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THE ZOMBIE DRUG

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ABSTRACT:

Introduction and objectives: The opioid overdose epidemic is exacerbated by the emergence of Xylazine as an illicit drug adulterant. Xylazine, a veterinary sedative, can potentiate opioid effects while also causing toxic and potentially fatal side effects. This systematic review aims to assess the impact of Xylazine use and overdoses within the opioid epidemic context.

Method:

A systematic search was conducted following PRISMA guidelines to identify relevant case reports, and case series related to Xylazine use. A comprehensive literature search included databases like Web of Science, PubMed, Embase, and Google Scholar, utilizing keywords and Medical Subject Headings (MeSH) terms related to Xylazine. Thirty-four articles met the inclusion criteria for this review.

Results:

Intravenous (IV) administration was a common route for Xylazine use among various methods, including subcutaneous (SC), intramuscular (IM), and inhalation, with overall doses ranging from 40 mg to 4300 mg. The average dose in fatal cases was 1,200 mg, compared to 525 mg in non-fatal cases. Concurrent administration of other drugs, primarily opioids, occurred in 28 cases (47.5%). Intoxication was identified as a notable concern in 32 out of 34 studies, and treatments varied, with the majority experiencing positive outcomes. Withdrawal symptoms were documented in one case study, but the low number of cases with withdrawal symptoms may be attributed to factors such as a limited number of cases or individual variation. Naloxone was administered in eight cases (13.6%), and all patients recovered, although it should not be misconstrued as an antidote for Xylazine intoxication. Of the 59 cases, 21 (35.6%) resulted in fatal outcomes, with 17 involving Xylazine use in conjunction with other drugs. The IV route was a common factor in six out of the 21 fatal cases (28.6%).

Conclusion:

This review highlights the clinical challenges associated with Xylazine use and its co-administration with other substances, particularly opioids. Intoxication was identified as a major concern, and treatments varied across the studies, including supportive care, naloxone, and other medications. Further research is needed to explore the epidemiology and clinical implications of Xylazine use. Understanding the motivations and circumstances leading to Xylazine use, as well as its effects on users, is essential for developing effective psychosocial support and treatment interventions to address this public health crisis.

Categories: Psychiatry, Epidemiology/Public Health, Substance Use and Addiction

Keywords: case report synthesis, a systematic review, overdose death, fatal outcome, naloxone, co-administration,intravenous injection, adulterant, opioid overdose, xylazine

Introduction And Background :

Xylazine, a veterinary tranquilizer, first identified in Puerto Rico as a more prevalent additive in street drugs in the early 2000s, is spreading to other states in the United States at an alarming rate . It is commonly added to opioids to boost their depressive effects on the central nervous system. Besides opioids, it is also common for individuals who abuse cocaine to be exposed to Xylazine, as it is frequently added to illicit substances as an adulterant .Xylazine is not approved for human use and is primarily used in veterinary settings as a sedative, analgesic ,and muscle relaxant. However, Xylazine is available over the internet to purchase. The easy availability and low cost of Xylazine online have made it an attractive "cutting agent" for drug traffickers. Xylazine sedative effects allow them to decrease the amount of fentanyl or heroin in drug mixtures while still producing similar effects,

making it a profitable addition. In fact, some people intentionally seek out. Xylazine-laced fentanyl or heroin as Xylazine is believed to increase the duration of action of fentanyl and heroin. Its use has been linked to an increase in overdose deaths and side effects including skin ulcers, abscesses, lesions, drowsiness, amnesia, hypotension, bradycardia, and bradypnea, making it a significant public health concern. Since Xylazine is not an opioid and unfortunately its sedative effects are not reversed by naloxone, an opioid overdose involving Xylazine is much more challenging to reverse and, consequently, more lethal to the user. The State Unintentional Drug Overdose Reporting System (SUDORS) provides comprehensive data on opioid overdose deaths and quickly identifies newer, dangerous drugs.

In Philadelphia, Xylazine went from being detected in less than 2% of cases of fatal heroin and/or fentanyl overdose between 2010 and 2015, to 262 (31%) of the 858 fatal heroin and/or fentanyl overdose cases in 2019. According to Philadelphia Department of Public Health reports, in 2021, 91% of samples of purported heroin or fentanyl from Philadelphia also contained Xylazine, making it the most common adulterant in the drug supply. Due to the growing number of Xylazine-containing substance confiscations in 2021, all opioid samples began to be tested for Xylazine. Because of this, Xylazine was found in 429 overdose deaths (19% of opioid-related overdose deaths), compared to 52 overdose deaths (3% of opioid-related overdose deaths) in 2020. The National Forensic Laboratory Information System's data supports these trends, showing a significant rise in Xylazine detection in drug items and cases analyzed by forensic labs over time. Several agencies at National and State levels, including the Drug Enforcement Administration (DEA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), and state public health departments, have put out warnings about Xylazine since it was found to be more common and to have a serious impact on opioid overdose deaths. Xylazine is still legal in the U.S., but the FDA has taken steps to prevent the drug from entering the U.S. market for illicit purposes on February 28, 2023. The aim of these measures is to limit the illicit use of Xylazine while ensuring it remains available for legitimate veterinary purposes. Moreover, various state health agencies have separately warned about the risks associated with Xylazine-contaminated drugs in their regions . In this review, we aimed to explore the impact of Xylazine use in exacerbating the opioid overdose epidemic. We also discussed the pharmacologic properties that contribute to Xylazine's potential lethality and reviewed the available data on treatment options.

XYLAZINE: ITS STRENGTH AND DANGER :

The strength of the drugs available on the street has only continued to increase since the time heroin was considered the most severe addiction. It wasn't so long ago that heroin was demonized as a one-way ticket to an inescapable dependency that would most assuredly destroy the life of anyone partaking of it. Heroin is now considered somewhat tame in comparison to far more powerful and readily available alternatives.

To put things in perspective, fentanyl is fifty times stronger than heroin. It kills people daily, and among groups of people who frequently use it, death is as commonplace as dinner. It's not uncommon for users to have many stories of their resuscitation from an overdose, or having saved the lives of others with a shot of Narcan.

The addition of xylazine to fentanyl is particularly disastrous for two reasons. Symptoms of withdrawal begin after only two hours without fentanyl, but the effects of xylazine persist for around eight, leaving users completely without agency against them. Some of the symptoms of acute fentanyl withdrawal are life-threatening, such as vomiting and sudden onset heart arrhythmia.

Xylazine is also not an opiate derivative. This means that when someone is overdosing on what's presumed to be fentanyl, Narcan does not affect it. It's worth noting that Narcan should be administered anyway in these situations, as it will still help if the sufferer has fentanyl in their system.

HEALTH IMPACTS OF XYLAZINE :

Xylazine use causes the user to nod off in the first 20 to 30 minutes after use, after which they'll be deeply sedated for several hours. In an atmosphere of drug abuse, this puts the user in significant danger from the people around them as they're unable to defend themselves. Even if left undisturbed, pressure sores and other complications can arise from lying in a single position for hours on end.

Death can occur at any moment for an unconscious individual under its effects. Xylazine causes severe depression in the normal functioning of our central nervous system, meaning people relax to such a degree that they'll choke to death on their tongue without realizing it. People also suffocate in their vomit without receiving any signals of distress to move or wake up like they would have done under the effects of a less potent drug.

Rhabdomyolysis is a severe condition that describes the process of muscle tissue breaking down. When muscle tissue releases proteins and electrolytes into the blood, our hearts and kidneys are often irreparably damaged. Rhabdomyolysis can cause permanent disability and sometimes even be fatal as its onset is often sudden and unexpected.

Skin wounds are also commonly occurring in people who use xylazine, both intravenously and otherwise. It's not yet understood why persistent skin wounds occur for people no matter their avenue of ingestion, but it's certainly a worrying unknown. As this addiction and its effects are studied, we may yet find xylazine to be even more sinister than first expected.

Review :

Methods:

This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) guidelines. We aimed to identify all relevant studies, including case reports and case series related to Xylazine use, its clinical features, and management. Due to the limited number of randomized controlled trials (RCTs) or clinical trials on this topic, our primary emphasis was on case reports and case series. Search strategy We conducted a comprehensive literature search using electronic databases, including Web of Science, PubMed, Embase, Google Scholar, and gray literature sources, such as conference proceedings and government reports, from inception until the present date. Our search strategy used a

combination of keywords and Medical Subject Headings (MeSH) terms related to "xylazine*," "xylazine use," xylazine overdose, "xylazine intoxication," "xylazine withdrawal," and "xylazine management." This search yielded 1,238 articles, of which 34 met the inclusion criteria. Two independent reviewers (SA and LJ) screened the titles and abstracts of identified articles for eligibility. Full-text articles were obtained for potentially relevant studies, and eligibility was determined based on the following inclusion criteria: (1) studies reporting on Xylazine use; (2) human case reports and case series; (3) articles published in English. Studies were excluded if they did not focus on Xylazine use or were not relevant to the objectives of this review. Disagreements between reviewers were resolved by consensus or by consulting a third reviewer (AB).Study selection A total of 1,238 articles were identified through the initial database search. After removing duplicates and screening titles and abstracts, 64 articles were selected for full-text review. From these, 34 articles met the inclusion criteria and were included in this systematic review. These articles encompassed 59 cases involving Xylazine use for recreational purposes, self harm,or accidental exposure.

Quality assessment:

Since there were not any controlled studies, we gauged the evidence quality by examining the reliability and validity of the public sources used in this review. We considered the relevance, reliability, and precision of these sources, discussing any potential biases we came across. Additionally, we evaluated the evidence quality by comparing the consistency of findings across different sources.

Literature review:

The literature review consists of Xylazine exposure, risks, consequences, mechanism of action, and clinical management in humans (evidence from human and animal studies).

FDA warning:

The FDA has warned healthcare professionals about the serious risks associated with Xylazine exposure inhumans. Xylazine is primarily used as a veterinary anesthetic and has no approved uses for humans. Xylazine is increasingly found in the illicit drug supply, often in combination with other drugs. Acute and repeated exposure to Xylazine can lead to significant harm, including delayed diagnosis and management of polysubstance overdose, interference with the successful treatment of opioid use disorder (OUD), and the development of severe, necrotic skin ulceration.

Mechanism of action:

Xylazine acts as an 2-receptor agonist in both central and peripheral nervous systems, causing a strong sympatholytic effect by activating central presynaptic 2 receptors [50]. It was originally synthesized with the goal of creating a new anti-hypertensive drug due to its similarity to clonidine. Its strong CNS depressant effects led to it being used as a veterinary sedative, analgesic, and muscle relaxant in the 1960s.

Pharmacokinetics and overdose:

Xylazine has a rapid elimination from the body, with a half-life ranging from 23 to 50 minutes, posing a significant challenge in the management of Xylazine overdose cases. Xylazine is a veterinary drug, and there is limited information available on its pharmacokinetics and clinical management in cases of human overdose. Its rapid metabolism and elimination from the body can lead to a quick onset of toxic effects, potentially overwhelming the patient's system before appropriate interventions can be implemented. Timely identification and treatment of this substance are critical in managing Xylazine overdose cases.

Toxicity and fatality:

The published literature demonstrates that Xylazine can produce toxicity and fatality in humans in doses ranging from 40 to 2400 mg, with plasma concentrations ranging from 0.03 to 4.6 mg/L in non-fatal cases. In fatalities, blood concentrations of Xylazine range from trace to 16 mg/L [52]. Due to the significant overlap between non-fatal concentration and postmortem blood concentration, there appears to be no defined safe, toxic, or fatal concentration of Xylazine in humans [50]. It is important to note that comprehensive pharmacokinetic data examining various routes of administration (IV, IM, inhalation) and their impact on bioavailability and fatal dosages are limited. This lack of comprehensive pharmacokinetic data may have an impact on the interpretation of the reported results, and readers should take this into account when assessing the findings presented in this study.

Health consequences and clinical management:

In humans, Xylazine usage has been linked to damage to multiple organs resulting in bradycardia, elevated blood sugar, hypotension, and even coma in an overdose. Although naloxone can be used to reverse opioid overdose, the literature indicates that it is not an effective medication for Xylazine overdose [30]. As a result, other supportive treatments must be provided to patients not responsive to naloxone therapy. Additionally, repeated exposure to Xylazine has been found to cause characteristic necrotic skin ulcers in patients. The exact mechanism of skin injury is not fully understood.

Complicating polysubstance intoxication management:

As Xylazine is frequently found mixed with other substances, it can significantly impact the clinical management of acute intoxication/withdrawal of other substances. While its interaction with opioids is described above; Xylazine was also shown to impair the anticonvulsant properties of phenobarbital, phenytoin, and diazepam in rats. Thus, Xylazine can impede the clinical treatment of withdrawal seizures and increase morbidity and mortality.

Abuse potential:

Xylazine has been identified as a substance with significant abuse potential. Xylazine combined with other drugs intensifies its sedative effects and can be dangerous. The exact mechanism of Xylazine abuse is unclear, but it may involve its impact on the brain's reward system through altering neurotransmitter levels, such as norepinephrine and dopamine. This alteration in neurotransmitter levels may produce pleasurable effects that lead to addiction. Studies published from Puerto Rico and Philadelphia indicate that it is commonly found as a mixed substance with speedball, a combination of stimulants and opioids. In other cases, it has been detected with heroin, fentanyl, and cocaine . According to a report published in Puerto Rico, Xylazine was found in more than 90% of the speedball samples. In light of these concerning findings, more attention and awareness are required in combating Xylazine abuse and developing specific interventions against it.

Hemodynamic effects:

Xylazine exposure has been associated with various cardiovascular and pulmonary effects, as well as challenges in managing hypotension and diuresis. Several studies and case reports emphasize the cardiac complications that can arise from Xylazine use, such as biventricular systolic failure, valvular dysfunction,and myocardial necrosis and fibrosis. In some cases, clinical treatment with nifedipine has been found effective in managing these cardiac complications [58]. In addition to its impact on the cardiovascular system, Xylazine has been linked to pulmonary issues. For example, a study conducted by Chavez et al. on nine Xylazine-related deaths in Puerto Rico discovered moderate to severe pulmonary congestion and edema in all cases. This could be attributed to either a direct effect of Xylazine on the pulmonary vasculature or as a consequence of the drug's impact on cardiac activity. When it comes to managing Xylazine- induced hypotension and diuresis, many patients respond well to intravenous (IV) fluids alone, without the need for additional interventions [19,20]. Animal studies have demonstrated that Xylazine can cause diuresis, which can be reversed by Atipamezole and yohimbine.

Effects on pregnancy:

While no human studies are currently available to establish the safety of Xylazine use during pregnancy, findings from animal studies raise concerns about its potential adverse effects on fetal development. In these studies, Xylazine has been shown to markedly reduce uterine blood flow and oxygen availability, which may critically impair the delivery of oxygen to the fetus during crucial stages of development or delivery.

Hyperglycemia and other long-term effects:

Xylazine use in animals can lead to hyperglycemia, induced in normoglycemic and insulin-dependent diabetic monkeys via reducing tissue sensitivity to insulin and glucose uptake. A metabolite of Xylazine, 2,6-xylidine, is also reported to be a genotoxic and carcinogenic compound. These can create challenges for people who use Xylazine chronically.

Ocular damage:

The use of Xylazine as anesthesia led to a decrease in intraocular pressure after intramuscular (IM) administration in monkeys and corneal lesions after IV administration in rats.

Results:

Route of Administration, Dose, and Outcomes

Doses ranged from 40 mg to 4300 mg, with many cases not reporting specific dosages. The average dose of Xylazine in fatal cases was 1,200 mg, compared to 525 mg in non-fatal cases, suggesting that higher doses might be associated with an increased risk of fatal outcomes. However, it is important to consider individual cases' details when interpreting these findings. Out of the 12 IV Xylazine use cases, two were fatal, and the rest recovered. However, it's important to consider the concomitant use of other drugs, which might have affected the outcomes. In the fatal IV cases, no other drugs were involved in the case, while in the case, clorazepate and alcohol were also involved. While the average dose in fatal cases is higher than in non-fatal cases, individual case outcomes do not always follow this pattern. Two case studies reported by Carruthers et al. and Hoffman et al. have shown that patients recovered after receiving high doses of Xylazine through IV and IM routes, respectively. However, while there is some evidence suggesting a link between higher doses of Xylazine and fatal outcomes, the relationship is complex and difficult to establish definitively based on the limited data available.

Co-administration of Other Drugs

In a review of 34 studies encompassing a total of 59 cases, it was found that 28 instances (47.5%) involved the concurrent administration of other drugs in combination with Xylazine. Of these cases, the majority involved the use of opioids, including fentanyl, morphine, and heroin, which highlights the potential exacerbation of the ongoing opioid crisis due to the misuse of Xylazine. Notably, several studies, including fentanyl, while Wong et al. reported the use of morphine, heroin, fentanyl, and codeine in seven case also reported the use of morphine, alcohol, and cocaine in several cases. Non-opioid substances, including benzodiazepines, ketamine, and cocaine, were reported in various cases, potentially adding to the complexity of clinical presentation and management of Xylazine overdose. Among the analyzed cases, reported the use of benzodiazepines; Liu CM et al. cited sulpiride, ketamine, and phenobarbital; and Shapses et al. identified cocaine. The co-administration of Xylazine with other drugs, particularly opioids, intensifies the challenges of managing intoxication and may lead to adverse outcomes.

Naloxone Use and Outcomes

In the context of Xylazine intoxication, the use of naloxone, an opioid antagonist, presents a complex and nuanced picture. We analyzed 59 cases involving Xylazine intoxication, in which eight patients (13.6%) were administered naloxone, and all of them recovered. In cases where Xylazine is used in conjunction with opioids, naloxone's effectiveness in reversing the effects of opioids may indirectly contribute to patient recovery by mitigating the impact of opioid intoxication. However, in cases of Xylazine intoxication without opioid involvement, naloxone may not be effective, as demonstrated by a case of a 16-year-old patient who showed no response to naloxone. It should be noted that observing the reversal of a Xylazine overdose with naloxone should not be taken as an indication that naloxone is a specific antidote for Xylazine intoxication. Further studies are needed to confirm the effectiveness of naloxone in a broader range of scenarios involving Xylazine intoxication and investigate its potential role in treating such cases, particularly when used in combination with other substances.

Xylazine Abuse and Outcomes

In our analysis of Xylazine abuse, we examined 34 studies, out of which 11 reported a total of 25 cases of Xylazine abuse. The cases varied in terms of administration routes, concomitant drug use, and outcomes. We observed that the most common route of Xylazine administration was IV, followed by inhalation, IM, and subcutaneous (SC). A significant number of cases involved the concomitant use of other drugs, particularly opioids such as fentanyl, heroin, and morphine. Other substances commonly reported in combination with Xylazine included cocaine, codeine, benzodiazepines, and ketamine. Out of the 25 Xylazine abuse cases, 16 (64%) resulted in fatal outcomes, emphasizing the severity of Xylazine overdoses in the context of the opioid crisis. The remaining cases had various outcomes, including recovery and the development of neurocognitive symptoms.

Intoxication and Withdrawal Symptoms

Intoxication was identified as a notable concern, as it was reported in 32 out of 34 studies. The treatments administered for intoxication varied among the studies, encompassing supportive care, IV fluids, and specific interventions such as naloxone administration, intubation, and cardiac catheterization. The majority of patients experienced positive outcomes and successful recovery. However, there were instances where intoxication proved fatal, emphasizing the critical need for timely and appropriate treatment in cases of Xylazine overdose. Withdrawal symptoms were documented in one case study, where the patient's withdrawal symptoms and potential for harmful autonomic instability were managed using a combination of medications, including dexmedetomidine infusion, phenobarbital, tizanidine, and clonidine. It is important to note that the low incidence of withdrawal symptoms may be attributed to factors such as a limited number of cases, overlapping symptoms resulting from the co-use of various drugs during withdrawal (which further complicates the identification of Xylazine's individual withdrawal symptoms), differing methodologies employed by researchers, or the possibility that certain individuals may not experience withdrawal symptoms associated with Xylazine use.

Xylazine-Related Fatal Outcomes

Out of the 59 cases, 21 (35.6%) had fatal outcomes. Among these fatal cases, 17 (81%) involved the use of Xylazine in combination with other drugs, including opioids (e.g., fentanyl, heroin, morphine, and codeine), stimulants (e.g., cocaine), and sedatives (e.g., alcohol, alprazolam, procaine, and lidocaine). The fatal cases reported in this paper involve a wide range of Xylazine doses, with only one case reporting a larger dose of 500 mg. The IV route of administration was reported in six of the 21 fatal cases (28.6%), and in the other 13 cases not reported. It is important to note that IV use was suspected in four of these cases due to indications of a needle found near the decedent or recent venipuncture sites. These findings suggest that the risks of Xylazine use are significantly increased when combined with other drugs, and IV use may have also increased the risk of adverse outcomes, as seen in some of the fatal cases. It is important to note that due to the limited data, establishing a definitive causal relationship between heavy doses of Xylazine and fatal outcomes is challenging.

Conclusions:

This research paper emphasizes the complex nature of Xylazine use and the urgent need for a comprehensive approach to its detection, management, and harm reduction. The potential association between IV injection, higher Xylazine doses, and fatal outcomes highlights the importance of harm reduction strategies. Moreover, our findings underscore the need to understand the interactions between Xylazine and co-administered substances, particularly in the context of polydrug use involving fentanyl. While naloxone may play a role in treating cases with concurrent opioid intoxication, it

is not a specific antidote for Xylazine overdose. Understanding the motivations and circumstances leading to Xylazine use is vital for developing effective psychosocial support and substance use disorder treatment interventions.

Strengths and limitations

This systematic review has several strengths, including a comprehensive search strategy covering multiple databases and gray literature, which increases the likelihood of identifying relevant studies. Incorporating case reports and case series provides a broader understanding of Xylazine use and its implications within the opioid crisis. The detailed analysis of 59 cases sheds light on patterns and risk factors associated with Xylazine-related overdoses and fatalities. By adhering to PRISMA guidelines, the review maintains a robust methodology, enhancing reliability and reproducibility. However, limitations include a small number of cases, potential publication bias, and heterogeneity in study design and reporting, which could affect generalizability and result interpretation. Establishing causality between identified factors and Xylazine-related overdoses or fatalities requires further research, such as prospective cohort studies or controlled trials.

Interpretation and Application of Findings in Clinical ContextsIt is important to acknowledge that this study's results are based on a systematic review of existing literature and should be interpreted with caution in clinical contexts. The findings presented in this review should not be regarded as definitive but as a synthesis of the current evidence on Xylazine use and its clinical implications. As with any literature review, limitations may exist in the included studies, such as potential publication bias, heterogeneity in study design and reporting, and the inability to establish causality. Therefore, clinicians and researchers should carefully consider the evidence presented in this review and weigh it against their knowledge, expertise, and the specific circumstances of their patients before making any clinical decisions or drawing conclusions. Further research, including prospective cohort studies or controlled trials, is needed to confirm the relationships identified in this review and to advance our understanding of Xylazine use

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