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The emerging fentanyl–xylazine syndemic in the USA: challenges and future directions

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Xylazine, a non-opioid analgesic and sedative approved only for non-chronic veterinary use, is spreading across unregulated North American drug markets and becoming increasingly implicated in opioid overdoses. Between 2018 and 2021 in the USA, estimated fatal drug poisonings involving xylazine, often co-occurring with synthetic opioids such as fentanyl, increased from 260 to 3480 cases.[1] This use of xylazine takes place in the context of the ongoing US opioid overdose crisis, which is expected to claim an estimated 1·2 million additional lives by 2029, barring urgent substantial policy reforms.[2] The White House Office of National Drug Control Policy identified fentanyl adulterated or associated with xylazine (FAAX) as an emerging threat and in July, 2023, issued a response plan leveraging the Emerging Threats Committee and other vital stakeholders.[3] Although this is a welcome strategy that sets out the federal government's plan to address xylazine, further non-punitive efforts and public health interventions are needed from health-care systems, policy makers, and community leaders to address the longer-term structural factors driving this crisis.

The rise in drug overdoses involving illicitly manufactured fentanyl (IMF) combined with xylazine could be characterised as a syndemic, demonstrating a strong ecological link and closely linked epidemiology.[4–7] This framing recognises the disproportionate impacts of FAAX on vulnerable populations, thereby exacerbating existing upstream social and structural disparities in health. Notably, the FAAX syndemic exhibits intricate

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biopsychosocial interactions that exploit health vulnerabilities among people who use drugs, fuelled by deeply rooted structural inequalities, including carceral prohibitionism, social exclusion, and limited access to social and health-care resources.[4–7]

Market differentiation and pharmacokinetics are two factors affecting the central role of IMF in ushering shifts in the illicit drug market and creating demand for potent adulterants such as FAAX. Although more evidence is needed about why xylazine is combined with fentanyl, some reports suggest that by adding xylazine as an adulterant for synthetic opioids such as IMF, manufacturers can potentially maximise profits and distinguish their brand in the market, attracting a wider customer base.[6,7] This has most notably been observed in Philadelphia, PA, USA—regarded as an epicentre of the emerging xylazine crisis in mainland USA—where over 90% of the city's street opioid supply has shifted to FAAX.[8] Further, xylazine has been described by people who use drugs as lengthening the sedative effects of IMF—solving the disadvantage of fentanyl's short duration of effect—thereby postponing craving and physical withdrawal symptoms.[6,7]

Existing national and local processes to report fatal and near-fatal overdose deaths are crucial, but we urge the public and the scientific community to recognise xylazine as a harbinger of a deeper problem: newfound challenges in proactive public health monitoring, prevention, treatment, and supportive care for people who use drugs in an increasingly synthetic, polysubstance, and IMF-dominated market in the USA.[6,7] Although most extensively documented in North America, rising global rates of opioid misuse and polysubstance overdose deaths suggest illicit use of xylazine and other synthetic adulterants could be of concern for other countries.[9] For instance, the UK reported the first xylazine-related overdose death outside of North America in December, 2022 and xylazine has been detected in a growing number of drug seizures.[10,11] We propose three priorities to help address the emerging use of fentanyl–xylazine (panel).

First, comprehensive drug checking and surveillance infrastructure are vital for capturing real-time information on xylazine-involved overdoses and unregulated drug market dynamics. Sentinel drug forecasting and early warning systems should be leveraged for effective pharmacovigilance and can be strengthened through cross-border collaboration, exemplified by initiatives such as the European Monitoring Centre for Drugs and Drug Addiction. Although several national agencies, such as the US Centers for Disease Control and Prevention, the State Unintentional Drug Overdose Reporting System, and the Drug Enforcement Administration, have shed light on early trends in the spread of xylazine in the USA, incomplete or limited high-quality regional and national data on FAAX is likely to underestimate its true prevalence.[1,6] This underestimation is partly due to fixed drug categorisations in standardised databases that do not precisely identify new substances (eg, absence of specific International Classification of Diseases (ICD)-10 and ICD-10-Clinical Modification codes for xylazine-related deaths) and various combinations of drugs involved in overdoses.[1,3] Moving forward, flexible data systems need to be implemented to improve precision. Additionally, these drug monitoring efforts should be complemented with non-punitive supply-side harm reduction and surveillance initiatives.[7] Such efforts could entail structured surveys of wholesale or retail-level drug sellers to elucidate the pathways through which FAAX infiltrates the supply chain, as well as contextualising the social and

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structural conditions that promote xylazine distribution; narcotics entrepreneurs should be pragmatically recognised as crucial interlocutors who may be potential risk-reduction allies.[7]

In clinical and community-based settings, FAAX should be routinely integrated into toxicological testing, together with rapid point-of-care testing technologies such as Fourier-transform infrared spectroscopy machines and test strips. Although preliminary findings indicate that xylazine test strips are sensitive and precise, false-positives can occur with certain compounds (eg, diphenhydramine, lidocaine, levamisole, and 3,4-methylenedioxymethamphetamine), highlighting the need to expand point-of-care testing in tandem with confirmatory analysis methods such as Fourier-transform infrared spectroscopy and gas chromatography with mass spectrometry.[12,13] Further collaborations among public health and legal actors could prove essential in addressing legal and regulatory barriers to the implementation of widespread FAAX testing at state and national levels. Proactive, harm reduction-informed drug testing and monitoring can guide clinical management, encourage less risky drug use behaviours, and reduce inadvertent xylazine exposure.[1,14]

Second, clinical knowledge related to use of xylazine needs to be reinforced among the addiction health-care workforce through education, training, and research. Health-care providers and emergency responders need to be promptly informed of new adulterants such as FAAX in the ever-changing unregulated drug market and trained accordingly. Hospitals should be prepared to provide appropriate care for people who have used FAAX, requiring more intensive or specialised treatment for soft tissue injuries (necrotic skin ulcers) and severe withdrawal symptoms.[1,3,5,15] Polysubstance withdrawal entails new challenges for clinical management; effective tools such as methadone and buprenorphine to treat opioid withdrawal syndromes do not fully address symptoms from xylazine withdrawal,[16] which might hamper effective substance cessation. Clinical guidelines for treating xylazine withdrawal symptoms in both inpatient and outpatient settings should be expanded to encompass the diverse array of the physiological and psychological risks associated with polysubstance use.

People who use drugs might also avoid clinical-based wound care due to negative past experiences and stigma.[1,17] The severity of these skin ulcers could compound the pervasive stigma already experienced by people who use drugs from some health-care providers, resulting in inadequate care.[5] Dehumanising and sensationalist news media portrayals of people who use xylazine could also exacerbate their social exclusion.[5] To address these issues, health-care systems must implement evidence-based risk-reduction clinical guidelines to offer accessible, trauma-informed, non-stigmatising urgent and continued care for patients affected by FAAX, while also expanding basic science and clinical research to clarify the effects of chronic xylazine use in animal models and humans.

Third, expanding opioid education and naloxone distribution programmes to address the unique public health challenges of the FAAX syndemic is essential. Naloxone, an opioid antagonist medication, cannot counteract the effects of xylazine, a non-opioid sedative.[18] Several α2-adrenergic receptor antagonists (eg, yohimbine, tolazoline, and atipamezole) are proposed as candidates to reverse the sedative, hypotensive, and bradycardic effects of

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xylazine in animal studies.[19] However, no approved xylazine-reversal agents for humans exist,[3] warranting further research.

Public health agencies and community leaders should also widely disseminate information on FAAX toxicity, evidence-based harm reduction strategies, and additional life-saving measures after naloxone administration (eg, supplemental oxygen and airway management techniques),[1,3,15] and actively combat misinformation. Multi-level, cross-sectoral partnerships are crucial to move beyond purely medical conceptualisations of FAAX and mitigate the adverse upstream social, economic, and environmental conditions that produce syndemic vulnerabilities among people who use drugs.[4,20] These efforts could include connecting patients affected by FAAX use with equitable access to vital social services such as housing assistance, health education, social support networks, and others, as well as community-based safer supply programmes. Local harm reduction leaders, including non-profits (eg, Savage Sisters in Philadelphia, PA, USA), are making crucial contributions to build trust and social capital with communities and provide culturally relevant, trauma-informed, non-stigmatising, and tailored solutions to local needs in response to xylazine's emergence.[3,20]

Concerted national and international efforts are imperative to address the FAAX syndemic. Health-care systems, providers, policy makers, and governments can take steps to redefine the future trajectory of the FAAX syndemic by adopting proactive measures to prevent its spread and addressing the fundamental social and structural conditions that can fuel similar emergent syndemics.

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Panel: Key policy priorities to address the fentanyl–xylazine syndemic

Strengthen drug testing and surveillance infrastructure for FAAX

- Develop robust drug surveillance and early warning systems for novel adulterants in the unregulated drug supply and monitor overdose trends
- Recognise street sellers and local wholesale suppliers as potential risk-reduction interlocutors
- Ensure widespread access to drug checking programmes and point-of-care-testing technologies, including xylazine test strips

Ensure access to high-quality treatment and continuity of care of FAAX

- Provide training and evidence-based, best practice guidelines to inform clinical management and continued care of FAAX patients
- Proactively combat xylazine-related stigma in both clinical and non-clinical (eg, news media) settings, while simultaneously highlighting FAAX's toxicity

Expand opioid education and naloxone distribution programmes and partnerships to encompass FAAX

- Conduct basic science and clinical research to develop novel xylazine-reversal agents and better understand the pathophysiology of chronic xylazine use
- Foster multi-level, cross-sectoral partnerships to widely disseminate FAAX harm reduction messaging and facilitate public health interventions tailored to local needs

FAAX=fentanyl adulterated or associated with xylazine