

Xylazine: A Zombie Drug Affecting Humans

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ABSTRACT

Xylazine, an α -2 adrenergic agonist exhibiting sedative, analgesic, and muscle-relaxant characteristics, is a veterinary medication predominantly utilized in large animals for anesthesia and pain alleviation. Chemically designated as $C_{12}H_{16}N_2S$, it was originally formulated as an antihypertensive drug but was repurposed for veterinary applications owing to its significant central nervous system depressant properties. Notwithstanding its therapeutic advantages in animals, xylazine has permeated illegal drug markets, especially as an adulterant in opioids such as fentanyl and heroin, acquiring monikers such "tranq" or "zombie Drug." Xylazine serves multiple purposes, but its misuse poses significant public health challenges, particularly because it does not respond to naloxone, the standard treatment for opioid overdoses. Its misuse is linked to significant health hazards, such as respiratory depression, necrotic skin ulcers, hyperglycemia, bradycardia, and cardiac necrosis. Incidents of xylazine-contaminated medications have increased, affecting overdose response and substance use treatment. This review explores xylazine's pharmacokinetics, toxicology, and clinical implications, with emphasis on its unique challenges in polysubstance overdose management. Furthermore, it underscores its essential veterinary applications. Comprehending xylazine's multiple functions is essential for tackling its abuse and alleviating its effects on public health during the persistent opioid epidemic.

Keywords: Xylazine; Tranq; Zombie Drug; Anesthesia; Opioid Overdose; Sedative

ABBREVIATIONS

DEA: Drug Enforcement Administration

IMF: Illegally Made Fentanyl

OD: Opioid Use Disorder

IV: Intravenous

IM: Intramuscular

SC: Subcutaneous

PCA: Patient-Controlled Analgesia

PICU: Paediatric Intensive Care Unit

INTRODUCTION

The molecular formula of xylazine is $C_{12}H_{16}N_2S$ with a molecular weight of 220.34 g/mol. The melting point of xylazine is approximately 140 °C. The boiling point of xylazine is reported to be around 334.2 °C, with a variability of ± 52.0 °C depending on the pressure conditions. (1)

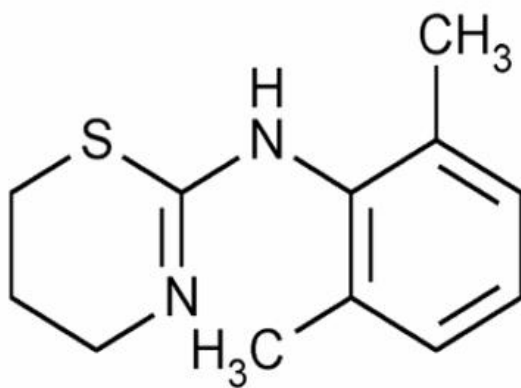


Fig 1: Structure of Xylazine

Xylazine is an alpha-2 adrenergic agonist initially developed as a sedative and an anesthetic for veterinary use, primarily in large animals like horses and cattle. It is known for its sedative, analgesic, and muscle-relaxant effects, xylazine has become an essential tool in veterinary medicine, helping practitioners perform minor surgical and diagnostic procedures with minimal stress on animals. (1) It is a central nervous system depressant, it makes people drowsy, slows brain activity, relaxes muscles, blood pressure to slow to dangerously low levels and slows heart rate and breathing. (2) Xylazine is increasingly detected in illicit drug markets, particularly as an adulterant in opioids like fentanyl and heroin. In many regions, especially in North America, overdose cases involving xylazine have surged, with affected individuals presenting with severe respiratory distress, prolonged sedation, and necrotic skin ulcers when administered repeatedly. (3) It is also known as "tranq", when combined with opioids such as fentanyl called "tranq dope" or when stigma directed at people called "zombie drug" xylazine's infiltration into the illegal drug market poses significant challenges, particularly in overdose management, as its effects do not respond to standard opioid antagonists like naloxone and nalmefene. (3,4) It was discovered in 1962 by Farbenfabriken Bayer, it was initially intended as an antihypertensive agent but was never approved for human use due to significant side effects, including hypotension and bradycardia. It is a central nervous system depressant that induces drowsiness, diminishes cerebral activity, relaxes musculature, reduces blood pressure to perilously low levels, and decelerates heart rate and respiration. Xylazine's effects can be life threatening at certain doses, especially if it is used with other depressants such as opioids (including fentanyl), cocaine, heroin, benzodiazepines, alcohol, gabapentin, and prescription opioid medications. (2,5) First reports of the illicit use of xylazine emerged in 2001 in Puerto Rico, where it was frequently combined with opiates such as heroin. Xylazine's prevalence in the drug supply started to proliferate throughout the continental United States, especially in urban centers such as Philadelphia, by the mid-2010s. (4) The DEA observed a substantial rise in the discovery of xylazine in drug samples, with reports indicating its presence in over 90% of specific drug samples analyzed in Philadelphia by 2021. The increase has prompted concern among public health professionals because there is no effective reversal therapy for xylazine overdose, in contrast to naloxone for opioids. (6)

USES OF XYLAZINE IN VETERINARY MEDICINE

Xylazine is extensively employed in veterinary medicine for its sedative, analgesic, and muscle relaxant effects. It is especially efficacious for sedation where xylazine is frequently utilized to tranquilize animals prior to surgical interventions or diagnostic assessments. (7) Xylazine serves as an emetic agent in felines, capable of inducing vomiting, which may be advantageous in some medical circumstances. Anesthesia is utilized in conjunction with other anesthetics, such as ketamine, to augment drowsiness and facilitate pain reduction during surgical procedures. The medication offers effective pain alleviation, making it beneficial for managing illnesses such as tetanus in animals. (6,8) The medication is usually delivered through injection (IV or IM) and functions by activating alpha-2 adrenergic receptors in the central nervous system, resulting in reduced norepinephrine release and subsequent drowsiness and analgesia. (9)

ABUSE OF XYLAZINE

1. Growing Prevalence in Illicit Drugs

Xylazine has been identified as an adulterant in an increasing number of illicit drug combinations. It is predominantly encountered in conjunction with IMF, but has also been detected in amalgamations with heroin, cocaine, and other drugs. Reports reveal that roughly 23% of seized fentanyl powder and 7% of confiscated fentanyl pills contained xylazine. (6,9) According to the DEA by complicating the realm of substance dependence therapy, it has been observed that xylazine frequently appears in polydrug combinations. (10)

2. Patterns of Use

Xylazine used amongst adults assessed for substance use therapy, individuals who indicated xylazine usage also reported elevated occurrences of utilizing other substances, such as prescription opioids and heroin. (3) A considerable proportion of users (65.2%) indicated the use of xylazine by non-injection means,

including ingestion or insufflation, whereas approximately 30.7% reported administering it through injection. (8)

3. Overdose Potential and Health Risks Involved

The abuse of xylazine is linked to several detrimental health consequences. Users exhibit symptoms including sleepiness, hypotension, respiratory depression, and significant skin lesions. (6) Xylazine is unresponsive to naloxone, the conventional opioid overdose reversal medication, hence increasing the likelihood of fatal consequences when used in conjunction with opioids. The people who have consumed xylazine are at a heightened risk of nonfatal overdoses relative to those who have not taken the substance. (11) Among 43,947 adults, 6,415 (14.6%) reported IMF or heroin as their primary lifetime substance-use problem; 5,344 (12.2%) reported recent (i.e., past-30-day) IMF or heroin use. Among adults reporting IMF or heroin as their primary lifetime substance-use problem, 817 (12.7%) reported ever using xylazine. Among adults reporting recent IMF or heroin use, 443 (8.3%) reported recent xylazine use. (8)

4. Geographic Distribution and Trends

The proliferation of xylazine misuse exhibits trends analogous to those observed with fentanyl. Originally identified in Puerto Rico, its application has proliferated across the United States, especially in urban regions. The DEA indicates substantial rises in xylazine detections in multiple areas, with the South observing a 193% rise from 2020 to 2021. (12)

5. Hemodynamic consequences

Xylazine exposure is linked to several cardiovascular and pulmonary consequences, along with difficulties in treating hypotension and diuresis. Numerous studies and case reports highlight the cardiac problems associated with Xylazine usage, including biventricular systolic failure, valve dysfunction, and myocardial necrosis and fibrosis. Clinical treatment with nifedipine has been useful in controlling certain cardiac problems. Xylazine is associated with pulmonary complications in addition to its effects on the cardiovascular system. (5) A research by Chavez et al. on nine Xylazine-related fatalities in Puerto Rico found moderate to severe lung congestion and edema in every instance. This may be due to either a direct effect of Xylazine on the pulmonary vasculature or a result of the drug's influence on cardiac function. (9) In the management of Xylazine-induced hypotension and diuresis, numerous patients exhibit favorable responses to IV fluids alone, without requiring supplementary therapies. Research with animals has shown that Xylazine induces diuresis, which can be counteracted by Atipamezole and Yohimbine. (7)

6. Hyperglycemia and other chronic consequences

The administration of xylazine in animals may result in hyperglycemia, which occurs in both normoglycemic and insulin-dependent diabetic monkeys due to diminished tissue sensitivity to insulin and impaired glucose uptake. 2,6-xylidine, a metabolite of Xylazine, is documented as a genotoxic and carcinogenic substance, increasing the difficulties for individuals who persistently utilize the drug. (10)

FDA ADVISORY

The FDA has cautioned healthcare providers of the significant dangers linked to Xylazine exposure in humans. This drug is predominantly utilized as a veterinary anesthetic and lacks any sanctioned applications for human use. (6) Xylazine is increasingly prevalent in the illegal drug market, frequently in conjunction with other substances. Acute and recurrent exposure to Xylazine can result in considerable damage, including delayed detection and treatment of polysubstance overdose, disruption of effective OUD management, and the onset of severe necrotic skin ulcerations. (9)

MODE OF ACTION

Xylazine functions as an α_2 -receptor agonist in both the central and peripheral nervous systems, inducing a pronounced sympatholytic action through the activation of central presynaptic α_2 receptors. (1) It was initially synthesized with the objective of developing a novel anti-hypertensive medication owing to its resemblance to clonidine. Its potent central nervous system depressant properties resulted in its application as a veterinary sedative, analgesic, and muscle relaxant during the 1960s. (9)

PHARMACOKINETICS AND OVERDOSE MANAGEMENT

Xylazine is rapidly eliminated from the body, exhibiting a half-life of 23 to 50 minutes, which presents a considerable challenge in managing overdose cases. (9) Xylazine is a veterinary medication, and information regarding its pharmacokinetics and therapeutic care in human overdose cases is few. The quick metabolism and expulsion from the body may result in an accelerated emergence of toxic consequences, potentially incapacitating the patient's system prior to the implementation of suitable therapies. The prompt recognition and intervention of this chemical are essential in addressing Xylazine overdose incidents. (13)

FATALITY AND TOXICITY

The existing research indicates that Xylazine can induce toxicity and mortality in humans at dosages between 40 to 2400 mg, with plasma values from 0.03 to 4.6 mg/L in non-fatal instances. In cases of mortality, blood concentrations of Xylazine vary from negligible amounts to 16 mg/L. (9) The substantial correlation between non-fatal concentration and postmortem blood concentration suggests that there is no clearly established safe, hazardous, or lethal concentration of Xylazine in humans. (7)

HEALTH RAMIFICATIONS AND CLINICAL MANAGEMENT

Xylazine use in humans has been associated with multi-organ damage, leading to bradycardia, hyperglycemia, hypotension, and even coma in cases of overdose. While naloxone is successful in reversing opioid overdoses, the evidence suggests it is not a viable treatment for Xylazine overdose. (6) Consequently, alternative supportive treatments must be administered to patients unresponsive to naloxone therapy. Furthermore, prolonged exposure to Xylazine has been shown to induce distinctive necrotic skin ulcers in individuals. The precise process of skin damage is incompletely elucidated. (9)

COMPLICATING THE MANAGEMENT OF POLYSUBSTANCE INTOXICATION

Xylazine is often combined with other substances, which can greatly affect the therapeutic management of acute intoxication or withdrawal from those substances. Xylazine, in addition to its interaction with opioids, has been demonstrated to diminish the anticonvulsant efficacy of phenobarbital, phenytoin, and diazepam in rats. Xylazine can hinder the clinical management of withdrawal seizures and elevate morbidity and fatality rates. (9)

DISCUSSION AND CONCLUSION

Xylazine, a veterinary sedative, has surfaced as a significant public health problem due to its increased presence in illegal drug markets, particularly as an adulterant in opioids such as fentanyl and heroin. The pharmacological attributes that make xylazine efficacious in veterinary medicine—its sedative, analgesic, and muscle-relaxant properties—exacerbate its perilous consequences on humans when misapplied. Xylazine, unlike opioids, is unresponsive to naloxone, hence complicating overdose care and heightening the likelihood of fatal outcomes. (2,3) One of the most serious characteristics associated with xylazine usage is its role in aggravating the opioid pandemic. Data reveal a significant rise in the identification of xylazine in illegal drug samples, with specific urban areas in North America documenting its occurrence in more than 90% of examined fentanyl samples. (9) This pattern indicates a calculated incorporation of xylazine by drug traffickers to extend the effects of opioids, notwithstanding the significant health hazards associated with the chemical. The sedative effects of xylazine, when coupled with opioids, markedly elevate the risk of fatal respiratory depression, bradycardia, and coma. (6) Beyond its immediate toxicity, xylazine is connected with persistent health consequences, including severe necrotic skin ulcers, diabetes, and cardiovascular impairment. These ulcers, typically reported in persons with continuous xylazine usage, remain poorly known in terms of their exact etiology but are likely owing to recurrent injection and vascular injury. (8) This phenomenon poses distinct issues in wound treatment and requires particular medical measures. Moreover, extended use of xylazine has been associated with immunosuppression, heightening users' vulnerability to infections and other secondary problems. (14) Xylazine has a

pharmacokinetic half-life of 23 to 50 minutes; however, its hazardous effects endure well beyond dosing due to its influence on the central nervous system and cardiovascular function. (9) The quick metabolism of xylazine implies that routine toxicological screenings typically fail to detect it in overdose instances, potentially leading to misdiagnoses and inappropriate treatment methods. The absence of a direct antidote needs supportive care, including breathing help and cardiovascular stability. Recent studies indicate that xylazine-induced toxicity may engage oxidative stress pathways, exacerbating tissue damage and multi-organ dysfunction. (1) Geographical trends reveal that xylazine usage first appeared in Puerto Rico in the early 2000s before proliferating to significant urban areas in the United States, including Philadelphia. (4) The significant rise in xylazine-related deaths, especially in the Southern and Northeastern United States, underscores an immediate necessity for focused public health measures, such as improved drug screening, harm reduction initiatives, and heightened awareness among healthcare providers concerning xylazine-related complications. Furthermore, there is a mounting concern regarding its identification in illicit drug supply across Europe and Asia, signaling a potential worldwide spread of the epidemic. (6,13) The hemodynamic effects of xylazine further complicate its influence on users. Research has indicated that xylazine adds to cardiac necrosis, valve failure, and pulmonary edema, further increasing the chance of morbidity and mortality. Animal studies suggest that xylazine-induced diuresis and hypotension can be alleviated using alpha-2 adrenergic antagonists such as yohimbine and atipamezole, but their usefulness in human overdose cases remains questionable and deserves additional exploration. (9) Emerging research also suggests that xylazine use may exacerbate pre-existing cardiovascular disorders, increasing mortality risk in those with underlying heart illnesses. (2) Additionally, xylazine has been reported to interfere with the management of other illnesses, such as opioid withdrawal and seizure disorders. Experimental investigations indicate that xylazine decreases the efficacy of anticonvulsants such phenobarbital and diazepam, raising concerns about its potential to worsen withdrawal-related seizures. (2) This complicates the management of individuals with polysubstance intoxication, requiring a multidisciplinary therapeutic strategy. Due to its rising frequency, there is an urgent necessity for additional research on its interactions with other central nervous system depressants and their combined effect on overdose fatality rates. (3,9) In light of the escalating public health concern, regulatory bodies including the FDA have released recommendations cautioning against the hazards linked to human exposure to xylazine. These cautions underscore the critical necessity for augmented surveillance, refined toxicological screening, and the formulation of targeted treatment regimens for xylazine overdose. Additionally, harm reduction initiatives, including safe injection techniques and better access to medical care, are vital in minimizing the long-term effects of xylazine usage. Furthermore, policymakers should contemplate categorizing xylazine under more stringent regulatory measures to avert its diversion from veterinary applications to illegal markets. (11,15) In conclusion, xylazine's emergence in the illicit drug market has added a new dimension of complexity to the persistent opioid pandemic. The distinctive pharmacological characteristics, along with its resistance to reversal by naloxone, present considerable difficulties for overdose intervention and substance use therapy. Mitigating the xylazine issue necessitates a comprehensive strategy, encompassing regulatory reforms, heightened clinical awareness, and ongoing research into potential antidotes and treatment methodologies. Without timely intervention, the rising incidence of xylazine will continue to contribute to increased morbidity and mortality among those battling with substance use disorders. (8,9)

ACKNOWLEDGEMENT

The first author formulated the idea behind writing this review article and collected the data under the supervision of the corresponding author.

CONFLICT OF INTREST

The authors declare no conflict of interest.

CASE STUDIES

S. No.	Auth or(s)	Number of cases	Accidental/ Intent	Route of Admi	Do sage	Synergistic drugs involved	Intoxication	Withdrawal	Treatment/intervention/management	Outcome/sequelae
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		each study	ional/ Abuse	nistrat ion		(concomi tant use of drugs)				
1	Ehrman-Dupree et al. (16)	1	Abuse	IV	na	Tramadol, Fentanyl	no	yes	Day 1 - Dexmedetomidine + Tizanidine; Day 2 Phenorbarbital + Clonidine; Hydromorphone PCA + Gabapentin + Ketamine for pain; Buprenorphine Microinduction	Recovered
2	Stillwell et al. (17)	1	na	IM	450mg	Paroxetine	yes	na	na	na
3	Elejalde et al. (18)	1	na	Inhalation	na	na	yes	no	IV fluids only	Recovered
4	Liu CM et al. (19)	1	Abuse	Inhalation	na	Sulpiride, Ketamine, Phenobarbital	yes	no	IV fluids only	Recovered
5	Deutsch et al. (20)	3	Accidental	na	na	Case 1 - Morphine and Fentanyl; Case 2 and 3 Fentanyl	yes	no	Case 1 - Naloxone (nasal+IV), Intubation, PICU; Case 2 - IV Naloxone; Case 3 - Intubation	Recovered
6	Anderson-Streight et al. (21)	1	Intentional	IM	na	na	yes	no	Supportive Treatment	Recovered
7	Mulders et al. (22)	1	Abuse	SC	500mg	na	no	no	Clonidine	Recovered
8	Spoerke et	3	Intentional	IV (1); IM (2)	40 mg	na	yes	no	Naloxone	Recovered

	al. (23)		(1), na (2)		, 24 00 mg					
9	Carruthers et al. (24)	1	Intentional	IV	90 0mg	na	yes	no	Lidocaine; Supportive Treatment	Recovered
10	Samanta et al. (25)	1	Accidental	SC	20 0mg	na	yes	no	Naloxone	Recovered
11	Ganapathy et al. (26)	1	Accidental	IM	na	na	yes	no	Supportive Treatment	Recovered
12	Hoffman et al. (14)	1	Intentional	IM	15 00 mg	na	yes	no	Supportive Treatment + Etomidate, Propofol	Recovered
13	Velez et al. (27)	1	Accidental	Ocular	80 0mg	na	yes	no	Supportive Treatment	Recovered
14	Kronqvist et al. (28)	3	Intentional	Ingestion	na	na	yes	no	Supportive Treatment	Recovered
15	Gallanos et al. (29)	1	Intentional	Ingestion	40 0mg	na	yes	no	IV Naloxone + Intubation	Recovered
16	Capraro et al. (30)	1	Abuse	Inhalation	43 00 mg	Benzodiazepines	yes	no	IV Naloxone + Intubation	Recovered
17	Meyer et al. (31)	1	Accidental	Arrow Injection (IM)	na	Ketamine	yes	no	Supportive Treatment	Recovered
18	Poklis et al. (32)	1	Intentional	IV	na	Chlorazepate, Alcohol	yes	no	na	Fatal
19	Aricano et al. (33)	1	Abuse	IV	15 00 mg	Ketamine (1000mg)	yes	no	IV fluids, Metoprolol	Recovered
21	Choon et al. (34)	2	Accidental	IM	na	na	yes	no	Supportive Treatment + IV Atropine in both; Case 1 - Oxygen, Case 2	Recovered

									IV Naloxone and Noradrenaline	
22	Ram on et al. (35)	1	Abuse	Inhala tion	na	na	yes	na	na	na
23	Lewis et al. (36)	1	Abuse	IM	na	na	yes	no	na	na
24	Won g et al. (37)	7	Abuse	IV (suspe cted in 2 cases 4,6) remai ning 5 na	na	7 Cases Fentanyl; 6 Cases Heroin; 5 Cases Morphin e; 5 Cases Codeine; 5 Cases Cocaine; 4 Cases Alcohol; 4 Cases Procaine; 3 Cases Lidocain e; 3 Cases Quinine /Quinidi ne; 2 Cases Alprazola m; 2 Cases Diltiaze m; 2 Cases Naprox e; 1 Case - PCP, Diphenh ydramine , Ibuprofe n, Citalopra m, Mirtazapi ne, Hydroxyz ine	yes	no	na	Fatal

25	Barro so et al. (38)	1	Accid ental	SC	na	na	yes	no	Supportive Treatment	Recove red
26	Mitte lman et al. (10)	2	Intent ional	na	na	na	yes	na	na	Fatal

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