REVIEW

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Xylazine Adulteration of the Heroin–Fentanyl Drug Supply

A Narrative Review

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Xylazine is an animal sedative, approved by the U.S. Food and Drug Administration, that is commonly used in veterinary medicine and is not approved for human use. Since 2016, xylazine has consistently appeared in the illicitly manufactured fentanyl supply and has significantly increased in prevalence, likely due to its low cost, easy availability, and presumed synergistic psychoactive effect. Clinical experience along with the available pertinent research were used to review xylazine adulteration of the drug supply and provide guidance on the care of patients exposed to xylazine. This review discusses xylazine pharmacology, animal and human clinical effects, and what is known to date about care of patients experiencing acute overdose, xylazine–fentanyl withdrawal, and xylazine-associated wounds.

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Adulterants enter the illicit drug supply in localized geographic regions and have historically cycled out as their toxic effects have emerged. Xylazine is an animal sedative that is approved by the U.S. Food and Drug Administration (FDA); it is commonly used in veterinary medicine and is not approved for human use. Since 2016, xylazine has consistently appeared in the illicitly manufactured fentanyl (IMF) supply and has significantly increased in prevalence, likely due to its low cost, easy availability, and presumed synergistic psychoactive effect. However, the true intent of adding xylazine as an adulterant remains unclear. In an ethnographic study of people exposed to xylazine–fentanyl in Philadelphia, Pennsylvania, some noted "tranq dope" (the combination of xylazine and fentanyl) was sought after because they felt xylazine prolonged the short-acting effects of IMF (1). Conversely, others have noted that xylazine did not extend or improve the euphoria associated with IMF and they actively tried to avoid xylazine because of safety concerns (2, 3). Xylazine's clinical significance in the opioid overdose crisis warrants further evaluation. The Office of National Drug Control Policy (ONDCP) report states that "Fentanyl was dangerous before and it is even more dangerous now due to its combination with xylazine." This statement reflects data, using advanced testing, that forensic laboratory identifications of xylazine increased recently in both drug samples and drug-related decedents (4, 5). The authors recommend exercising caution not to assign causality to this association without dedicated research on this topic. In the following narrative, we used our clinical experience along with the available pertinent research to review xylazine adulteration of the drug supply.

History and Epidemiology

The first reports of xylazine use date back to Puerto Rico around 2001 as "anestesia de caballo" (horse anesthetic). Xylazine was first identified in the continental United States in 2006 in a small percentage of fatal heroin and/or fentanyl overdoses (~2%), but detections have steadily increased since 2016 (6). Xylazine–fentanyl combinations have now been identified in 48 states and were identified in 23% of IMF powder and 7% of fentanyl tablets seized in 2022 (7). However, these rates vary widely by geography.

Older reports from the U.S. Drug Enforcement Administration (DEA) suggest that xylazine enters the drug supply via veterinary pharmaceutical sources and is added at the local level rather than being imported with IMF. More recent reports suggest that the supply has shifted to overseas suppliers. The DEA estimates that a kilogram of xylazine powder can be purchased online from Chinese suppliers for $6 to $20 (2). The increasing prevalence of xylazine detected in fentanyl tablets, which are typically produced before entering the U.S. drug supply chain, may indicate a shift away from local adulteration.

A toxicosurveillance study of drug paraphernalia in Maryland found xylazine in 80% of samples tested between 2021 and 2022 (8). Similarly in Philadelphia, which many believe is the epicenter of the xylazine drug supply adulteration crisis, xylazine was detected in 90% of street opioid samples tested in 2021 (9). The DEA reports that "the emergence of xylazine across the United States appears to be following the same path as IMF, beginning with white powder heroin markets in the Northeast before spreading to the South, and then working its way into drug markets westward" (4). The DEA estimates the presence of xylazine in drugs tested in DEA laboratories increased in every region of the United States from 2020 to 2021 (7). Although the Northeast region had detected the highest total number of drug samples with xylazine over the 2 years, the South region showed the largest percentage increase (193%) in 2021 (4).

The increase in laboratory detection of drug samples is associated with an increase in decedents testing positive for xylazine (4). In Philadelphia, xylazine was detected in 2% of unintentional opioid overdose deaths from 2010 to 2015 and 31% in 2019 (6). A DEA report in 2021 found that xylazine-positive overdose deaths increased by 1127% in the South ($n = 1423$), 750% in the West ($n = 34$), 516% in the Midwest ($n = 351$), and 103% in the Northeast ($n = 1281$) (4). Similarly, a recent report from

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the Centers for Disease Control and Prevention (CDC) notes an increase in the percentage of fentanyl-involved deaths with xylazine detected (5). However, neither this report nor the DEA report can be used to assign causality. It remains unknown what percentage of this increase was due to expanded testing or the increased prevalence of xylazine rather than enhanced toxicity of the combination.

PHARMACOLOGY

Xylazine was investigated for human use in the 1960s, but trials were halted due to reported side effects of oversedation and hypotension (10). Unfortunately, details of those studies are not available and knowledge of the clinical pharmacology of xylazine is largely derived from animal studies and limited case reports in humans with overdose.

Xylazine exerts its sympatholytic activity via presynaptic α-2 adrenergic receptors, which are part of a negative feedback loop that reduces the release of norepinephrine, resulting in reduced sympathetic outflow, sedation, analgesia, and muscle relaxation (11, 12). Analgesic effects in animals have been attributed to spinal and central actions (13, 14). In horses, combining opioids with xylazine resulted in an enhanced duration of sedation and analgesia compared with either alone (15).

In some animal species, xylazine causes bradycardia. The slowed heart rate is attributed to increased vagal and enhanced baroreceptor activity and can be blocked via pretreatment with vagolytics (16–18). As in clonidine overdose in humans, intravenous administration of xylazine can cause transient hypertension due to peripheral vascular α-2 adrenergic stimulation, which has been seen in dogs and other animals (18). The subsequent hypotension is due to centrally mediated sympatholytic effects (19). This finding has not been reported in humans.

Respiratory tract obstruction occurs in horses when there is a lowering of the head due to upper airway muscle relaxation, which can compromise airway patency similar to positional asphyxiation in humans (20–23). The effects of xylazine on respiration vary not only according to species but also with an anesthetic combination (20, 24, 25). This is pertinent to human exposure because, currently, xylazine is almost always found in combination with IMF.

Clonidine and dexmedetomidine, both of which are used in humans, affect the central α-2 receptor similarly to xylazine. However, in addition to central α-2 adrenergic agonist actions, clonidine, an imidazoline, has a strong affinity for the imidazoline-type 1 receptor, which is responsible for its potent antihypertensive effects (26). Dexmedetomidine, also an imidazoline, is approximately 8 times more selective for α-2 agonist receptors than clonidine (26, 27). Xylazine is not known to affect imidazoline receptors (28, 29). In animal species, xylazine sedation is easily reversible using α-2 adrenergic antagonists such as yohimbine, tolazoline, atipamezole, and idazoxan (30–32).

PHARMACOKINETICS—DIAGNOSTICS

Published pharmacokinetic data in humans are limited to case studies and forensic testing or are extrapolated from animal pharmacokinetic studies. Most clinical reports lack definitive information regarding the dose or time of exposure. With limited analytic testing, interpretation of the pharmacokinetics is complicated, especially in the setting of overdose. The literature describing the pharmacokinetics in animals is much more robust, but it is difficult to directly extrapolate these findings to humans. The general pharmacokinetics of xylazine in animal species have been summarized as rapidly absorbed, distributed, metabolized, and eliminated (33). The typical onset of effects with intravenous use occurs within minutes with a duration as long as 4 hours (19, 33). The rapid elimination half-life reported in animals (23 to 50 minutes) suggests that xylazine would likely provide a limited window for detection in biological matrices (12). However, xylazine is extensively metabolized, with over 20 identified phase I and II metabolites (33–35). The pharmacologic profile and clinical impact of these metabolites in humans are unknown.

Xylazine is not an analyte in standard urine drug screen immunoassays. Clinical xylazine testing is limited to testing within academic centers and reference laboratories using definitive testing methods including liquid chromatography with mass spectrometry (LC-MS), LC with tandem MS (LC-MS/MS), gas chromatography with MS, and LC–quadrupole time-of-flight (QTOF)–MS (36–38). The development of diagnostic assays targeting xylazine metabolites could extend the window of detection (39).

Immunoassay-based xylazine test strips have recently become available for forensic testing and community drug checking (40). However, many questions remain regarding their use, such as best practices for sample dilution before strip testing; actions following a positive,

Key Summary Points

Educate providers in many settings (emergency departments, primary care, low-barrier clinics, opioid treatment programs, office-based opioid treatment programs) on the alterations in recognition, acknowledgment, prophylaxis, and treatment of fentanyl use in the presence of xylazine.

Conduct animal and human research to further investigate xylazine–fentanyl pharmacology, toxicology, adverse effects, withdrawal syndrome, and treatment strategies.

Expand screening to include xylazine on standard urine drug testing; further define the test characteristics to understand the parameters and timing of testing.

Intensify harm-reduction efforts including increased surveillance of the drug supply and xylazine test strip distribution.

Expand access to low-barrier treatment settings with co-located substance use disorder and wound care treatment.

Expand access to inpatient and residential settings where both wound care and substance use disorder treatment are offered.

negative, or indeterminate result; and utility in xylazine-saturated markets (41). Test strips are inexpensive, provide rapid results, and do not require extensive training. The recommended use is currently limited to opioid drug samples rather than biological samples. Use with stimulants is not recommended as diphenhydramine, levamisole, lidocaine, MDMA (3,4-methylenedioxy-methamphetamine), and methamphetamine can cause false-positive results (42).

Human Clinical Effects

The reported cases of human exposure to xylazine–fentanyl typically include sedation, but patients did not require airway intervention, consistent with our experiences (43). Hypotension and bradycardia have been variably reported (43, 44). In our experience, hypotension is rarely noted and is often multifactorial. Similarly, bradycardia in humans is most often asymptomatic and the need for intervention has not been reported (45).

Further research is needed to determine the correlation of vital sign changes in typical xylazine–fentanyl combinations rather than assigning xylazine with the attributes of imidazolines such as clonidine. Also, xylazine is nearly always found in the presence of fentanyl. Their clinical effects may be overlapping or synergistic and may contribute to clinical findings, especially in overdose (1, 9).

Acute Overdose

Although xylazine is undoubtedly an emerging concern in the current drug supply, the spectrum of clinical consequences is not well studied. There is no convincing evidence to suggest that xylazine has contributed significantly to opioid overdose mortality; fentanyl-induced respiratory depression continues to be the critical factor in overdose deaths. In a multicenter, prospective cohort study of opioid overdoses, the presence of xylazine–fentanyl versus fentanyl alone revealed lower rates of cardiac arrest and coma (37). There were no increased rates of bradycardia, hypotension, admission to intensive care units, or death among patients testing positive for xylazine, suggesting that xylazine may not contribute significantly to opioid overdose morbidity or mortality.

Clinically, it is difficult to distinguish patients with xylazine–fentanyl exposure from those with an isolated fentanyl overdose. Given the numerous confounders, including the variable potency of the IMF supply, it is not clear how xylazine impacts the sedative or respiratory effects of fentanyl. Preclinical animal data suggest that xylazine may exacerbate cerebral hypoxia in opioid overdose (46).

In the acute setting, supportive airway management and monitoring with pulse oximetry and/or capnometry should be used, as is conventional for patients at risk for clinically significant sedation or respiratory depression after opioid overdose.

There are no approved xylazine reversal agents for human use, and reversal agents used in animals, such as tolazoline and atipamezole, have not been studied for use in humans for this indication. Naloxone, a μ-opioid receptor antagonist, is not expected to reverse the effects of xylazine. It is often stated that "naloxone is ineffective in xylazine intoxication." Statements such as these propagate misinformation that naloxone should not be used in patients with xylazine–fentanyl overdose. Because the life-threatening effects of xylazine–fentanyl are attributable to fentanyl, adequate reversal of the opioid-induced respiratory effects remains the goal in xylazine–fentanyl overdose management. Naloxone is a highly effective antidote to reverse respiratory depression induced by fentanyl, despite ongoing sedation from xylazine (or other co-exposures such as benzodiazepines or alcohol). Providers should use the lowest effective dose (0.04 to 0.4 mg intravenously) of naloxone to reverse respiratory depression to avoid precipitating opioid withdrawal in patients with opioid dependence.

Xylazine–Fentanyl Withdrawal

Patients and providers have described a unique syndrome of xylazine withdrawal possibly distinct from opioid withdrawal, but there are no animal or human models to study xylazine chronic exposure. Many patients report irritability, anxiety, restlessness, and dysphoria beginning 6 to 12 hours after the last use. These findings overlap with those of opioid withdrawal and complicate the use of Clinical Opiate Withdrawal Scale scoring to determine buprenorphine readiness (3, 45, 47, 48). Although little is known about xylazine withdrawal, if it occurs, it does not appear to cause life-threatening effects (45). Dedicated research is required to identify and define this syndrome more completely.

It is important to exclude (by detailed and collateral history, chart review, and review of past and current drug screen results when available) concomitant use of other agents, including benzodiazepines or alcohol, and initiate prophylaxis or treatment of these withdrawal syndromes.

For patients in whom there is concern about withdrawal from xylazine, the authors recommend optimization of opioid withdrawal management as a primary goal because xylazine is almost always found in combination with fentanyl or other opioids. Treatment strategies should center on optimizing medications for opioid use disorder (MOUD) treatment while adding adjunct supportive medications such as clonidine, benzodiazepines, antipsychotics, and gabapentin when necessary (48). In our experience, the management of opioid withdrawal and initiation of MOUD has been more challenging in the xylazine–fentanyl era. A more complete list of supportive medications is provided in the Table.

Xylazine use disorder and long-term treatment have not been described in the literature. For patients with ongoing symptoms, supportive pharmacologic and nonpharmacologic treatment should be tailored to patient symptoms.

Wounds

Xylazine use has been associated with open skin ulcerations and chronic wounds leading to substantial morbidity and is frequently a significant barrier for patients seeking shelter, residential treatment, inpatient drug and alcohol rehabilitation, and other levels of care.

Although abscess and wound development has been a common complication of injection drug use for decades, xylazine-associated wounds seem to represent a unique clinical entity. These wounds were first noted in Puerto Rico in the early 2000s. Patients with skin ulcers were more likely to be using xylazine compared with those using heroin only (38.5% vs. 7%) (49). Today, patients report ulceration development directly at injection sites, areas distant from injection, and even with intranasal or inhalational use. Wounds typically start as small round lesions and eventually develop into ulcers (1, 50–52). Patients have described continued injection into the wound or along the wound edge as the wound may be insensate and allow for rapid absorption when vascular access is difficult. Some wounds progress, leading to extensive necrosis and secondary infections including cellulitis, deep space infection, and osteomyelitis. Wounds are most commonly noted on extensor surfaces of the extremities and can lead to limb necrosis when severe and untreated.

There are multiple postulated causes of xylazine-associated wounds, including the cytotoxic effect of xylazine and/or contents of the drug supply, peripheral vasoconstrictive effects of the drug, increased frequency of injection, and compression effect from prolonged periods of sedation. However, none of these hypotheses fully explain what is currently seen clinically. A punch biopsy of a necrotic skin ulcer in a patient with self-reported xylazine use demonstrated epidermal necrosis with focal fibrin thrombi within superficial small vessels without vasculitis (52). A serologic work-up for vasculitis was negative. We hypothesize that small-vessel vasculopathy may be a contributing factor. Many questions remain, including understanding the pathophysiology and mechanisms for wound development at noninjection sites and in people who use xylazine fentanyl intranasally.

Models of skin oxygenation in mice demonstrate that xylazine resulted in significantly decreased tissue P_{O_2} (53), which may be responsible for poor wound healing. Hyperglycemia and insulinopenia, likely due to the α-2 adrenergic effect, may impact wound healing (33, 54, 55). Xylazine has been shown to be cytotoxic in several in vitro and in vivo animal studies (56–59).

Although there is a lack of data-driven recommendations, from collective clinical experience, we recommend that a typical wound care plan should include local debridement (manual or enzymatic) followed by the administration of hydrogel to keep a moist wound environment, topical antimicrobial agents, and nonadhesive dressings. Cessation of injection into the wound along with consistent, methodical wound care are keys to appropriate wound healing. Topical antibiotic ointments are typically sufficient for the typical xylazine-associated wound, and systemic antibiotics are rarely needed. Accessibility to wound supplies, clean water, stable housing, and regular medical care significantly impacts wound healing. Advanced surgical care may be needed in cases of severe or advanced wounds. Tissue-sparing debridement may prevent wound progression to amputation for patients who continue to have the inability to care for wounds. In extreme circumstances, amputations may be required for necrotic limbs,

Table. Medications for Prophylaxis and Treatment of Xylazine–Fentanyl Withdrawal

Drug	Alternatives	Description
Primary		
Clonidine	Tizanidine, lofexidine, guanfacine	α-2 Adrenergic agonist; antihypertensive; efficacy in opioid withdrawal attributed to binding to central α-2 adrenergic receptor that shares potassium channels with opioids and blunts symptoms of withdrawal; starting dose 0.1 mg every 8 h recommended as standing dose/prophylaxis if blood pressure can tolerate; caution: sedation, bradycardia, and hypotension
Secondary		
Olanzapine	Ziprasidone, risperidone, quetiapine	Atypical antipsychotic; 2.5 mg starting dose; 2.5–10 mg daily
Lorazepam	Clonazepam, midazolam, diazepam	GABA agonists; lorazepam 1–2 mg orally/intravenously/intramuscularly; titrate to effect; caution: sedation
Gabapentin	–	Anticonvulsant; reduces transmission of voltage-gated calcium channels reducing excitatory neurotransmitters; best efficacy in neuropathic pain; can optimize sedation effects; 300–600 mg every 8 h and 300 mg once daily at bedtime
Phenobarbital	–	GABA agonist; long-acting barbiturate; 130 mg intravenously; caution: sedation
Dexmedetomidine	–	α-2 agonist; sedation; antihypertensive; use in monitored settings after maximizing oral α-2 agonists: dose ≥0.2–1 mcg/kg/h
Others		
Ropinirole	–	Non-ergoline dopamine agonist used to treat motor symptoms of Parkinson disease as well as to treat restless legs syndrome; it can aid in muscle relaxation, anxiety, and motor restlessness–myoclonus; starting dose 0.25–0.5 mg every 8 h
Ketamine	–	NMDA receptor antagonist; effective as an opioid-sparing analgesic adjunct; 10 mg postoperatively every 6 h; 0.3 mg/kg intravenously over 15 min; short-acting unless followed by continuous infusion
Pregabalin	–	Anticonvulsant; adjunct treatment for neuropathic pain and anxiety; 100 mg 3 times per day up to 600 mg 3 times per day

GABA = γ-aminobutyric acid; NMDA = *N*-methyl-D-aspartic acid.

but providers should consider limb-sparing care as even a nonfunctional limb may help retain function for some patients. Wound closure with grafts, natural barriers, or even synthetic barriers may be used in severe wounds. Still, closure should be delayed to allow a period of tissue healing and prevent creation of a barrier to promote a contained space infection (60).

Further Concerns, Recommendations, and Research Questions

Although it remains unclear whether a distinct xylazine withdrawal syndrome occurs, it appears that xylazine may alter the findings and management of patients with fentanyl overdose and withdrawal. Increasingly, it appears that inadequately treated opioid (and possibly xylazine) withdrawal contributes to the increase in self-directed discharges from treatment settings. Initiation of buprenorphine and perhaps methadone, recently recognized as more challenging in the fentanyl era, may be compounded by the concomitant use of xylazine. Lastly, the presence of extensive wounds in people who use xylazine prevents them from accessing resources, including medically managed withdrawal treatment, leading to a cycle of continued and escalating use.

Because this is a rapidly evolving challenge, this article is a compendium of best practice and critical research needs derived from our experiences, literature review, and personal communication with expert colleagues. The limited understanding of the clinical pharmacology and clinical effects of xylazine in humans leaves an important gap in our ability to diagnose and treat patients with complicated use dependence syndromes. It seems reasonable given the increasing prevalence of xylazine adulteration to perform human pharmacokinetic investigations and pragmatic trials to better understand the clinical effects of the drug, including overdose, treatment options for overdose and withdrawal, and testing limitations of this drug. These in turn would help clarify the clinical syndromes that are poorly understood and enhance our epidemiologic and clinical research. Xylazine-associated wounds are another area of limited knowledge. Ongoing research regarding the pathophysiology and best treatment practices is urgently needed.

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