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Xylazine Misuse: Pharmacology, Toxicity, and Public Health Implications

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Abstract:

A non-opioid α_2-adrenergic receptor agonist, xylazine is mainly authorized for use in veterinary medicine as a sedative, analgesic, and muscle relaxant. Its growing presence in the illegal drug supply, especially when combined with opioids like fentanyl and heroin, has made it a major public health concern in recent years. The danger of severe toxicity and overdose increases when xylazine is added to these drugs since it intensifies and prolongs their sedative effects. Xylazine does not react to naloxone like opioids do, which makes emergency care more difficult and raises morbidity and mortality.The pharmacology, abuse patterns, side effects, and public health implications of xylazine misuse are all examined in this review. Research indicates that xylazine is often utilized as an adulterant in illegal substances due to its affordability, accessibility, and capacity to intensify the effects of opioids. Both acute and long-term exposure can cause bradycardia, hypotension, hyperglycemia, respiratory depression, central nervous system depression, and severe skin ulcers. Additionally, tissue necrosis, wound infections, and, in extreme situations, limb amputations have been linked to repeated use. Furthermore, because there are few clinical management guidelines and no recognized human antidotes, the rising incidence of xylazine in polysubstance overdoses poses significant hurdles for healthcare providers.The increasing abuse of xylazine emphasizes the need for harm reduction programs, regular toxicological testing, enhanced monitoring systems, and public awareness campaigns. Reducing the health burden associated with xylazine exposure requires bolstering evidence-based therapies and strengthening healthcare responses. All things considered, xylazine abuse is a growing problem that calls for concerted efforts by medical professionals, researchers, legislators, and public health organizations to stop more negative consequences.

Keywords: Xylazine; Drug Abuse; Toxicity; Public Health; Opioids; Harm Reduction; Overdose; Substance Use Disorder

1. Introduction

Xylazine is a veterinary drug commonly used as a sedative, analgesic, and adjunct to general anesthesia. It acts primarily by stimulating alpha-2 adrenergic receptors in both the central and peripheral nervous systems, leading to decreased norepinephrine release. This mechanism produces profound sedation, analgesia, muscle relaxation, and respiratory depression. In addition to its primary alpha-2 adrenergic activity, other possible mechanisms involving dopaminergic, cholinergic, histaminergic, alpha-1 adrenergic, and opioid pathways have also been suggested. Acute toxicity associated with xylazine mainly affects the respiratory and cardiovascular systems. Clinical manifestations commonly include respiratory depression, hypotension, bradycardia, and mild disturbances in thermoregulation. Management of xylazine overdose is largely supportive, with emphasis on maintaining airway patency, respiratory support, intravenous fluid administration, and stabilization of blood pressure. In severe cases, intubation and aggressive supportive care may be required. The increasing misuse of xylazine in combination with opioids,

particularly Fentanyl, has created significant public health concerns. Co-exposure to fentanyl and xylazine complicates overdose management because the opioid antagonist Naloxone effectively reverses opioid-induced respiratory depression but has little to no effect on the sedative and respiratory depressive effects caused by xylazine. This limitation makes treatment of mixed overdoses particularly challenging. Another distinguishing feature of xylazine misuse is the development of severe dermatological complications, including skin ulcers, abscesses, necrotic wounds, and secondary infections. These complications are increasingly reported among individuals exposed to xylazine-adulterated illicit drugs and contribute substantially to morbidity and healthcare burden.[1]

2.Pharmacology of Xylazine

Mechanism of Xylazine-Related Death

Xylazine is a potent alpha-2 adrenergic agonist pharmacologically related to agents such as Clonidine, Lofexidine, and Dexmedetomidine. It demonstrates a high affinity for alpha-2 adrenergic receptors compared to alpha-1 receptors. The alpha-2 receptor family consists of alpha-2A, alpha-2B, and alpha-2C subtypes, with the presynaptic alpha-2A and alpha-2C receptors primarily responsible for the sedative, analgesic, and sympatholytic actions of xylazine. These effects are mediated mainly through the locus coeruleus and dorsal horn of the spinal cord. Clinically, xylazine intoxication commonly presents with profound sedation, drowsiness, muscle relaxation, bradycardia, hypotension, and respiratory depression. However, sympathomimetic manifestations such as localized vasoconstriction at injection sites and rebound sympathetic activity during withdrawal may also occur. In addition to its alpha-2 adrenergic action, xylazine interacts less strongly with a number of other receptor systems, such as cholinergic, serotonergic, dopaminergic, histaminergic, and maybe opioid receptors. Its hazardous effects, especially respiratory depression and cardiovascular instability, may be exacerbated by these additional pharmaceutical actions. Due to its high lipophilicity, xylazine can enter adipose tissue quickly and prolong its pharmacological effects by redistribution. Despite the elimination half-life in animal models being between 23 and 50 minutes, tissue buildup may cause the clinical duration of action to last longer. Significant drug interactions are more likely due to its lipophilic nature and multi-receptor activity, particularly when taken with opioids like fentanyl. Xylazine's involvement in substance abuse and withdrawal symptoms is also explained by its pharmacological nature. Similar to clonidine, xylazine may lessen noradrenergic withdrawal symptoms during acute exposure, resulting in intoxication that resembles sedative-hypnotic poisoning and is marked by decreased consciousness, decreased respiratory rate, hypotension, bradycardia, and muscle relaxation. Chronic use, however, can lead to severe withdrawal symptoms and substantial physiological dependence. Autonomic instability and noradrenergic rebound symptoms, such as agitation, hypertension, tachycardia, anxiety, and sympathetic hyperactivity, are linked to xylazine withdrawal. These symptoms are similar to acute clonidine withdrawal syndrome. These consequences underscore the need for more investigation into the pharmacology and toxicity of xylazine as well as the growing worry over its misuse.[2]

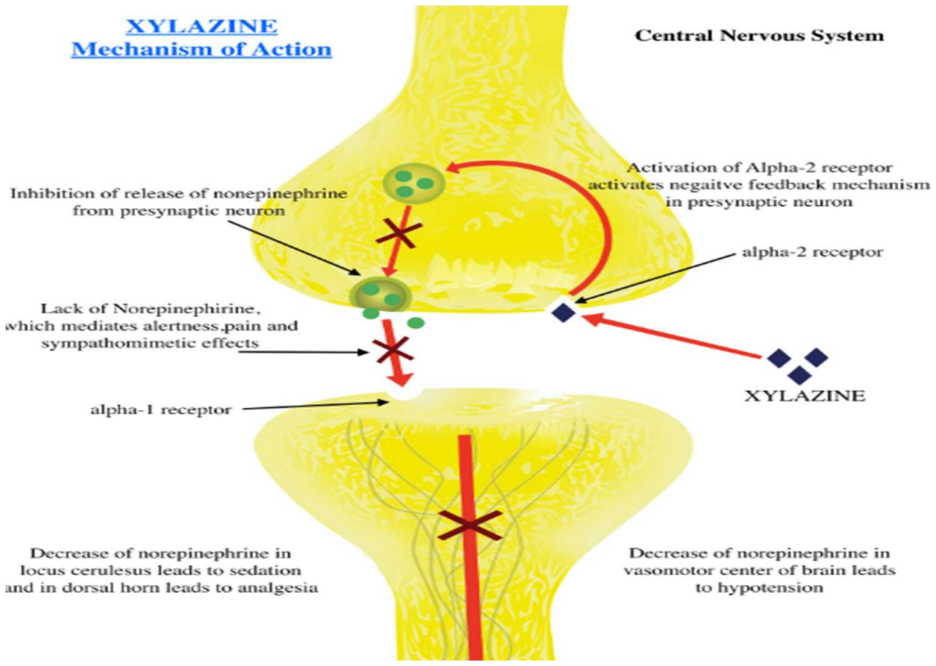

Fig-1: Mechanism of xylazine

Mechanism of Xylazine-Related Death

The first reports of xylazine usage by humans were made in Puerto Rico in 2007. Since then, drug abuse has spread to many parts of the country, especially the northeastern states, and drug-related deaths have increased at the same time. Since xylazine lengthens the duration of cerebral hypoxia and prolongs the effects of fentanyl, it was later shown to be an adulterant frequently used with fentanyl. Xylazine plus opioids have synergistic effects that can worsen central nervous system depression and increase the risk of overdose and death. Bradycardia, hypotension, and severe central nervous system depression are the most commonly documented clinical signs of xylazine poisoning in humans. A precise definition of xylazine toxicity in humans has not yet been established, and lethal blood concentrations are still not well characterized, despite the rising frequency of xylazine-related intoxications and fatalities. Furthermore, since fentanyl or other opioids are also involved in the majority of recorded instances, it is still unclear how exactly xylazine contributes to drug-related fatalities. To further understand the toxicological processes of xylazine alone and in combination with fentanyl, more research is necessary.[3]

Therapeutic Uses

In veterinary medicine, xylazine and kindred alpha-2 adrenergic agonists including detomidine, medetomidine, and romifidine are frequently used for sedation, analgesia, muscular relaxation, and animal restraint. Alpha-2 adrenergic receptors found in both the central and peripheral nervous systems are the main mechanism by which these medications work. While postsynaptic receptor stimulation contributes to analgesic and cardiovascular effects, presynaptic receptor activation suppresses norepinephrine release, resulting in drowsiness and decreased sympathetic activity. While analgesia is mediated by altering pain pathways in the brain and spinal cord, sedation is mostly caused by receptor activation within the brain's locus coeruleus. Furthermore, these substances increase the activation of potassium channels in neuronal membranes, which causes hyperpolarization and inhibits the transmission of pain signals.Because of these characteristics, alpha-2 agonists are often used in conjunction with anesthetics like ketamine, greatly lowering the dosage required for inhalational and injectable anesthetics. Because of its efficacy, simplicity of use, and capacity to produce profound drowsiness and visceral analgesia, especially in large animals like horses and cattle, xylazine continues to be one of the most widely used medications among these compounds. It has also been demonstrated that xylazine administered epidurally can effectively give regional analgesia for surgical procedures,

particularly in the management of cows. Nevertheless, alpha-2 agonists have major effects on the heart and lungs despite their therapeutic advantages.Bradycardia, hypotension, decreased cardiac output, arrhythmias, respiratory depression, and decreased tissue perfusion are common side effects. Vomiting, decreased motility, tympany in ruminants, and decreased gastroesophageal tone are examples of gastrointestinal disorders. In addition, these substances can cause uterine contractions, polyuria, hyperglycemia, and thermoregulatory problems in pregnant animals. There have been reports of species-specific differences in xylazine sensitivity; pigs need much higher doses, while cattle and goats are particularly sensitive.Alpha-2 agonists are very useful in veterinary anesthesia and analgesia, but in order to reduce problems, their usage necessitates careful dose selection, monitoring, and species-specific consideration. The medications have a ceiling effect, meaning that higher dosages prolong sedation and side effects without appreciably deepening sedation.Many species can recover quickly from the sedative and cardiovascular effects of these medications thanks to reversal medicines like yohimbine and atipamezole. However, overdosing or improper administration might cause violent behavioral reactions, persistent recumbency, excitement, or severe cardiac depression. Serious disruptions to the central nervous system can also result from unintentional human exposure by mucosal contact or self-injection. Thus, to guarantee the safety of both humans and animals, xylazine and comparable alpha-2 agonists must be used carefully.[4]

Muscle relaxation and analgesia Because of its sedative, analgesic, and muscle-relaxant qualities, xylazine is a powerful α_2-adrenergic receptor agonist that is frequently utilized in veterinary medicine. When α_2-adrenergic receptors in the central nervous system are activated, less norepinephrine is released, which lowers neuronal excitability and inhibits the transmission of pain signals. Xylazine is helpful for surgical procedures, animal restraint, and pre-anesthetic treatment because of this mechanism, which results in substantial analgesia and helps to relax muscles. While central nervous system depression and decreased skeletal muscle tone cause muscular relaxation, the analgesic action is mostly mediated through spinal α_2-receptors. Xylazine is not authorized for use in humans despite these positive therapeutic outcomes in animals due to the possibility of serious side effects, such as bradycardia, hypotension, respiratory depression, and central nervous system depression.[5]

Clinical Overview of Xylazine Intoxication, Overdose.

Intoxication Because of its alpha-2 adrenergic agonist action, xylazine intoxication frequently manifests as drowsiness, bradycardia, hypotension, and respiratory depression. When xylazine is used with synthetic opioids like fentanyl, these symptoms can mirror opioid intoxication but are frequently more severe. Although xylazine test strips have lately surfaced as a possible diagnostic tool, xylazine is not typically found on normal urine drug screening tests. However, drugs including diphenhydramine, lidocaine, levamisole, and MDMA might produce false-positive results. Because xylazine has local vasoconstrictive effects, necrotic skin lesions and ulcers are thought to be typical findings in prolonged exposure. The coexisting chemicals implicated and related consequences, such as soft tissue wounds, play a major role in the supportive management of acute intoxication. Overdosing Most frequently, xylazine is found as an adulterant along with opioids, especially fentanyl, where it may increase sedation, hypotension, and respiratory depression in a synergistic way. The research that is currently available indicates that xylazine can considerably increase the severity of an overdose when taken with opioids, even if the dose-response correlations in humans are still unknown. While acknowledging that naloxone may only partially cure symptoms in situations of combined fentanyl-xylazine overdose, current overdose management recommendations advise giving priority to treating opioid toxicity. As of right now, no particular reversal medication for xylazine intoxication has been authorized for use in humans.[6]

Toxic Effects

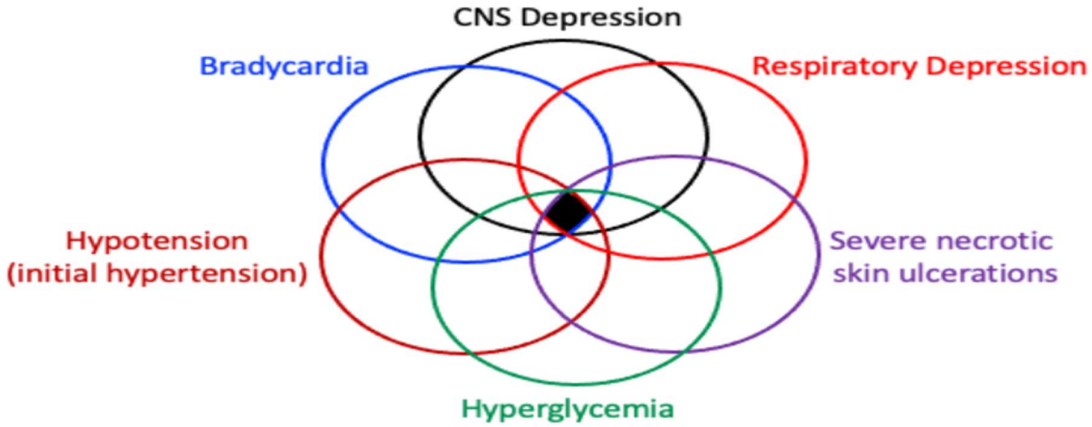

Fig-2:Toxic effects

Numerous clinical investigations have revealed Xylazine's toxicological evaluation, underscoring the increasing significance of precise toxicology screening in the face of rising drug adulteration. Because xylazine poisoning is not commonly included in standard toxicology panels and commercial immunoassays are sometimes unavailable, it is typically neglected during first diagnosis, according to numerous publications. Atypical appearances and a lack of clinical awareness make diagnosis even more difficult. Xylazine toxicity and overdose have increasingly contributed to avoidable deaths, despite the fact that some recorded exposures were not fatal. This highlights the necessity of evidence-based assessment, management techniques, and harm-reduction efforts. As of right now, there is no particular FDA-approved treatment for xylazine abuse or its related side effects.Human exposure to xylazine has been reported at a wide range of dosages, from about 40 mg to 4300 mg. With plasma concentrations ranging from trace levels to 16 mg/L in fatal cases and from 0.03 to 4.6 mg/L in nonfatal cases, toxic and fatal effects have been reported at dosages between 40 and 2400 mg. Although there is significant overlap between fatal and nonfatal blood concentrations, the average fatal dose has been assessed to be larger than that seen in surviving patients. As a result, there is currently no documented safe, hazardous, or deadly concentration of xylazine in humans. The most frequently reported exposure method is still intravenous injection, especially for those who use contaminated illegal substances. Bradycardia, hypotension, respiratory depression, central nervous system depression, and, in extreme situations, coma necessitating airway care and intubation are typical clinical signs of xylazine toxicity. Lower dosages were used in the majority of documented oral ingestion cases, which ended without long-term issues. However, there have also been reports of severe intoxications after ingestion, with some individuals experiencing serious neurological and cardiovascular issues. Furthermore, problems including hyperpyrexia and homicidal poisoning have been connected to xylazine-related deaths. These results highlight the unpredictable nature of xylazine toxicity and the pressing need for better clinical identification, toxicological screening, and treatment recommendations.[7]

Other effects

Effects of Hemodynamics Significant cardiovascular and pulmonary problems, such as hypotension, bradycardia, myocardial damage, valve malfunction, pulmonary congestion, and pulmonary edema, can result from xylazine exposure. While medications like nifedipine may assist control specific cardiac problems, other individuals react well to supportive care with intravenous fluids. Studies on animals also demonstrate that atipamezole and yohimbine can reverse the diuresis caused by xylazine. Pregnancy-Related Effects Animal research indicates that xylazine may lower uterine blood flow and fetal oxygen delivery, potentially impacting fetal development and pregnancy outcomes, despite the paucity of human data. Hyperglycemia and Its Long-Term Consequences Because xylazine reduces glucose absorption and insulin sensitivity, it may cause hyperglycemia. Concerns about long-term exposure are raised

by reports that its metabolite, 2,6-xylidine, has carcinogenic and genotoxic qualities. Effects on the Eyes According to research on animals, xylazine can lower intraocular pressure and, if continuous or intravenous exposure, may result in corneal lesions.[8]

FIG- Xylazine-associated skin ulcers, cellulitis, and osteomyelitis of the lower extremity in a person who injects drugs in Philadelphia.[8]

In Acute poisoning

Reduced consciousness, bradycardia, hypotension, respiratory depression, persistent sedation, and, in extreme situations, the requirement for mechanical ventilation are all signs of substantial central nervous system depression linked to xylazine exposure. The majority of xylazine-related overdose deaths include concurrent use of fentanyl or other opioids, indicating a possibly synergistic effect on respiratory depression, even though xylazine-related deaths are rare. Naloxone is still necessary for treating concomitant opioid overdoses even though it does not directly reverse xylazine toxicity. Because abrupt reversal of alpha-2 agonist effects may theoretically cause rebound hypertension and autonomic instability, chronic xylazine exposure may also make withdrawal management more difficult.Xylazine-induced prolonged drowsiness and immobility raise the risk of pressure ulcers, traumatic injuries, theft, assault, and other consequences, especially in vulnerable groups like the homeless. The development of severe skin and soft tissue lesions, such as massive necrotic ulcers, abscesses, cellulitis, and tissue damage that frequently occur away from injection sites, is another characteristic consequence of xylazine exposure. These wounds can develop from small, clustered lesions into large areas of necrosis, and they frequently have a burn-like appearance. While hydrogen peroxide should be avoided as it may hinder wound healing, proper wound care, including cleaning, debridement, dressing changes, and infection monitoring, is crucial.Patient-centered care and harm reduction-based outpatient wound care are highly advised, particularly for drug injectors with restricted access to healthcare. Further human research is required to better understand these long-term effects and develop evidence-based management methods, however persistent xylazine exposure may also contribute to problems such transitory anemia and hyperglycemia**.**[9]

Harm domain	Mechanism	Clinical implications	Harm reduction strategies
Heavy sedation	Alpha-2 receptor agonism	Continued sedation after naloxone administration Pressure ulcers and skin breakdown likely Elevated risk for DVT Elevated risk of compartment syndrome Nerve, muscle, and soft tissue injury Rhabdomyolysis	Encourage using drugs with a friend Roll people nodding onto their side Move people nodding every two hours Pad under bony areas (sacrum, heels, shoulders, etc.) Avoid wrinkled or hard surfaces under nodding person
Skin wounds	Unknown	Bacterial superinfection possible Ensure adequate longitudinal wound care Can cause shame and reduced care-seeking Individuals may be deemed ineligible for in-patient substance use disorder care due to untreated wounds	Coach to avoid injecting into or near wounds Facilitate wound care access Teach individual and friends/family how to care for wounds Provide wound care supplies Teach on signs of worsening condition
Anemia	Unknown; perhaps sympathetic antagonism	Vague symptoms may delay care-seeking Important to rule out dietary or other causes	Coach communities on signs and symptoms; when care-seeking is necessary Encourage and facilitate community support to identify changes in health status in self and others
Dysglycemia	Unknown	Vague symptoms may delay care-seeking Important to rule out other causes of metabolic derangement Potential to worsen skin wound progress	Coach communities on signs and symptoms; when care-seeking is necessary Encourage and facilitate community support to identify changes in health status in self and others

Table-1: Xylazine harm domains and clinical approaches [9]

Clinical diagnosis

Xylazine Concentrations in Blood and Urine

Although Xylazine's pharmacological actions are known to exacerbate central nervous system and respiratory depression brought on by other medications, its precise role in overdose-related deaths is still unknown. Due to significant overlap between quantities seen in fatal and nonfatal instances, toxic and deadly concentrations of xylazine

in humans have not yet been definitively determined. While blood or plasma concentrations in nonfatal intoxication cases have ranged from 30 to 460 ng/mL, with some surviving patients exhibiting even higher levels, reported blood concentrations in xylazine-related deaths have ranged from roughly 5 to 49 ng/mL. These results suggest that clinical outcome or mortality may not be accurately predicted by xylazine levels alone.Additionally, research indicates that cases with less co-intoxicants may have higher xylazine concentrations, indicating that xylazine itself may play a major role in toxicity and mortality mechanisms. Blood xylazine concentrations were typically greater in reported homicide cases than in suicide cases, especially when xylazine was used alone rather than in conjunction with other drugs. Nevertheless, the connection between co-intoxicants, xylazine concentration, and way of death is still unclear and needs more research. Xylazine concentrations in urine are usually significantly greater than those in blood; in certain nonfatal cases, urine levels have been reported to be higher than 500 ng/mL. Because postmortem redistribution may change drug concentrations after death, peripheral blood samples are typically regarded as more reliable than cardiac blood samples for toxicological investigation. Additionally, in postmortem toxicology examinations, elements like putrefaction and tissue autolysis may make sample collection and interpretation more difficult.[10]

management

Several strategies for handling xylazine intoxication and withdrawal were detailed in the examined research. The majority of patients got supportive care, which included symptomatic therapy, continuous monitoring, and intravenous fluids. Although naloxone does not reverse the sedative effects of xylazine itself, it was provided in a number of cases due to suspected or confirmed co-exposure to opioids like fentanyl. Insulin, dextrose (D50), calcium gluconate, antibiotics, gastric lavage, atropine injection, and eye irrigation in cases of ocular exposure were among the additional treatments mentioned. Patients with severe respiratory depression frequently needed mechanical ventilation, endotracheal intubation, and bag-valve-mask ventilation as forms of airway support. Medications that act on α2-adrenergic receptors and GABAergic pathways, such as gabapentin, clonidine, tizanidine, and dexmedetomidine, are frequently used to treat symptoms. For the removal of xylazine, benzodiazepinesIn addition to treating co-occurring substance use disorders, es, clonidine, and gabapentin were frequently advised as adjuvant therapy. Because of its α2-adrenergic agonist action, which may lessen withdrawal symptoms by acting on receptors shared with xylazine, clonidine was thought to be the main pharmaceutical alternative. Starting at 0.1 mg every 8 hours is advised, and side effects such drowsiness, bradycardia, and hypotension should be closely monitored. Olanzapine, lorazepam, gabapentin, phenobarbital, dexmedetomidine, ropinirole, ketamine, and pregabalin were additional drugs used to treat withdrawal. These medications were used to manage symptoms like agitation, anxiety, neuropathic pain, restless muscles, and autonomic instability. When oral α2-agonists were insufficient, dexmedetomidine was often saved for closely supervised clinical settings. Because xylazine misuse typically coexists with opioid usage, experts recommend giving opioid withdrawal treatment high priority.Despite its minimal impact on sedation caused by xylazine, naloxone is an essential intervention insuspected combination opioid-xylazine overdoses because it successfully reverses opioid-induced respiratory depression. In general, supportive care, stabilizing essential functions, treating withdrawal

symptoms, and treating co-occurring substance use disorders are the main goals of management.[11]

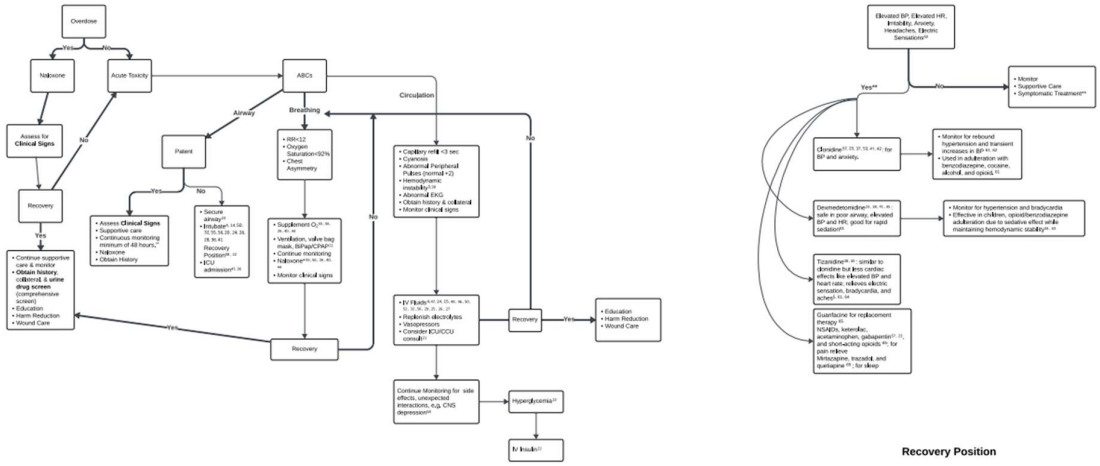

Fig-3: Outlines a recommended step-by-step process for managing xylazine overdose toxicity and withdrawal [11]

Public Health Concerns

In North America, the growing amount of xylazine in the illegal drug supply has become a serious public health issue. Its frequent co-occurrence with fentanyl and other drugs has led to an increase in polysubstance overdose rates, posing significant difficulties for public health organizations, harm reduction initiatives, and healthcare systems. This tendency has been caused by a number of causes, such as insufficient epidemiological surveillance, restricted access to specialist healthcare services, stigma associated with drug use, and obstacles to putting effective harm reduction techniques into practice.The absence of systematic surveillance and toxicological testing is a significant obstacle in resolving the xylazine crisis. Many overdose instances may go unreported or be incorrectly diagnosed since xylazine is a relatively new adulterant. Accurate assessment of the burden of xylazine-related overdoses is further hampered by inconsistent testing procedures, inadequate funding for forensic labs, and delays in data reporting. To enhance monitoring and direct public health measures, it is crucial to implement routine toxicological testing, standardize diagnostic coding, and strengthen surveillance systems.Point-of-care testing devices and drug-checking programs are crucial instruments for harm reduction. People can identify contaminated drug sources and make educated judgments if xylazine test strips are more widely available and community-based drug-checking services are offered. While avoiding stigmatizing language that would deter people from seeking care, public health messaging should concentrate on informing communities about the dangers of xylazine exposure.In addressing the xylazine epidemic, community-based organizations are essential. These groups frequently offer integrated services, such as food aid, housing help, wound care, referrals for addiction treatment, and education about overdose prevention. They are important collaborators in lowering the negative effects of xylazine use because of their capacity to provide trauma-informed, culturally aware, and nonjudgmental treatment.Naloxone does not directly counteract the sedative effects of xylazine, but it is still necessary for correcting opioid-induced respiratory depression in combination opioid-xylazine overdoses. Therefore, more research is required to create reversal medicines and focused treatments for xylazine toxicity. Healthcare systems should also increase access to evidence-based treatment for xylazine withdrawal and xylazine-related skin ulcers, which frequently call for specialist care.For those impacted by xylazine use, stigma continues to be a major obstacle to accessing healthcare. Patients may be deterred from seeking therapy or finishing care due to visible skin wounds and unfavorable societal judgments.To enhance patient engagement and health outcomes, healthcare providers should employ person-centered, trauma-informed strategies and non-stigmatizing language. In order to prevent sensationalized depictions that could perpetuate discrimination and social exclusion, responsible media reporting is also essential.Finding the socioeconomic, demographic, and structural elements connected to xylazine-related overdoses should be the main goal of future studies. To better identify vulnerable populations and

create focused interventions, research on socioeconomic position, race and ethnicity, mental health issues, geographic location, and healthcare accessibility is required.[12]

Awareness, Harm Reduction, and Future Perspectives Xylazine's

quick rise in the illegal drug market serves as a reminder of how substance usage patterns are changing and the problems they pose for public health. There are substantial gaps in our knowledge of its pharmacology, toxicity, and long-term health impacts because to our limited understanding of its effects on humans. There is a pressing need for scientific study to elucidate the mechanisms of xylazine toxicity and create evidence-based preventative and treatment measures as new chemicals continue to find their way into unregulated medicine markets.Severe skin ulcers and soft tissue injuries are among the most worrisome side effects of xylazine use. People with these diseases frequently encounter obstacles to receiving healthcare, such as discrimination and stigma in medical settings. In order to offer accessible wound care, health education, and referral services, harm reduction organizations, outreach initiatives, and community-based services must to be reinforced and supported. Incorporating wound care into current harm reduction initiatives may increase treatment adherence and lower complications.Another crucial tactic for reducing the negative effects of xylazine is drug-checking programs. By identifying the presence of xylazine in drug samples, methods like test strips and analytical testing can help people make safer choices. Drug-checking data can enhance individual risk reduction as well as monitoring efforts by revealing regional patterns of xylazine distribution and trends in drug contamination. Increasing access to these services can improve overdose prevention initiatives and public health interventions.Effective harm reduction interventions require the participation of those who have personally experienced substance use. Their expertise and close interaction with impacted communities can enhance public health initiatives' applicability, acceptability, and efficacy. Drug users' meaningful involvement in research, teaching, and service delivery can also lessen stigma and foster trust between vulnerable communities and healthcare professionals.A thorough assessment of policy responses to the escalating xylazine crisis is necessary. Regulations should be weighed against possible effects on scientific research and veterinary practice, even though their goal may be to lessen abuse. Research indicates that restrictive laws by themselves might not be able to adequately address the root causes of substance abuse and might inadvertently encourage the development of substitute, possibly more dangerous substances in the black market. Therefore, rather than depending exclusively on prohibition-based methods, public health policies should give priority to surveillance, harm reduction, research, community participation, and access to healthcare services.In general, a thorough and interdisciplinary strategy involving researchers, medical professionals, legislators, harm reduction organizations, and impacted communities is needed to address the issues related to xylazine. Reducing the burden of xylazine-related harms requires ongoing research, enhanced surveillance systems, easily accessible treatment facilities, and evidence-based public health measures.[13]

Xylazine and the "Zombie Drug" Myth

Xylazine is a veterinary sedative and α_2-adrenergic agonist first synthesized in Germany in 1962 and approved for veterinary use in 1972. Although not approved for human use, it has increasingly appeared in illicit drug supplies, particularly when mixed with opioids such as fentanyl and heroin. Xylazine enhances sedative effects, prolongs intoxication, and increases the risk of respiratory depression, hypotension, bradycardia, and overdose. Because it is not an opioid, its effects cannot be reversed by naloxone, although naloxone should still be administered in suspected opioid co-exposure. Xylazine acts primarily by stimulating central α_2-adrenergic receptors, reducing norepinephrine release and producing sedation, analgesia, muscle relaxation, and central nervous system depression. It is rapidly absorbed, metabolized in the liver, and excreted through the kidneys. Repeated use has been associated with severe skin ulcers, soft-tissue infections, tissue necrosis, and, in extreme cases, amputation. Media reports have frequently referred to xylazine as the **"zombie drug"** because individuals with advanced xylazine-associated wounds may appear severely debilitated and develop extensive skin ulcerations. However, this term is considered misleading and stigmatizing. The wounds are not caused by people "turning into zombies" but are thought to result from repeated exposure, vasoconstriction, poor wound healing, and associated infections. Public health experts recommend avoiding

sensationalized language and instead focusing on evidence-based descriptions of xylazine-related health harms. The increasing prevalence of xylazine in the illicit drug market represents a significant public health concern. Its widespread use in combination with fentanyl and other substances has contributed to rising overdose deaths and complicated clinical management. Addressing this issue requires enhanced surveillance, harm reduction strategies, healthcare access, wound care services, and continued research into effective treatments and prevention measures.[14]

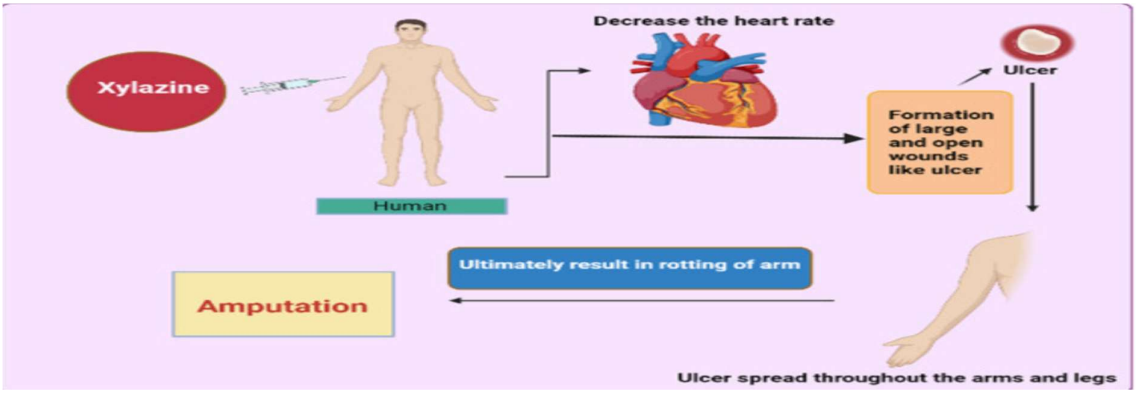

Fig-4: Effects of xylazine after entering into the body.[14]

Conclusion

Xylazine has emerged as a growing public health concern due to its increasing presence in the illicit drug supply, particularly in combination with opioids such as fentanyl. Its misuse is associated with serious health consequences, including respiratory depression, cardiovascular complications, severe skin ulcers, tissue necrosis, and increased risk of overdose. Overdose therapy is more difficult because naloxone cannot completely reverse the effects of xylazine because it is not an opioid.The rising prevalence of xylazine highlights the need for improved surveillance, routine toxicological testing, healthcare provider awareness, and evidence-based treatment strategies. Harm reduction measures, including drug-checking services, wound care programs, and community outreach initiatives, are essential to reduce xylazine-related harms. Further research is required to better understand its pharmacology, toxicity, and long-term effects. A coordinated approach involving healthcare professionals, researchers, policymakers, and public health organizations is crucial to address the growing impact of xylazine misuse and improve patient outcomes.

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