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Review Article

Xylazine With Opioid Cause Epidemic: Review of Cases, Statistics, Mode of Action, and Impacts

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ABSTRACT

Xylazine with opioid can cause huge epidemic due to illicit drug Adulterant, and its misuse. Xylazine is a sedative and analgesic in veterinary, muscle relaxant and with the combination of an opioid drug cause toxicity and potentially fatal side effects, and deaths. Overdosing of Xylazine within opioid causes a major impact and illicitly supplied to persons who inject drug which cause opioid epidemic situation. In this review paper, Discussion on cases, their stats and how Xylazine with opioid cause toxicity with their impacts. There was tremendous increase in the percentage of death involving illegally made fentanyl (IMF) (an opioid drug) with Xylazine detected from 3% in January 2019 to 11% in June 2022. The increased number of opioid overdose deaths in which non-opioid drug Xylazine was involved. Xylazine is not classified as a controlled substance; it is marketed as a veterinary drug and employed as a sedative, analgesic, and muscle relaxant. In humans, central nervous system depression, respiratory, bradycardia, hypotension, and even death can be caused by it. The article is to making an awareness regarding overdoses of such fatal drug but with combination of opioid drug it makes it mor deadly, such as (fentanyl, cocaine, heroin etc.).

INTRODUCTION

Xylazine is normal veterinary tranquilizer in animals as muscle relaxant and analgesic during surgical process. Xylazine was first for humans but ended up being really useful for animals too, especially in veterinary care. It helps animals relax and relieves their pain by targeting certain

receptors in their brains. Usually, it's given as a shot in liquid form to be swallowed. There's no passive form of it that does anything. Its use has made it much easier to calm and treat animals in vet clinics. As per Food and Drug Administration (FDA), xylazine is a marketed veterinary medicine

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as Sedazine™, Rompun™ etc. These medicine which contain xylazine, they are approved for use in dogs, cats, horses, etc. Xylazine is like know drug phenothiazine, which having chemical structure closely as resembled between them.[1]
[2]



Xylazine, primarily intended for veterinary purpose as pain reliever, and muscle relaxant, has found its way into illicit markets due its easy availability online. This accessibility, coupled with its affordability, has made it an appealing “cutting agent” for drug traffickers. By incorporating xylazine into drug mixtures such as fentanyl or heroin, traffickers can reduce the amount of these potent substance while maintaining similar effects. This paper explores the implications of xylazine’s misuse in illegal drug trade, highlighting its role as a profitable addition for traffickers.[3] Xylazine function as a potent α_2 -adrenergic agonist, primarily acting through the stimulation of central α_2 -receptors. This stimulation leads to reduction in the release of nor-epinephrine and dopamine within the central nervous system, resulting in sedation, muscle relaxation, and diminished perception (loss) of painful stimuli. Its effects may additionally involve various other mechanism, including cholinergic, serotonergic, dopaminergic, α_1 -adrenergic, histaminergic, or opiate pathways. notable side effects observed in animals encompass transient hypertension, and respiratory depression.[4] Xylazine, though utilized in veterinary medicine for pain relief and sedative, lacks FDA approval for human use due to its potential hazards. Despite its widespread use, there is no specific antidote for human xylazine

intoxication. Naloxone has been suggested as a possible antidote, but its effectiveness remain uncertain. In a case series where naloxone was administered, there was no evident reversal of xylazine’s toxic effects promoting question about the suitability of naloxone for managing xylazine intoxication in human.[5] Xylazine overdose deaths are most common in Philadelphia, them in Maryland and Connecticut. More and more people are dying from overdoses involving xylazine, a drug often with opioids. In 2015, only 0.36% of overdose deaths involved xylazine, but by 2020, it jumped to 6.7%. In 2021, xylazine was in 19% of all drug overdose deaths in Maryland. In 2020, it was involved in 10% of drug overdose deaths in Connecticut [6][7]. This review paper, we aim to explain the toxication on human, the mechanism how the xylazine act when injected in human body, and the impact simultaneously. We also shade on the physiology and the major damages to the body parts.

Methods Review

This review paper was prepared by analysis of all relate articles and literature studies. We aim to mainly focus on the physiology and mode of action of xylazine intoxication in human body. We studied the cases relate to accidentally and non-accidentally inject of xylazine involve with opioid drug. Mostly our primary work is to shade, how xylazine act on human body in detail.

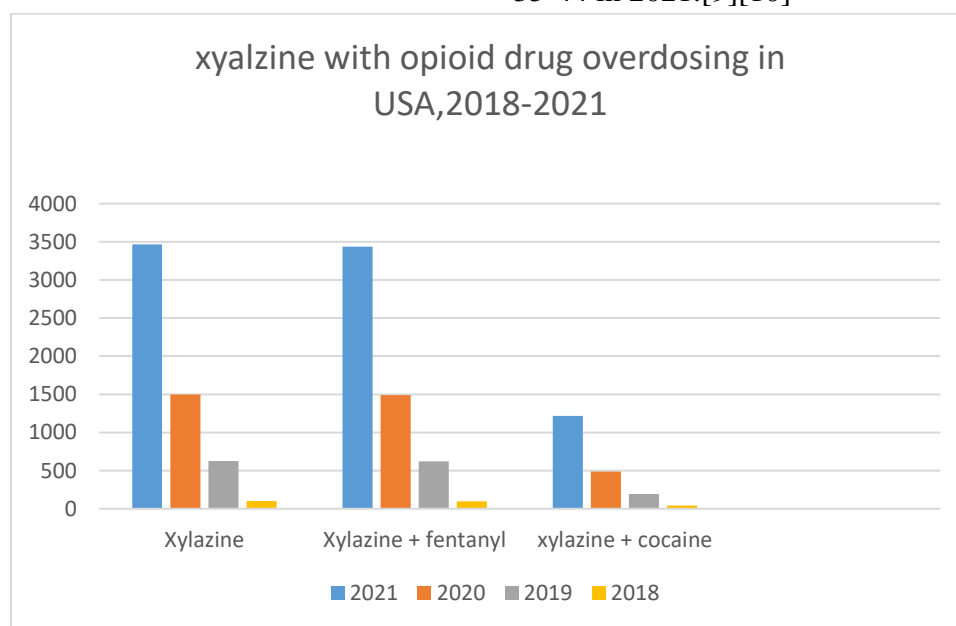
Statistics Review

An analysis of drug overdose deaths spanning from January 2019 to June 2022 was conducted across several U.S. jurisdictions, including Connecticut, Delaware, District of Columbia, Georgia, Illinois, Maine, new jersey etc. Washington, notably, Illinois reported deaths primarily from countries representing at least 75% of the state’s drug overdose fatalities in 2017. In analysis, jurisdiction had to provide data for six-months period within the specified timeframes, with toxicology reports available for a minimum

of 75% of deaths during the respective periods. Decedents with either an accessible toxicology reports or with xylazine listed as a cause of death on their certificates were included in the analysis, ensuring a comprehensive examination of drug-related fatalities across the specified regions and timeframes[8]. Below tables no 1 states that deaths detected with xylazine and IMF (Illicitly-manufacturing fentanyl) opioid drug in 31 states of US states and district of Columbia.

Sex	Total	With xylazine detected
Female	14,638	1,318
Male	39,330	3,541

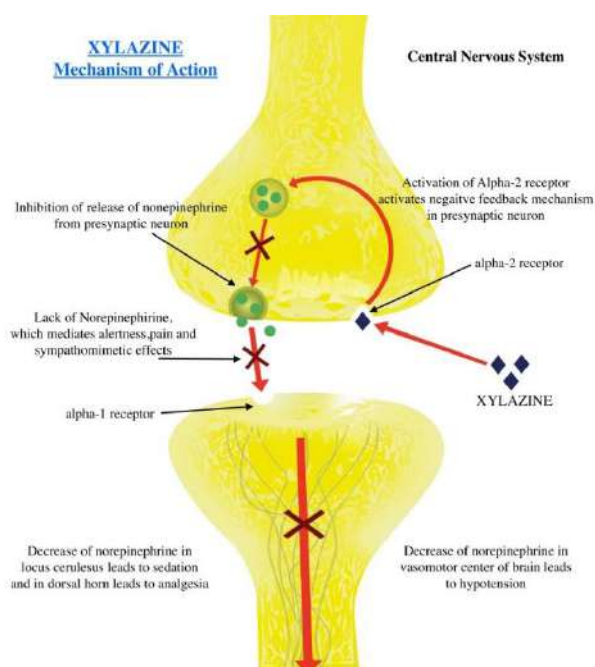
The study shows a significant rise in drug overdose deaths involving xylazine since 2018, with 102 deaths reports in 2018, 627 in 2019, 1499 in 2020, and staggering 3,468 in 2021. The marks as 35-fold increase in the age-adjusted rete of drug overdose deaths involving xylazine, from 0.03 per 100,000 standard population in 2018 to 1.06 in 2021. Both males and females experienced increased rates, although males consistently had more then double the rates of females each year. Rates for all ages groups rise from 2020-2021, with the highest rates observed among those ages 25-35 and 35-44 in 2020, and among those aged 35-44 in 2021.[9][10]



Mode of action:

Xylazine is drug that is like others medications used for various conditions like depression and high blood pressure. It belongs to group of drugs that affect a specific type of receptor in body called alpha-2 receptors. When you take xylazine, it blinds to these receptors in both central (brain and spinal cord) nervous systems. After administering xylazine, it spread throughout the body in about 30 to 40 min. By doing this, it stops the release of a chemical call norepinephrine, which usually causes things like increased heart rate and blood pressure. So, xylazine causes effects like lowering

blood pressure, slowing down the heart rate, making you feel relaxed and sleepy, reducing pain, and relaxing muscle. Even though it clouds potentially have some effects that mimic the body’s response to stress, its strong attachment to these receptors mainly leads to calming effect [11][12][13].



When you're stressed or in danger, your body releases a neurotransmitter called norepinephrine, which kicks your "fight or flight" response into gear. But when you take xylazine, it attaches to certain receptors in your body, called alpha-receptors, which stops norepinephrine from being released. This means that the part of your nervous system responsible for getting you all worked up and ready to fight or run away (the sympathetic nervous system) slow down. So, xylazine helps to down in your body [14].

IMPACTS / ADVERSE EFFECTS

Skin disorders

Many cases have been reported where abscesses and painful ulcers developed on different parts of the body, regardless of where the drug was injected into the veins. This is believed to happen because the drug directly causes blood vessels near the skin to narrow, which reduces blood flow to the skin. This narrowing of blood vessels also leads to low blood pressure, slow heart rate, and shallow breathing, which can result in less oxygen reaching the skin tissues [15][16].

While the exact way xylazine cause tissue death(necrosis) isn't completely understood, one idea is that it happens because xylazine makes the blood vessels in the area tighten up (vasoconstriction) due to its alpha-2-agonist properties. This tightening reduces blood flow, which means less oxygen and nutrients reach the tissue. Without enough oxygen and nutrients, the tissue become more prone to inflammation and infections, which can lead to tissue death [17].

CONCLUSION

In summary, the rise of xylazine as an adulterant in illicit drug trade, especially when mixed with opioids, poses a grave public health risk due to its accessibility, affordability, and potent effects. Despite being intended for veterinary use, its ingestion by humans lacks FDA approval, highlighting its dangers. The increasing number of deaths linked to xylazine, particularly alongside opioids, emphasizes the urgent need for awareness, prevention, and intervention measures. This necessitates a comprehensive approach involving enhanced surveillance, education, treatment access, and research into effective antidotes. Collaboration among law enforcement, healthcare, and public health sectors is essential to address the root causes of xylazine misuse and safeguard the well-being of affected individuals and communities.

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