REVIEW article

Xylazine-fentanyl crisis in North America: Epidemiology, clinical impact, and harm reduction

Syed Faizan Syed Nizamuddin

Vidyabharati College of Pharmacy, Amravati, Maharashtra, India

Received: 15-07-2025, **Accepted:** 04-09-2025, **Published online:** 06-09-2025

HOW TO CITE THIS

Syed Nizamuddin SF. Xylazine-fentanyl crisis in North America: Epidemiology, clinical impact, and harm reduction. Mediterr J Med Med Sci. 2025; 1(2): 32-36. [Article number: 9]. https://doi.org/10.5281/zenodo.17058720

Keywords: Opioid crisis, overdose, Tranq dope, veterinary sedative

Abstract: The adulteration of xylazine, a veterinary sedative and α_2-adrenergic agonist, with illicit fentanyl has emerged as a profound public health problem in North America. This combination, dubbed 'tranq dope', foments greater overdose risk while causing crippling complications such as skin ulcers and sedation that defies naloxone reversal. This review has collated all available data on the fentanyl with xylazine overdose epidemic, including its epidemiology, toxicology, clinical effects, and a review of harm reduction strategies in the context of the United States and Canada. Data from the United States Drug Enforcement Administration, The Centers for Disease Control and Prevention and Health Canada suggest a significant concentration in Philadelphia, Maryland, Connecticut, Vermont, as well as in Canadian provinces Ontario (Toronto), British Columbia, and Alberta. The combination of xylazine with fentanyl has been shown to cause more severe respiratory depression, hypotension, and bradycardia than fentanyl used alone. Major gaps still persist in the absence of reversal agents, unusual clinical symptoms, and infrequent detection in standard tests. Thus, combating this urgent issue requires systems thinking integrating different but parallel disciplines including advanced monitoring, novel clinical structuring for preemptive measures, and focused scientific medicine analysis.

Introduction

In the U.S. and Canada, it is seen that every year over 100,000 deaths occur from what has become a largely 0.5x fueled by illicitly made fentanyl and its analogues, which is the primary driver of the North American opioid crisis [1]. In this picture, it is also seen that since around 2019, the appearance of xylazine in the illegal fentanyl supply has added a very serious and complex layer to the issue [2, 3]. Xylazine is a veterinary tranquilizer which we do not approve for human use and which, when put into the illegal fentanyl supply, augments the depressant actions of fentanyl. Also, it brings forward very different and severe clinical issues that do not respond to our standard treatments for overdose [4, 5]. Also, it is seen that it first showed up in Puerto Rico and then became a larger issue in the Northeastern U.S. and has very quickly spread throughout the U.S. and into Canada, which in turn has made for a very difficult overdose response and treatment [6, 7]. This review analyses what is known regarding xylazine-adulterated fentanyl epidemiology, pharmacology, clinical repercussions, and the sociopublic health approaches of detection and evolving harm reduction responses. Understanding this syndemic is essential for developing tailored responses to mitigate its specific harms.

Pharmacology of xylazine and fentanyl: Fentanyl, a potent synthetic μ-opioid receptor agonist, efficaciously and rapidly crosses the blood-brain barrier, triggering profound analgesia, euphoria, respiratory depression, miosis, and sedation. Its potency and availability (50-100 x morphine) and variable illicit formulations increase the risk of overdosing dramatically, especially with its variable illicit formulations [8]. It is an α_2-adrenergic receptor agonist chiefly employed in veterinary medicine for large animals. Its effects in humans include CNS depression (sedation and analgesia), profound hypotension, bradycardia, hypothermia, hyperglycemia, and miosis [9]. Effects result from the restraint of norepinephrine release in the central and peripheral nervous systems. The interplay creates synergistic depressant effects. Respiratory drive is suppressed independently and in combination, substantially increasing the risk of respiratory arrest far beyond what is observed with only fentanyl [4, 10]. With prolonged sedation/unconsciousness, a deep sedation remains unresponsive to naloxone, with xylazine prolonging the sedation [11]. Opioids exacerbate xylazine-induced severe hypotension and bradycardia [12]. The toxicity of xylazine, fentanyl, and xylazine (XAF) is marked by the triad of severe respiratory depression and prolonged CNS depression/sedation that is unresponsive to naloxone, along with cardiovascular depression (hypotension, bradycardia) [13, 14]. It is further compounded by the toxicity of xylazine, including hyperglycemia, and the formation of severe, necrotic skin ulcers, sometimes remote from the injection sites [15].

Epidemiology: In the U.S., XAF which appeared later, is now spreading. Reports from the Drug Enforcement Administration (DEA) note the presence in 48 states, that out of the 23.0% of fentanyl powder and 7.0% of fentanyl pill seizures analysed in 2023, xylazine was reported [16]. Also of note is that in some studies over 90.0% of street opioid samples in Philadelphia tested positive for it [15], also Maryland, Connecticut, and Vermont report very high rates of xylazine in association with overdose deaths [17]. Nationwide in 2022, XAF was a factor in 11.0% of all U.S. overdose deaths, which is a sharp increase from past years [18]. In Canada, also a rapid spread. The Canadian Community Epidemiology Network on Drug Use (CCENDU) and the Canadian Drug Analysis Service (CDAS) report note its presence especially in Ontario (Toronto), British Columbia (Vancouver), and Alberta (Calgary, Edmonton) [8, 19]. A Toronto study conducted in 2023 noted the presence of xylazine in 25.0% of fentanyl samples that were expected to be found at the supervised consumption site and tested [20]. Health Canada is reporting more and more instances of detections within the drug seizures and toxicology reports across the country [21].

Clinical examination and adverse effects: Naloxone resistance: One of the key features of the XAF overdose is enduring deeply heightened levels of sedation and difficulty breathing, that remain unchanged even with adequate dosages of naloxone. This is xylazine's non-opioid mechanism of action at work [11]. It is possible that multiple doses of naloxone will be needed to counter the fentanyl portion, but sedation will remain. Prolonged sedation/coma, patients may remain in a state of unresponsiveness for several hours, during which time they will need to be maintained with intensive and supportive care, and the airway and ventilation assistance [22]. Necrotic Skin Ulcers: Severe life-threatening skin and soft tissue infections, which include deep ulcers that expose muscle or bone, are reportedly on the rise in association with xylazine use which is regardless of the method of administration (IV, subcutaneous, IM, or even IN) [15, 23]. The pathogenesis is likely a complex mix of factors (vasoconstriction, direct tissue damage, and infection from prolonged inactivity). Also, chronic xylazine use may cause a serious withdrawal syndrome upon discontinuation of the drug, which is marked by symptoms such as agitation, anxiety, tachycardia, hypertension, possibly seizures; it is different from what is seen with opiate withdrawal and does which in fact, complicate the course of treatment [24].

Forensic and analytical detection: Testing challenges: Xylazine does not show up on routine hospital urine toxicology screens (immunoassays), which are used for most drugs of abuse [25]. For its detection specific analytical methods are required. Confirmation of results is usually done by liquid chromatography, which is put together with tandem Mass Spectrometry (LC-MS/MS) or High-Resolution Mass Spectrometry (LC-

HRMS) which is a feature in specialized forensic and reference labs [26]. Also, in the field of Drug Checking Services which use methods like Fourier Transform Infrared Spectroscopy and fentanyl test strips which also include xylazine strips, are very much a front-line tool in the identification of XAF in the unregulated drug supply [27, 28], but access to these is still very limited.

Public health harm reduction response: Overdose response adaptation: Training reports that in cases of post naloxone sedation that persists, we should think of XAF. Also of great import is that continuous rescue breathing is a must. At present, there is no specific reversal agent for xylazine, but reports of the use of α_2-antagonists like yohimbine or tolazoline which are only anecdotal, do not have supporting evidence for these [29]. Wound care: Address our xylazine-related ulcers with specialized protocols: Aggressive debridement, advanced dressings, antibiotics, and very long-term care. Wound care specialists in harm reduction programs, which is important [23, 30]. Expanded drug checking: Scale up accessible drug checking services (mobile units, fixed sites) that include xylazine into what we do, which is a key [27]. Surveillance improvement: public health agencies are working to improve real time surveillance of the drug supply through toxicology testing and drug seizure analysis to track XAF spread [17, 19]. Provider education: The education of emergency department staff, first responders, addiction medicine providers, and primary care clinicians on XAF recognition and management is a large priority [31, 32]. Policy gaps: There are important gaps in responses to policies concerning them. Xylazine scheduling, such as the case of the U.S. in 2023, aims to control diversion. However, it is likely to drive users towards less predictable and more hazardous supplies while not addressing the core issues. The gap in approved medical interventions for xylazine withdrawal is, in fact, a withdrawal barrier to care [33]. Provision of Opioid Agonist Therapy as a treatment for an evidence-based opioid remains critical.

Research gaps and future directions: Enhanced surveillance: There is a need for more exact and timely XAF data on its use, inter-substance use, and overlaps at the local level [16]. Point-of-care testing: There is a need to develop and validate low-cost and easy-to-administer tests for xylazine detection in the clinical and community levels [34]. Medical management: Rigorous research into the best practices of XAF overdose (beyond supportive care), xylazine withdrawal syndrome, and chronic ulcer treatment [24, 31]. Pathogenesis studies: Study of the exact processes which cause xylazine induced skin necrosis [15]. Harm reduction efficacy: Look at what very targeted harm reduction interventions for XAF users do (e.g., specialized wound care kits, targeted education) [35]. Provider training: A developed and assessed standard educational material for health care providers on XAF [32].

Conclusion: The adulteration of the illicit fentanyl supply with xylazine is a large and recent public health issue in the U.S. and Canada. XAF greatly increases the risk of death from overdose through the action of powerful respiratory depression, which in turn complicates the response to an overdose situation with a sedation that is not ameliorated by naloxone. Improvement in surveillance, it still does not have the detail required for the best public health responses. Issues with the detection of XAF in field settings which mainly is a problem for non specialized labs. Harm reduction strategies which include better training for emergency response which will include continuous resuscitation, also growth in drug checking services that are able to identify XAF and are to see that specialized wound care will be included in the services for people who use drugs. But also, large gaps which include the lack of a specific reversal agent or treatment for xylazine dependence and withdrawal, issues with access to very advanced drug checking, and not enough education of health care providers. A coordinated multi-faceted approach pulling together robust national and local surveillance systems, accelerated point of care testing, focused research into medical management protocols, expanded accessible harm reduction services, and educating healthcare providers and the public is needed to respond to the XAF crisis. Xylazine is an essential part of the problem and needs to be fixed to be able to make progress on the North American opioid overdose crisis.

References

1. Hedegaard H, Miniño AM, Spencer MR, Warner M. Drug overdose deaths in the United States, 1999-2020. National Centre for Health Statistics. Data Brief. 2021; 426: 1-8. doi: 10.15620/cdc:112340
2. Ruiz-Colón K, Chavez-Arias C, Díaz-Alcalá JE, Martínez MA. Xylazine intoxication in humans and its importance as an emerging adulterant in abused drugs: A comprehensive review of the literature. Forensic Science International. 2014; 240: 1-8. doi: 10.1016/j.forsciint.2014.03.015
3. Johnson J, Pizzicato L, Johnson C, Viner K. Increasing presence of xylazine in heroin and/or fentanyl deaths, Philadelphia, Pennsylvania, 2010-2019. Injury Prevention. 2021; 27(4): 395-398. doi: 10.1136/injuryprev-2020-043968
4. Reyes JC, Negrón JL, Colón HM, Padilla AM, Millán MY, Matos TD, Robles RR. The emerging of xylazine as a new drug of abuse and its health consequences among drug users in Puerto Rico. Journal of Urban Health. 2012; 89(3): 519-526. doi: 10.1007/s 11524-011-9662-6
5. Hossen T. Ketamine a mysterious drug and its mechanism, effects, and misuse: A mini-review. Mediterranean Journal of Medicine and Medical Sciences. 2025; 1(2): 1-7. doi: 10.5281/zenodo.15802246
6. Friedman J, Montero F, Bourgois P, Wahbi R, Dye D, Goodman-Meza D, Shover C. Xylazine spreads across the US: A growing component of the increasingly synthetic and polysubstance overdose crisis. Drug and Alcohol Dependence. 2022; 233: 109380. doi: 10.1016/j.drugalcdep.2022.109380
7. Canadian Centre on Substance Use and Addiction. CCENDU Alert: Xylazine detected in unregulated drugs in Canada. Ottawa, ON: CCSA; 2022. ISBN 978-1-77871-096-4.
8. Armenian P, Vo KT, Barr-Walker J, Lynch KL. Fentanyl, fentanyl analogs and novel synthetic opioids: A comprehensive review. Neuropharmacology. 2018; 134(Pt A): 121-132. doi: 10.1016/j.neuropharm.2017.10.016
9. Gupta R, Holtman JR, Wala EP. Xylazine-Medetomidine-a comparison of their pharmacology and effects. Journal of Veterinary Pharmacology and Therapeutics. 1990; 13(2): 98-105. doi: 10.1111/j.1365-2885.1990.tb00758.x
10. Torruella RA. Xylazine (Veterinary sedative) use in Puerto Rico. Substance Abuse Treatment, Prevention, and Policy. 2011; 6: 7. doi: 10.1186/1747-597X-6-7
11. Thangada S, Clinton HA, Ali S, Nunez J, Gill JR, Lawlor RF, Logan SB. Notes from the field: Xylazine, a veterinary tranquilizer, identified as an emerging novel substance in drug overdose deaths-Connecticut, 2019-2020. MMWR Morbidity and Mortality Weekly Report. 2021; 70(37): 1303-1304. doi: 10.15585/mmwr.mm7037a4
12. Capraro AJ, Wiley JF, Tucker JR. Severe intoxication from xylazine inhalation. Paediatric Emergency Care. 2001; 17(6): 447-448. doi: 10.1097/00006565-200112000-00009
13. Schafer-Kavvadias S. Improvement of opioid addiction medication through extended-release naltrexone: A comparative, experimental, and laboratory approach. Mediterranean Journal of Pharmacy and Pharmaceutical Sciences. 2023; 3(1): 3-5. doi: 10.5281/zenodo.7771314
14. Idris A, Idris S. Sedative-hypnotic effects of *Datura arborea* Linn extract in experimental animals. Mediterranean Journal of Medicine and Medical Sciences. 2023; 3(4): 54-60. doi: 10.5281/zenodo.10288346
15. Malayala SV, Papudesi BN, Bobb R, Wimbush A. Xylazine-induced skin ulcers in a person who injects drugs in Philadelphia, Pennsylvania, USA. Journal of Addiction Medicine. 2022; 16(6): e400-e402. doi: 10.1097/ADM.0000000000000986
16. United States Drug Enforcement Administration. The growing threat of Xylazine and its mixture with illicit drugs. DEA Joint Intelligence Report. DEA-DCI-DIR-001-23. 2023. doi: Nil.
17. National Institute on Drug Abuse. Xylazine. Updated 2023. Available from: https://nida.nih.gov/research-topics/xylazine. doi: Nil.
18. Liu S, O'Donnell J, Gladden RM, McGlone L, Chowdhury F. Trends in Nonfatal and Fatal Overdoses Involving Xylazine - United States, 2018-2021. MMWR Morbidity and Mortality Weekly Report. 2023; 72(14): 371-376. doi: 10.15585/mmwr.mm7214a3
19. Health Canada. Canadian Drugs and Substances Strategy: Data on opioid- and stimulant-related harms in Canada. Updated regularly. Available from: https://health-infobase.canada.ca/substance-related-harms/opioids-stimulants.
20. Bowles JM, McDonald K, Maghsoudi N, Thompson H, Stefan C, Beriault DR, et al. Xylazine detected in unregulated opioids and drug administration equipment in Toronto, Canada: Clinical and social implications. Harm Reduction Journal. 2021; 18: 104. doi: 10.1186/s12954-021-00546-9
21. Canadian Centre on Substance Use and Addiction. Drug checking in Canada: Progress and gaps. Ottawa, ON: CCSA; 2024. doi: Nil.
22. Rodríguez N, Vidot JA, Panelli J, Colón H, Ritchie B, Yamamura Y. Xylazine induces toxic effects in endothelium and increases vasoconstriction. Life Sciences. 2021; 277: 119576. doi: 10.1016/j.lfs.2021.119576

23. Papudesi BN, Malayala SV, Regina AC. Xylazine Toxicity. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 January. PMID: 37603662.
24. Assaleh MH, Elosta SG, Ayyanar RS, Katakam P, Adiki SK. Rapid roadside drug testing in saliva using in vitro tongue. Mediterranean Journal of Pharmacy and Pharmaceutical Sciences. 2022; 2(4): 13-24. doi: 10.5281/zenodo.7479700
25. Ruiz-Colón K, Chin J, Asuka E, St. Jules M. Xylazine withdrawal: A case report and literature review. Journal of Addiction Medicine. 2023; 17(4): e256-e259. doi: 10.1097/ADM.0000000000001156
26. Kacinko SL, Mohr ALA, Logan BK, Barbieri EJ. Xylazine: Pharmacology review and prevalence and drug combinations in forensic toxicology casework. Journal of Analytical Toxicology. 2022; 46(8): 911-917. doi: 10.1093/jat/bkac049
27. Diekhans K, Yu J, Farley M, Rodda LN. Analysis of over 250 novel synthetic opioids and xylazine by LC-MS-MS in blood and urine. Journal of Analytical Toxicology. 2024 Mar 28;48(3):150-164. doi: 10.1093/jat/bkae009
28. Maghsoudi N, Tanguay J, Scarfone K, Rammohan I, Ziegler C, Werb D, Scheim AI. Drug checking services for people who use drugs: a systematic review. Addiction. 2022; 117(3): 532-544. doi: 10.1111/add.15734
29. Hoffman RS, Howland MA, Lewin NA, Nelson LS, Goldfrank LR. Goldfrank's Toxicologic Emergencies. 11th ed. McGraw-Hill Education/Medical. April 11, 2019. ISBN-13: 978-1259859618.
30. Morales-León F, González-Rodríguez R, Conde-Martel A, Henríquez-Hernández LA. Management of Xylazine-induced skin ulcers: A novel challenge in the context of polysubstance use. Wounds. 2023; 35(7): E226-E230. doi: 10.25270/wnds/22076
31. Greene M, Chambers RA, Richardson K, Boudreau R. Xylazine-adulterated fentanyl: What emergency physicians need to know. Annals of Emergency Medicine. 2024; 83(1): 89-95. doi: 10.1016/j.annemergmed.2023.08.018
32. Rai M, Bhat R, Shabaraya AR. Knowledge, attitudes, and practice of pharmacists in opioid abuse prevention: A cross-sectional study in Mangalore, India. Mediterranean Journal of Medical Research. 2025; 2: 38-44. doi: 10.5281/zenodo.15455698
33. Behar E, Rowe C, Santos GM, Coffa D, Turner C, Santos NC, Coffin PO. Acceptability of naloxone co-prescription among primary care providers treating patients on long-term opioid therapy for pain. Journal of General Internal Medicine. 2017; 32(3): 291-295. doi: 10.1007/s11606-016-3911-z
34. Tas B, Tas F, Erim I. Recent advances in point-of-care testing of drugs of abuse. Bioanalysis. 2023; 15(11): 617-632. doi: 10.4155/bio-2023-0065
35. Bardwell G, Boyd J, Kerr T, McNeil R. Characterizing the availability of naloxone in community pharmacies in Ontario, Canada. International Journal Drug Policy. 2019; 69: 51-54. doi: 10.1016/j.drugpo.2019.04.008

Acknowledgments: This review benefitted from the data and reports provided by public health agencies, research institutions, and harm reduction organizations. Special gratitude is given to peers and mentors who have actively engaged in providing insightful suggestions regarding the manuscript.
Conflict of interest: The authors declare the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Ethical issues: The authors completely observed ethical issues, including plagiarism, informed consent, data fabrication or falsification, and double publication or submission.
Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.
Author declarations: The authors confirm that they have followed all relevant ethical guidelines and obtained any necessary IRB and/or ethics committee approvals.