Journal of Frontiers in Multidisciplinary Research

Xylazine and Fentanyl Co-Involvement in U.S. Overdose Deaths: A Systematic Review of Public Health Trends, Mechanisms, and Intervention Gaps

Aisha Katsina Isa [1*], Idowu Adeyemo [2]
[1] University of Illinois Springfield, USA
[2] Ohio University, USA

* Corresponding Author: **Aisha Katsina Isa**

Article Info

E-ISSN: 3050-9726
P-ISSN: 3050-9718
Volume: 06
Issue: 02
July – December 2025
Received: 12-05-2025
Accepted: 15-06-2025
Published: 04-07-2025
Page No: 96-102

Abstract
The increasing presence of xylazine, a veterinary tranquilizer, in the illicit opioid supply across the United States has intensified the public health burden of overdose mortality. Commonly referred to as "tranq," xylazine is frequently combined with fentanyl, complicating clinical management due to its non-opioid pharmacological profile and unresponsiveness to naloxone reversal. Its physiological effects including profound central nervous system depression, hypotension, and vasoconstriction contribute to unique clinical presentations such as non-healing skin ulcers, rapid tissue necrosis, and bloodstream infections. These effects are particularly devastating among high-risk populations, including individuals experiencing homelessness, polysubstance use, and untreated psychiatric disorders. This systematic review synthesizes current data from toxicological studies, surveillance reports, and public health literature to examine the mechanisms, health impacts, and research gaps related to xylazine-fentanyl co-use. Our analysis highlights a pressing need for targeted surveillance, the development of clinical antagonists, and the expansion of housing-integrated harm reduction frameworks to address this evolving drug crisis.

DOI: https://doi.org/10.54660/.JFMR.2025.6.2.96-102

Keywords: Xylazine, Tranq, Fentanyl, Synthetic Opioids, Overdose, Homelessness, Public Health, Wound Necrosis, Predictive Modeling

1. Introduction

The United States continues to face a devastating public health emergency driven by synthetic opioids, with fentanyl at the center of an escalating overdose crisis. In recent years, this crisis has evolved into a more complex and dangerous epidemic with the emergence of xylazine, a veterinary sedative that is now frequently found in the unregulated drug supply. Known on the streets as "tranq," xylazine is not an opioid, yet it is increasingly combined with fentanyl to intensify or prolong euphoric effects. This combination has introduced new clinical, toxicological, and policy challenges that current overdose response systems are not equipped to handle.

Xylazine induces deep sedation, bradycardia, and hypotension and significantly increases the risk of fatal overdose when used with opioids. Because it does not act on opioid receptors, xylazine-related toxicity cannot be reversed with naloxone, which is the frontline treatment for opioid overdose. This has created a disturbing pattern of overdose presentations where individuals remain unresponsive even after receiving appropriate doses of naloxone, leading to confusion among first responders and delays in care (CDC, 2024).

The effects of xylazine extend far beyond overdose risk. People who inject drugs are increasingly presenting with painful, necrotic skin ulcers that often require surgical intervention or lead to amputation. These injuries are not limited to injection sites and have been observed in individuals who do not inject drugs, raising concerns about systemic toxicity and widespread vascular damage (Ciccarone *et al*., 2025; Mercer University, 2024).

In Vermont, for instance, the introduction of xylazine into the drug supply was associated with a sharp increase in invasive bloodstream infections and soft tissue injuries, with many patients requiring multiple hospital admissions (Storey, 2024).

Surveillance data show a steep rise in xylazine detection across the United States. From 2019 to 2022, the number of forensic drug reports testing positive for xylazine more than doubled in over 30 states. In Philadelphia, nearly all fentanyl samples tested in 2023 contained xylazine, and similar patterns have been reported in Maryland, New York, and Connecticut (Department of Health, 2024). Despite this rapid spread, xylazine is still not classified as a controlled substance at the federal level, which has contributed to inconsistent monitoring, underreporting, and a lack of clinical preparedness.

This evolving threat disproportionately affects people living in poverty, those experiencing homelessness, and individuals with co-occurring psychiatric conditions. These populations often face barriers to accessing care, limited housing stability, and heightened exposure to unregulated drug markets. As a result, xylazine-related harms are not evenly distributed. They are most severe among those who are already marginalized by systems that fail to meet their complex health and social needs.

This review aims to synthesize the available evidence on the public health implications of xylazine and fentanyl co-use in the United States. We explore the pharmacological and toxicological mechanisms of xylazine, its clinical impact when combined with synthetic opioids, and the population-level vulnerabilities that increase its harms. We also identify key gaps in research and clinical response and outline opportunities for intervention, including the development of clinical antagonists, improved diagnostic strategies, and the integration of housing support with harm reduction services. In doing so, we call for a coordinated, science-driven response that reflects the severity and urgency of this emerging public health crisis.

2. Methods

2.1 Review Design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The primary aim was to synthesize existing evidence on the clinical, pharmacological, and public health implications of xylazine use in the United States, particularly in the context of its co-involvement with fentanyl and other synthetic opioids. The review was designed to support data-informed strategies for harm reduction, emergency clinical management, and public health response planning.

2.2 Eligibility Criteria

Studies were eligible for inclusion if they were peer-reviewed, published in English between January 1, 2010, and June 30, 2025, and focused on human subjects or provided data directly relevant to human clinical or public health outcomes. Eligible articles had to be conducted in the United States or involve U.S.-relevant populations and report on one or more of the following areas: xylazine toxicity; xylazine-fentanyl co-use or overdose; clinical outcomes; diagnostic or therapeutic strategies; wound-related complications such as necrosis or infection; or public health challenges affecting vulnerable populations, including those experiencing homelessness, psychiatric illness, or polysubstance use.

Studies were excluded if they focused solely on veterinary or agricultural applications of xylazine without human relevance, were written in a language other than English, lacked full-text availability, or consisted solely of opinion pieces, commentaries, or editorials unsupported by empirical evidence. Animal-only studies were excluded unless they contained findings clearly translatable to human clinical care or public health implications.

2.3 Information Sources and Search Strategy

A comprehensive literature search was performed using several academic databases, including PubMed, Scopus, Embase, Web of Science, and Google Scholar. The search was completed in June 2025 and included studies published up to that date. Keywords and Medical Subject Headings (MeSH) terms were used in combination to capture the full scope of xylazine-related research. These included terms such as “xylazine,” “fentanyl,” “synthetic opioids,” “overdose,” “wound necrosis,” “skin ulcer,” “naloxone failure,” “harm reduction,” “homelessness,” “mental health,” and “drug adulterants.” Boolean operators were used to refine and broaden the search where appropriate. Additionally, reference lists of relevant studies were manually screened to identify further articles not captured in the initial database queries.

2.4 Study Selection Process

After removing duplicates, all titles and abstracts were independently screened for relevance by two reviewers. Full-text articles were retrieved for those that met the initial criteria or required further evaluation. Studies were then assessed against the predefined inclusion and exclusion criteria. Any disagreements between reviewers were resolved through discussion until consensus was reached. The selection process was documented in a PRISMA flow diagram, which details the number of studies identified, screened, excluded, and ultimately included in the final synthesis.

2.5 Data Extraction and Analysis

Data from each included study were systematically extracted and organized into a structured synthesis. Extracted information included publication details, study population and setting, research objectives, study design, key outcomes related to xylazine exposure and fentanyl co-use, and the public health or clinical significance of findings. Given the diversity of study types and reporting formats, the data were synthesized narratively rather than statistically. No meta-analysis was performed due to variability in study design, sample characteristics, and outcome measures.

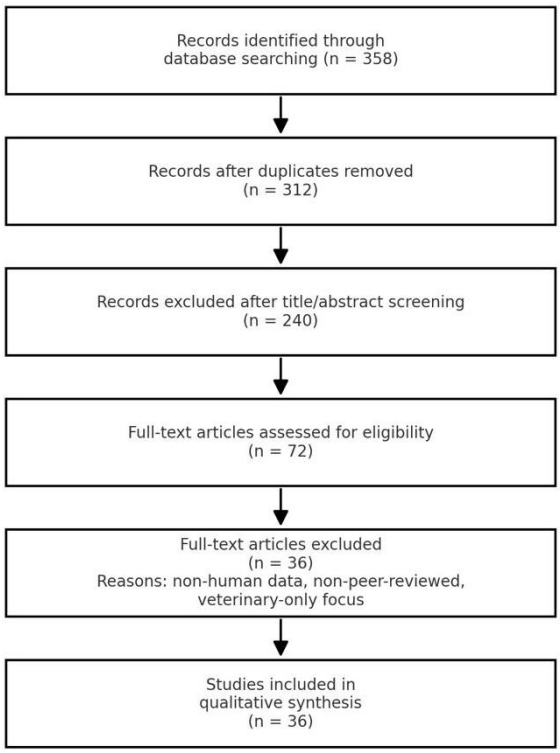

Fig 1: PRISMA 2020 Flow Diagram

3. Pharmacology and Toxicodynamic of Xylazine

Xylazine is a veterinary sedative originally developed in the 1960s for use in large animals such as horses and cattle. It acts as a powerful alpha-2 adrenergic receptor agonist, which means it reduces the release of norepinephrine and other neurotransmitters in both the central and peripheral nervous systems. This results in deep sedation, muscle relaxation, and a significant slowing of heart rate and breathing. These effects make xylazine effective for animal procedures but dangerous and unpredictable in humans, especially when mixed with opioids like fentanyl (StatPearls, 2025; Department of Health, 2024).

When used in humans, xylazine can cause central nervous system depression, respiratory failure, hypotension, and bradycardia. Unlike opioids, xylazine does not bind to opioid receptors, which means that the standard opioid overdose reversal medication, naloxone, has no effect on its toxic effects. This has led to a growing number of overdose cases in which patients remain unconscious and at risk even after receiving repeated doses of naloxone. This challenge has serious implications for emergency response protocols and hospital-based treatment plans (CDC, 2024).

The onset of xylazine is rapid, often within minutes, and its effects can last for several hours. When injected, it is known to cause a burning sensation at the site, which can lead to vein damage and tissue irritation. As it circulates through the body, xylazine contributes to poor tissue perfusion by constricting blood vessels, a mechanism that may partly explain the severe skin ulcers and infections that are increasingly associated with its use (Ciccarone *et al*., 2025; Carroll, 2024).

Pharmacologically, xylazine resembles clonidine, a drug used to treat hypertension and withdrawal symptoms. Like clonidine, xylazine lowers blood pressure and heart rate, but in uncontrolled doses, it can push these vital signs to life-threatening levels. High doses can also cause coma, seizures, and death. Its combination with fentanyl, which already carries a high risk of respiratory depression, creates a dangerous interaction that is much more lethal than either drug alone (Montero *et al*., 2025).

Despite its growing presence in the illicit drug supply, xylazine remains poorly understood in clinical practice. Most clinicians are not trained to recognize or treat its specific effects, and few emergency departments routinely test for it. There are no FDA-approved medications to reverse or treat xylazine toxicity, and the lack of human pharmacokinetic data makes it difficult to predict how it behaves in the body under different conditions or dosages. This knowledge gap leaves health professionals unprepared, and communities unprotected in the face of a rapidly growing threat (StatPearls, 2025; Ruiz-Colón *et al*., 2014).

Xylazine's unique pharmacology and the absence of effective treatments make it a high-risk contaminant in the illicit opioid supply. Its role in overdose deaths, soft tissue injury, and cardiovascular compromise demands urgent attention from clinicians, toxicologists, and public health officials. Without targeted research and clinical education, the health system will continue to fall short in responding to this evolving emergency.

4. Co-Involvement with Fentanyl and Other Synthetic Opioids

The rise of xylazine in the unregulated drug supply is closely linked to its widespread combination with fentanyl, the synthetic opioid responsible for most overdose deaths in the United States today. While fentanyl is extremely potent on its own, it produces a relatively short-lived euphoric effect. This has led to the increasing use of xylazine as a low-cost additive that prolongs the sedative "high," creating a more intense and longer-lasting experience for users (Ciccarone, 2023; Carroll *et al*., 2022). However, the interaction between the two drugs is far from benign. Together, they form a toxic mix that sharply increases the risk of fatal overdose and complicates both detection and treatment.

Co-involvement of xylazine and fentanyl has been confirmed in a growing number of postmortem toxicology reports. Between 2019 and 2022, xylazine was detected in approximately 11 percent of overdose deaths involving fentanyl in some states. In Philadelphia, the number was even higher, with xylazine found in more than 90 percent of drug samples tested from suspected fentanyl cases (Department of Health, 2024). Similar increases have been observed in Maryland, New York, and Connecticut, signaling a disturbing national trend (Cicero *et al*., 2023).

From a clinical standpoint, this co-involvement presents unique challenges. Fentanyl overdose alone causes profound respiratory depression, bradycardia, and unconsciousness. These effects are often rapidly reversible with naloxone if administered early. But when fentanyl is combined with xylazine, patients often remain unresponsive despite multiple doses of naloxone. The reason lies in the fact that xylazine does not interact with opioid receptors, meaning that naloxone offers no reversal benefit for its sedative and cardiovascular effects. As a result, emergency responders are increasingly encountering overdoses that do not follow the expected course of recovery, leading to higher rates of complications and death (CDC, 2024; StatPearls, 2025).

The widespread presence of xylazine in fentanyl has also made it harder to estimate the true scope of its public health impact. In many jurisdictions, toxicology screens do not routinely test for xylazine, leading to underreporting and missed opportunities for intervention. This lack of consistent surveillance masks the extent to which xylazine is contributing to overdose deaths and limits the effectiveness of epidemiological tracking and resource allocation (Ruiz-Colón *et al*., 2014).

In addition to fentanyl, xylazine has been detected in drug samples containing heroin, methamphetamine, cocaine, and benzodiazepines. This indicates not only a deepening of polysubstance use but also a growing unpredictability in the street drug market. For individuals who use drugs, this unpredictability increases the risk of unintentional overdose, as users often do not know that xylazine is present in the substances they consume. Many people who inject drugs report experiencing prolonged unconsciousness, confusion, and severe skin wounds with no awareness that xylazine was involved (Carroll *et al*., 2022).

Xylazine's co-involvement with fentanyl and other drugs represents a dangerous shift in the overdose crisis. Its pharmacological profile, lack of detectability, and resistance to opioid antagonists make it a silent driver of death and injury in already vulnerable communities. To reduce mortality and improve clinical outcomes, there is an urgent need for broader drug testing protocols, early warning systems, and tailored intervention strategies that reflect the complexity of modern polysubstance use.

5. Clinical Manifestations and Diagnostic Challenges

Xylazine produces a range of clinical effects that are distinct from those caused by opioids alone. Its primary action as an alpha-2 adrenergic agonist results in deep sedation, muscle relaxation, respiratory depression, and cardiovascular suppression. When combined with fentanyl, these effects become more severe and unpredictable. The overlapping toxicity of both drugs creates a clinical picture that is often more difficult to manage than typical opioid overdoses (StatPearls, 2025; CDC, 2024).

In emergency settings, patients who have used fentanyl mixed with xylazine often present with profound unresponsiveness, bradycardia, hypotension, and shallow breathing. Unlike pure opioid overdoses, which frequently respond to a timely dose of naloxone, these cases may remain unchanged even after several rounds of naloxone administration. This resistance to naloxone has become one of the most troubling features of xylazine-related toxicity, often leading to delays in proper diagnosis and treatment (Carroll *et al*., 2022; Ruiz-Colón *et al*., 2014).

Another major clinical challenge is the presentation of extensive skin damage. Individuals exposed to xylazine, especially through intravenous injection, frequently develop large necrotic ulcers. These wounds are often painful, slow to heal, and susceptible to infection. Some users develop soft tissue infections that progress to abscesses, cellulitis, or even systemic bloodstream infections like sepsis or group A Streptococcus bacteremia. In some regions, such as Vermont, xylazine use has been directly linked to a ninefold increase in serious blood infections among people who inject drugs (Storey, 2024).

These skin injuries are not limited to injection sites. In many cases, necrosis occurs in areas of the body that were not involved in drug administration. This suggests that xylazine has systemic effects on vascular function, possibly through vasoconstriction and impaired blood flow to the extremities. The exact mechanism remains unclear, but the severity of the tissue damage has made "tranq wounds" a defining clinical feature of xylazine toxicity (Moniri and Canal, 2024; Ciccarone *et al*., 2025).

Diagnostically, xylazine presents unique barriers. Standard urine drug screens do not detect xylazine, and many hospitals lack access to specialized toxicology panels that include it. This means clinicians often rely on clinical suspicion and patient history, both of which can be unreliable. In the absence of confirmatory testing, health professionals may misinterpret prolonged unconsciousness or failure to respond to naloxone as an atypical opioid reaction or a psychiatric condition. This diagnostic uncertainty places patients at greater risk for mismanagement or stigmatization (Cicero *et al*., 2023).

Furthermore, patients who survive xylazine overdose or injection-related injuries frequently cycle through emergency departments without receiving long-term care. Many are discharged with untreated wounds, no access to addiction treatment, and no connection to housing or harm reduction services. These missed opportunities for intervention contribute to worsening health outcomes and ongoing cycles of morbidity (CDC, 2024).

In sum, xylazine creates a constellation of clinical symptoms that differ from classic opioid overdose. Its toxic effects on the skin, central nervous system, and cardiovascular system require specialized clinical protocols and improved diagnostic tools. Until xylazine becomes a standard part of toxicology screening and medical training, patients will continue to face dangerous gaps in care.

6. Tissue Injury, Necrosis, and Blood Infections

One of the most alarming consequences of xylazine use is its association with deep tissue injury, skin necrosis, and severe bloodstream infections. These conditions often appear in individuals who inject drugs, but increasingly, wounds are also reported in people who snort, smoke, or unknowingly ingest xylazine-contaminated substances. The exact biological mechanism behind these effects is still under

investigation, but the prevailing theory points to a combination of vasoconstriction, inflammation, and reduced peripheral perfusion, all of which impair wound healing and promote tissue breakdown (Ciccarone *et al*., 2025).

Unlike typical injection-related abscesses or track marks, xylazine wounds are described as large, ulcerating, and necrotic, with a tendency to spread rapidly. These injuries often develop away from injection sites, implicating systemic vascular damage rather than localized irritation. In many cases, the wounds require surgical debridement, skin grafts, or even limb amputation. Standard wound care, including antibiotics and dressings, is often ineffective because the tissue is poorly perfused and slow to regenerate (Moniri and Canal, 2024; Carroll *et al*., 2022).

In one confirmed case, a man who injected xylazine-laced opioids developed extensive ulcerations on his lower extremities. The wounds extended well beyond the injection point and were resistant to outpatient treatment, ultimately requiring hospitalization (Moniri and Canal, 2024). Another report detailed multiple patients presenting with wounds that exposed muscle or bone, often in the absence of any recent injection. These cases suggest that xylazine may impair microvascular circulation, leading to ischemic injury that mimics conditions such as necrotizing fasciitis or arterial insufficiency (Ciccarone *et al*., 2025).

Wound complications are not the only concern. Xylazine-related soft tissue damage significantly increases the risk of secondary bacterial infections, including cellulitis, abscesses, and sepsis. Perhaps most troubling is the link between xylazine exposure and invasive group A Streptococcus (GAS) bloodstream infection. In Vermont, clinicians observed a 900 percent increase in GAS infections over a two-year period following the introduction of xylazine into the regional drug supply. Most of these patients had visible necrotic wounds and a history of injection drug use, and 70 percent were unhoused (Storey, 2024).

These infections are often life-threatening and require prolonged antibiotic treatment and hospitalization. Delayed wound healing and reinjury are common, particularly in patients who return to environments with limited access to hygiene, housing, or follow-up care. The frequency and severity of these infections suggest that xylazine is more than just an additive, it is a primary driver of long-term morbidity in affected communities (Cicero *et al*., 2023).

From a public health perspective, the presence of xylazine-related wounds presents both clinical and logistical challenges. Emergency departments must not only stabilize patients in crisis but also initiate long-term wound care, addiction treatment, and social support. However, many hospitals are not equipped or funded to provide comprehensive follow-up, and patients are often discharged back into unstable conditions that perpetuate the cycle of injury and reinfection (CDC, 2024).

7. Population Vulnerability: Mental Health, Housing Instability, and Harm Reduction Gaps

The rising prevalence of xylazine and fentanyl mixtures has disproportionately affected individuals facing social and structural disadvantage, particularly people experiencing homelessness, untreated mental illness, and co-occurring substance use disorders. These populations are more likely to encounter unregulated drug supplies, have limited access to timely medical care, and face persistent barriers to treatment and housing. As a result, the toxic effects of xylazine are concentrated among those who are already navigating extreme health and social vulnerability (Ciccarone *et al*., 2025; Storey, 2024).

A systematic review in the Harm Reduction Journal highlights that xylazine causes harm across several domains, including deep sedation, complex withdrawal symptoms, necrotic wound formation, anemia, and altered glucose metabolism. The review calls for an urgent expansion of drug checking programs, community-based wound care, and culturally responsive harm reduction models tailored to people who inject drugs (Johnson *et al*., 2023).

The clinical burden is compounded by mental health challenges and systemic gaps in care. Individuals living with serious mental illness often use fentanyl as a form of self-medication, making them particularly vulnerable to the sedative and disorienting effects of xylazine. The repeated trauma of overdose, wound development, and hospitalization may further destabilize psychiatric conditions, especially when long-term care is unavailable (Cicero *et al*., 2023).

In some cities, xylazine exposure has contributed to a significant rise in severe bloodstream infections. A report from Vermont's Department of Health documented a ninefold increase in invasive group A Streptococcus infection among people who inject drugs following the entry of xylazine into the local drug supply. Many of these patients were unhoused, had visible necrotic wounds, and lacked consistent access to outpatient wound management or addiction services (Storey, 2024).

Clinical case reports have described ethical dilemmas in surgical treatment for patients with xylazine-related skin necrosis. One publication in SurgiColl detailed a patient with bilateral forearm wounds that required multiple surgical debridements, negative pressure therapy, and eventual skin grafts. Despite successful interventions, the patient was lost to follow-up, raising concerns about the sustainability of high-cost care for individuals with untreated addiction (Kumar *et al*., 2024).

Similarly, an observational study in the Journal of Hand Surgery described extensive upper extremity wounds in patients with xylazine exposure, many of whom developed permanent nerve damage. The authors recommended early referrals to surgical and rehabilitation services to prevent disability and improve recovery outcomes (Martinez *et al*., 2024).

On the prevention side, xylazine test strips have emerged as a promising harm reduction tool. A 2024 study demonstrated their accuracy in detecting xylazine residue in real-world drug-checking settings. These strips allow users to identify xylazine before use, potentially reducing unintentional exposure and prompting safer behaviors. Although still in pilot stages, these tools may become vital in responding to the unpredictable composition of street drugs (Chen *et al*., 2024).

The harms of xylazine are amplified among people with psychiatric illness, housing instability, and limited access to health care. The clinical system alone cannot address these harms without structural interventions. Community-based harm reduction programs, supportive housing, integrated mental health services, and surveillance-informed outreach must be prioritized to reduce preventable injuries and deaths among those most at risk.

8. Research Gaps and Need for Therapeutic Strategies

Despite its growing presence in overdose deaths and clinical

case reports, xylazine remains one of the least understood substances in the unregulated drug supply. Most of what is known about its pharmacology and health effects has been extrapolated from animal studies and scattered clinical observations. This lack of foundational research has left critical gaps in prevention, diagnosis, and treatment — gaps that must be addressed if public health responses are to match the urgency of this crisis.

One of the most pressing gaps is the absence of an effective pharmacologic antidote. Because xylazine does not bind to opioid receptors, naloxone cannot reverse its sedative or cardiovascular effects. This leaves emergency responders with few options beyond basic airway and circulatory support. While alpha-2 adrenergic antagonists like yohimbine or atipamezole are used in veterinary settings to reverse xylazine sedation, they are not approved for human use and remain largely unavailable in hospitals and emergency departments. Without clinical trials or toxicokinetic data, it is impossible to determine their safety or efficacy in human overdose scenarios (Ruiz-Colón *et al*., 2014; CDC, 2024).

A second gap involves diagnostic testing. Most routine toxicology screens do not include xylazine, and confirmatory tests are expensive, slow, or unavailable in many jurisdictions. This results in underreporting, delayed diagnosis, and missed opportunities for intervention. Standardizing xylazine testing in emergency departments, coroner offices, and harm reduction programs would offer a clearer picture of its geographic spread and burden of harm (Cicero *et al*., 2023).

Xylazine's impact on wound pathology is another area that remains poorly characterized. While case reports have described skin necrosis, deep tissue injury, and vascular compromise, the biological mechanism behind these effects has yet to be fully explored. Whether the damage is primarily due to vasoconstriction, cytotoxicity, or contaminated drug formulations is still unknown. Histopathological studies and animal models could help clarify these processes and guide treatment protocols for wound care (Ciccarone *et al*., 2025; Kumar *et al*., 2024).

On a population level, there is limited data on how xylazine affects health outcomes in people with co-occurring psychiatric disorders, substance use histories, and housing instability. Understanding the interaction between structural vulnerability and clinical risk is essential to designing equitable public health responses. Studies that integrate epidemiologic, behavioral, and environmental data could help identify which communities are most at risk and how best to reach them with harm reduction and treatment services (Johnson *et al*., 2023; Storey, 2024).

Intervention strategies also remain underdeveloped. Harm reduction programs have started distributing xylazine test strips, but their availability is limited, and their long-term impact has not been evaluated in controlled studies. Similarly, wound care protocols are often improvised, relying on emergency departments or outreach workers without consistent clinical guidelines. Research into integrated care models — combining addiction treatment, housing support, mental health services, and wound management — could offer more durable solutions for affected individuals (Chen *et al*., 2024; Martinez *et al*., 2024).

Finally, policy gaps hinder a coordinated national response. As of 2025, xylazine is not classified as a controlled substance at the federal level, and regulatory oversight is inconsistent across states. This lack of regulation has enabled its continued use as a fentanyl additive and limited the ability of public health agencies to monitor and respond to its spread. Evidence-informed policy reform, grounded in clinical and epidemiological data, is needed to close these gaps and improve public safety.

Xylazine presents urgent and multifaceted challenges that the scientific and clinical communities are only beginning to address. From antidote development and diagnostic tools to surveillance and integrated care, a wide range of research and intervention strategies remain underdeveloped. Closing these gaps will require investment, coordination, and sustained attention from clinicians, researchers, and policymakers alike.

9. Conclusion

The increasing prevalence of xylazine in the United States drug supply has introduced a new and deeply concerning dimension to the opioid crisis. What began as a veterinary sedative has now become a widespread contaminant in fentanyl and other street drugs, driving up rates of overdose, tissue damage, bloodstream infections, and complex clinical presentations that challenge even experienced emergency responders. Unlike opioids, xylazine does not respond to naloxone and lacks a dedicated human antidote, forcing healthcare providers to rely on supportive care while managing unpredictable and often life-threatening symptoms.

Beyond its physiological harms, xylazine has revealed profound weaknesses in the nation's public health and addiction treatment infrastructure. The people most affected are often those already failed by the system, those without housing, with untreated mental health conditions, and with histories of trauma and stigma. For them, xylazine is not just a contaminant in the drug supply, it is a marker of structural neglect. Its emergence has made existing disparities more visible and more deadly.

At the same time, the response to xylazine has been fragmented. Testing is limited. Clinical awareness is low. Harm reduction efforts are underfunded. And policy remains reactive rather than preventive. Yet the evidence is clear: xylazine is here, it is spreading, and its impact is growing. Without targeted, coordinated, and evidence-based interventions, the consequences will only become more severe.

This review calls for a bold and sustained public health response. We need better toxicological research, faster diagnostics, clinical trials for potential antagonists, and care models that treat both wounds and addiction in tandem. We need policies that reflect the lived realities of people who use drugs, and we need surveillance systems that detect emerging threats before they become national emergencies.

In confronting xylazine, we have the opportunity not only to manage a growing crisis but also to strengthen our response to the broader overdose epidemic. By centering science, compassion, and equity, we can begin to turn the tide saving lives, restoring dignity, and preventing the next wave of preventable harm.

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