal studies that are now available show that using Xylazine can result in potentially fatal side effects such as biventricular failure, pulmonary edema, cardiac necrosis, valve malfunction, and insulin-dependent diabetic mellitus[28]. Research conducted in the veterinary field has shown that when Xylazine is administered to pregnant cattle and goats, it increases uterine contractions, decreases uterine blood flow, and causes fetal loss[29,30]. One of the most significant concerns revolves around the documented adverse effects on the CNS. Xylazine, known for its sedative properties, contributes to a profound depression of the CNS, heightening the risk of respiratory and cardiovascular compromise[2]. Users frequently note pronounced lethargy, drowsiness, and slowed cognitive functions.

Furthermore, the synergistic effects of Xylazine with other substances in illicit drug mixtures intensify the overall physiological impact, potentially leading to life-threatening outcomes[31]. Understanding the intricate physiological responses of Xylazine is paramount for public health initiatives, as it informs targeted intervention strategies and underscores the urgency of addressing the escalating threat posed by the inclusion of Xylazine in illicit drug formulations. Despite the palpable risks associated with Xylazine use, scientific attention to this emerging substance has been notably scant. Existing studies, though limited, point to the urgent need for comprehensive investigations to bridge the existing scientific research gap. The scarcity of scientific studies on the inclusion of Xylazine in illicit drug mixtures is a critical gap that demands urgent attention. Despite the escalating threat posed by this phenomenon, the existing body of research remains notably limited. Comprehensive investigations into the physiological, psychological, and sociological aspects of xylazine use are essential to understanding its impact on the human body. The paucity of studies impedes our ability to formulate evidence-based interventions, thereby compromising public health efforts to address the growing dangers associated with xylazine-containing drug formulations.

Regarding pharmacological mechanisms and potential symptomatic antagonists, further research is needed to elucidate the precise interactions between Xylazine and other substances, as well as the pharmacokinetics and pharmacodynamics of Xylazine in combination with illicit drugs. Understanding these mechanisms can inform the development of targeted treatment approaches and harm-reduction strategies to mitigate the adverse effects of xylazine-containing drug formulations. There is an unmistakable need for more studies that delve into the pharmacological intricacies, long-term health consequences, and socio-demographic factors influencing xylazine use. Bridging this research gap is imperative to inform effective harm reduction strategies, policy initiatives, and treatment interventions. Policymakers, healthcare professionals, and researchers must prioritize allocating resources to conduct rigorous scientific studies, fostering a comprehensive understanding of the implications of xylazine inclusion in illicit drug mixtures and guiding evidence-based responses to this emerging public health challenge. Through an exhaustive review of existing literature and a call for increased research initiatives, we endeavor to effectively enhance our collective ability to address this growing threat.

Underreported presence and detection

The potential underreporting of Xylazine in forensic laboratory and toxicology testing across jurisdictions is a concerning aspect that warrants immediate attention[4]. Due to the relative novelty of Xylazine's inclusion in illicit drug mixtures, traditional testing protocols may not routinely screen for its presence[19,32,33]. This oversight raises the risk of inaccurate prevalence assessments, hindering our understanding of the true scope of Xylazine-related incidents, especially fatal overdoses. Raising awareness about incorporating Xylazine in routine testing procedures is imperative to address this. Forensic laboratories and toxicology facilities must adapt their methodologies to include specific tests for Xylazine, ensuring a comprehensive analysis of drug-related fatalities. This awareness campaign should extend to law enforcement agencies, healthcare providers, and relevant stakeholders to underscore the significance of accurate testing practices. By incorporating Xylazine into routine screenings, jurisdictions can enhance their ability to detect and report instances of Xylazine use, contributing to a more precise evaluation of its prevalence and facilitating evidence-based public health responses. This proactive approach is crucial for mitigating the potential harm associated with Xylazine in illicit drug mixtures and underscores the importance of adapting testing protocols to evolving drug trends.

Preventive strategies

The increased risk of Xylazine in illicit drug mixes calls for preventive actions such as improved law enforcement-healthcare collaboration and reevaluation of drug scheduling. To recognize and manage xylazine-related issues, medical practitioners should receive specific training. Meanwhile, community-level initiatives should concentrate on harm reduction strategies, such as distributing naloxone and awareness campaigns. Collaborations in multidisciplinary research are crucial for expanding knowledge. This all-encompassing strategy, which crosses the fields of legislation, healthcare, community, and research, attempts to stop the growing risks connected to Xylazine in illegal drug compositions.

Conclusion

The escalating presence of Xylazine in illicit drug mixtures poses a growing threat to public health yet remains an overlooked danger in many jurisdictions. Recognizing and addressing the threat posed by Xylazine requires a concerted effort to adapt testing protocols, raise awareness, and foster collaboration among key stakeholders. This approach is vital for safeguarding public health and curbing the detrimental effects of Xylazine in the context of evolving drug trends.

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