

INTRODUCTION

- The White House Office of National Drug Control Policy (ONDCP) officially designated xylazine an emerging threat to the United States. Xylazine, a veterinary $\alpha 2$ agonist, is an inexpensive additive to illicit drugs that intensifies the “high” and worsens withdrawal symptoms.
- Drug overdose deaths exceeded 111,000 in the year ending February 2023 and continue to rise.
- While illegal opioids, particularly fentanyl, are the primary agents of abuse, other drugs are comingled. In Philadelphia, virtually all (>90%) of the illegal drug supply is fentanyl-xylazine combined. We present the management of a critically ill patient suffering with the complications of fentanyl-xylazine abuse.

CASE REPORT

- A 39-year-old male with a medical history of opioid use disorder (OUD), methicillin-resistant Staphylococcus aureus (MRSA) bacteremia, suspected infectious endocarditis, septic emboli, open humeral fracture complicated by osteomyelitis and bilateral upper extremity necrotic wounds presented with worsening fentanyl-xylazine related wounds.
- To assist in the management of pain and withdrawal symptoms, the patient was started on intravenous ketamine at 10mg/hr, transdermal clonidine patch (TTS1 0.1 mg/hr), lorazepam 0.5 mg as needed, intravenous hydromorphone patient-controlled analgesia (PCA), acetaminophen 1000mg every six hours, intravenous ketorolac 15mg every 6 hours, tizanidine 4mg TID as needed, gabapentin 800 TID, and methadone 20mg TID.
- To manage increasing xylazine withdrawal symptoms, we added clonidine 0.1mg PO TID, increased the clonidine patch to 0.2mg/hr, and guanfacine 2mg TID. A continuous right-sided interscalene block was performed for optimization of pre- and post-operative pain. For the left lower extremity wounds, a continuous sciatic nerve block performed prior to surgical debridement, with excellent post-operative pain control.
- As withdrawal symptoms improved, all adjunctive medications were tapered. The patient’s PCA was eventually discontinued while optimizing methadone MOUD dosing by addiction medicine. The patient was discharged on methadone 260mg daily, and oxycodone 30mg every six hours as needed.



DISCUSSION

- Patients with fentanyl-xylazine use make repeated visits to emergency rooms in acute overdose, withdrawal, or with painful necrotic wounds, which require management different from fentanyl or heroin overdose alone.
- Inexpensive illegal fentanyl is supplied by China finding its way across our southern border. While the fentanyl “high” is intense, it is of relatively short duration. Xylazine prolongs the duration of the “high” and increases its intensity but produces a more severe withdrawal than opioids alone.
- Xylazine withdrawal remains poorly defined in its characteristics and is complex to manage. There are overlapping symptoms with that of opioid withdrawal (e.g., irritability, restlessness, anxiety and dysphoria), but no hallmark symptoms have been diagnostically established.
- Standard opioid withdrawal treatment should be started early and liberally, with the addition of $\alpha 2$ agonists to specifically target xylazine withdrawal. It is safe to utilize multiple $\alpha 2$ agonist in conjunction, and we recommend an $\alpha 2$ agonist as part of initial opioid withdrawal standard of care, as opioids alone will not treat xylazine withdrawal. In addition to an $\alpha 2$ agonist, we recommend secondary analgesic treatment options to complement acute withdrawal treatment, including benzodiazepines, gabapentinoids, and ketamine. Dexmedetomidine can be effective as well, but requires continuous monitoring.
- Xylazine-associated skin ulcers are well described, and frequently seen in opioid use disorder patients. Patients have reported wounds from direct injection, intranasal and inhalational administration of xylazine, but wounds can occur distant to the injection site. General and supportive wound care is recommended (i.e., local debridement, topical antimicrobial agents, non-adhesive dressing changes, or amputation) .
- Regional anesthesia demonstrated significant value as a potentially beneficial addition to wound management pre- and post-operatively. We recommend use of regional anesthesia as an additional tool for managing the intense pain from xylazine wounds with multimodal analgesia.

Table 1: Xylazine withdrawal medications with associated receptor selectivity, dosing, route of administration, and clinical considerations.

Medication	Selectivity	Common Dosing	Routes of Administration	Clinical Considerations
		Max dose		
Primary Alpha-2 (α2) Adrenergic Agonists for Treatment of Withdrawal				
Dexmedetomidine	nonselective; α2 agonist (α2a, α2b, α2c)	0.2-1.5mcg/kg/hr	IV, sublingual	Hemodynamic effects; restrictions on where in hospital medication can be used
Clonidine	nonselective; α2 agonist (α2a, α2b, α2c)	PO: 0.1-0.3mg TID; TD: 0.1-0.3mg/24h 2.4mg/day	Transdermal, oral, IV (off-label), intrathecal	Hemodynamic effects
Guanfacine	selective; α2 agonist (α2a)	0.5-1mg BID	Oral	Less hemodynamic effects
		4mg/day 2.88mg/day		
Tizanidine	nonselective; α2 agonist (unknown selectivity)	2mg-4mg TID	Oral	QTC prolongation; limited hemodynamic effects; renal and hepatic dosing considerations
		36mg/day		
Lofexidine	nonselective; α2 agonist (α2a)	0.54mg QID	Oral	Less hemodynamic effects; hepatic dosing considerations
Secondary Withdrawal Medication Agents				
Lorazepam	GABA agonist	1-2mg/day	Oral, IV, IM	Reduces anxiety, may cause sedation
Ketamine	NMDA antagonist	0.3 mg/kg intravenously over 15 min with continue dosing as needed	IV	Neuropathic pain and anxiety; may cause vivid dreams and hallucinations

CONCLUSION

- Xylazine exposure is rapidly increasing, because of its low cost and easy accessibility for illegal drug suppliers. Xylazine is sought by users because it intensifies and prolongs the otherwise short duration of a fentanyl “high.” Only 43 cases involved xylazine use between 1966 to 2013. However, in recent years, multiple localities, especially Philadelphia, have noted a surge in xylazine-related overdoses. Philadelphia remains the epicenter of the adulterant, and our hospital’s experience with xylazine continues to expand.
- We present here a case of fentanyl-xylazine use with life-threatening sepsis and wounds. We outline a coordinated multidisciplinary approach encompassing withdrawal treatment utilizing aggressive $\alpha 2$ agonist and opioid therapies and multimodal analgesia, including regional anesthesia.
- As the opioid epidemic expands, exposure to xylazine and other agents will expand. There has been a 10-fold increase of stimulant use in the last decade. All are creating devastating complications. We hope this report brings awareness of this complex condition to practitioners, and helps to provide treatment strategies for patients presenting with xylazine related complications.

REFERENCES

- White House ONDCP Director Statement on Flattening Overdose Death Rate Over the Past Year | ONDCP. The White House. Published August 17, 2023. <https://www.whitehouse.gov/ondcp/briefing-room/2023/08/17/white-house-ondcp-director-statement-on-flattening-overdose-death-rate-over-the-past-year/#:~:text=This%20latest%20CDC%20report%20shows>
- Urine Drug Surveillance in Philadelphia, PA, with Emphasis on Xylazine and its Metabolites. www.cfsre.org. Accessed November 28, 2023. <https://www.cfsre.org/resources/presentations/urine-drug-surveillance-in-philadelphia-pa-with-emphasis-on-xylazine-and-its-metabolites>
- Ruiz-Colón K, Chavez-Arias C, Díaz-Alcalá JDA, Martínez M. 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:<https://doi.org/10.1016/j.forsciint.2014.03.015>
- D'Orazio J, Nelson L, Perrone J, Wightman R, Haroz R. Xylazine Adulteration of the Heroin-Fentanyl Drug Supply : A Narrative Review. *Ann Intern Med*. 2023;176(10):1370-1376. doi:10.7326/M23-2001
- Alexander RS, Canver BR, Sue KL, Morford KL. Xylazine and Overdoses: Trends, Concerns, and Recommendations. *American Journal of Public Health*. 2022;112(8):1212-1216. doi:<https://doi.org/10.2105/ajph.2022.306881>

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