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Tranq drug – A new threat to public health

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Abstract. The Tranq drog represents the new combination of substances at increased risk of abuse (fentanyl/fentanyl analogs and xylazine) currently affecting states such as Puerto Rico, the United States, and Canada. This type of drug is responsible for both the occurrence of necrotizing infected ulcers at the injection site of users, as well as the ineffectiveness of the antidote naloxone in treating overdoses and the lack of testing for xylazine detection. Public Health Departments in the US are conducting an ongoing battle to inform the public of the existence of xylazine as a prevalent contaminant in street drugs and to educate in first aid measures to limit adverse effects and deaths occurring post Tranq use. This paper aimed to warn of the new urgent public health challenge emerging among American drug users, responsible for the highest overdose mortality rates at this time.

Keywords. opioids, fentanyl, xylazine, drug abuse, tranq.

1. Introduction

Along with placing on the drug market of synthetic sedatives (fentanyl, xylazine) and stimulants (metamphetamine) much more potent than regular drugs has led to an explosion in fatal overdose rates, violence and the emergence of difficult-to-treat infectious diseases [1]. This major shift in the North American drug market began in 2012-2013 with the use of fentanyl/fentanyl analogs as potentiating adulterants in the heroin supply chains in the United States and continued with the birth of a new drug known as the name *Tranq/Zombie*, by joining synthetic opioids with xylazine, a Food and Drug Administration (FDA)-approved tranquilizer for veterinary use only [2-3].

2. Fentanyl/Fentanyl analogs

Fentanyl **(Figure 1A),** the most well-known opioid, was first synthesized in 1960 by the physician Paul Janseen and marketed as a pain medication [4]. In the United States of America, it was approved by the Food and Drug Administration (FDA) as an intravenous anesthetic in 1972, under the trade name of *Sublimaze*. With the patent period ending, the year 1981 saw a ten times increase in sales of fentanyl and reports of misuse and illicit use by anesthesiologists and surgeons with access to the drug were stated. Access to the general public was facilitated with the introduction of transdermal fentanyl in the pharmaceutical

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market in the 1990s through controlled-release patches, and an increase in overdose cases caused by their misuse was also observed [4]. Following the synthesis of fentanyl in 1960, many fentanyl analogs were developed for medicinal and veterinary use including sufentanil, alfentanil, carfentanil, remifentanil, lofentanil, cyclopentanylfentanyl, furanylfentanil, etc. Alfentanil **(Figure 1C)** has a lower potency and action than fentanyl, but has a faster onset, so it is used as both an anesthetic and an analgesic. Remifentanil has a rapid onset of action but short duration, being used as an adjuvant in anesthesia and allowing rapid post-surgical recovery. Sufentanil **(Figure 1B)** is more potent than fentanyl and 100 times more potent than morphine, thus being preferred in the management of post-operative or oncological pain for opioid-dependent or tolerant patients. Carfentanil is the most potent opioid in commercial use, 100 times more potent than fentanyl and 10.000 times more potent than morphine, making it unusable for medical use in humans, but used as an anesthetic in large animals [5].

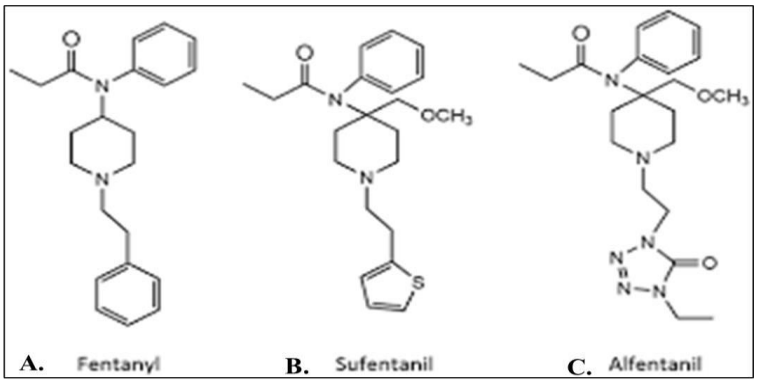

Figure 1. Chemical structures
A. Fentanyl, **B.** Sufentanil, **C.** Alfentanil

The same pharmacological and pharmacokinetic properties that introduced fentanyl and its analogues into the class of effective therapeutic drugs such as action on the central nervous system, rapid diffusion in the brain, high potency, have led to the predisposition to human abuse [6].

3. Xylazine

Xylazine **(Figure 2)** is a nonopioid substance synthesized in 1962 by the Bayer company (Leverkusen, Germany) used as a sedative, analgesic and muscle relaxant in animals. According to the FDA, xylazine is only licensed as a veterinary drug as a tranquilizer under trade names such as *Rompun*, *Anased*, *Sedazine*, and *Chanazine*. This substance has a chemical structure similar to clonidine, phenothiazines and tricyclic antidepressants, being a very potent α-2 adrenergic agonist [7].

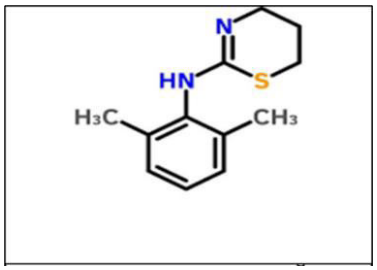

Figure 2. Xylazine – chemical structure

It was first identified as an adulterant in heroin products two decades ago in Puerto Rico, USA, where it is known as "anestesia de caballo" (horse anesthesia) and remains particularly prevalent in the composition of *speedballs* (mixture of heroin and cocaine) [8]. Specialized studies in Puerto Rico indicated that xylazine causes infected ulcerative skin lesions, which are subsequently exacerbated by consumers injecting it directly into the lesion in order to reduce existing pain [9]. There have also been reports that it has been misused as a horse doping agent, drug of abuse, drug of attempted sexual assault, and as a source of accidental or intentional poisoning [10]. The main side effects of xylazine in humans include depression of the central nervous system and the respiratory center, arterial hypotension, bradycardia, hyperglycemia and necrotic ulcers **(Figure 3)** [7]. Xylazine is legitimately sold directly through pharmaceutical distributors and veterinary websites, but is also readily available for purchase on other websites (China) in liquid and powder form, with no association required with the profession of veterinarian or with the requirement to prove the legitimacy of the possession of this profession, with prices ranging between $6-$20 U.S. dollars per kilogram [11]. Spectrophotometric drug testing data conducted from May to September 2022 by the Center for Forensic Science Research and Education (CFSRE) in partnership with the Philadelphia Department of Health shows that the average drug sample in Philadelphia today it consists of approximately 0 – 64.8 % xylazine and 0.3 – 34.8 % fentanyl. Thus, xylazine becomes the main adulterant consumed by Philadelphia (USA) street drug users [12].

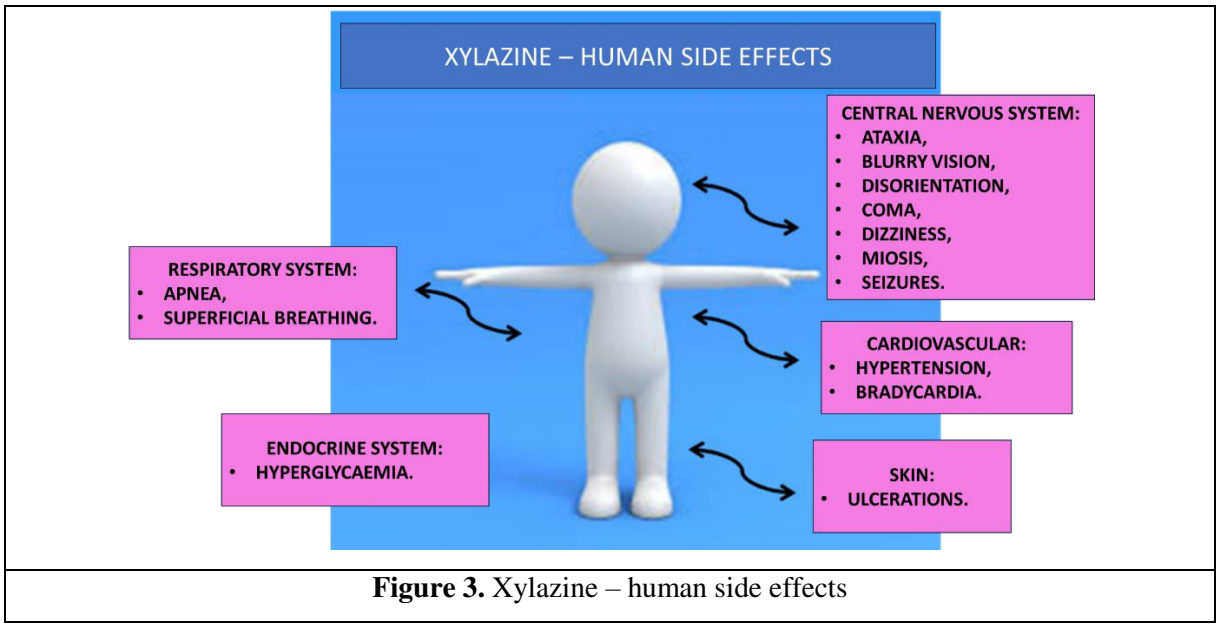

Figure 3. Xylazine – human side effects

A study conducted by the Philadelphia, US Department of Public Health analyzed data from the Medical Examiner's Office in Philadelphia, Pennsylvania on unintentional heroin and/or fentanyl overdose deaths with xylazine detections over a 10-year period (2010 - 2019) and concluded that xylazine went from being detected in less than 2 % of fatal heroin and/or fentanyl overdoses between 2010 and 2015 to 262 (31 %) of 858 fatal overdoses of heroin and/or fentanyl in 2019 [13]. Aditionally, the paper points out the phenomenon whereby xylazine becomes the main adulterant in drugs combined with heroin and fentanyl in percentages of 5 % in 2015 and reaching 25 % in 2019 according to laboratory tests carried out by the US National Anti-Drug Agency (U.S. DEA) [13]. Another study conducted between 2017 and 2021 in Illinois, USA (Chhabra N. et all, 2022) reported 210 deaths associated with xylazine abuse, also establishing a peak incidence in October 2021. According

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to this research the association of xylazine with fentanyl/fentanyl analogs was detected in 99.1 % of overdose deaths [14]. The research conducted between 2019 and 2020 in Connecticut, USA (Thangada S. *et al.*, September 2021) reported 146 deaths associated with xylazine abuse. According to it, the association of xylazine with fentanyl/fentanyl analogs was detected in 99.3 % of overdose deaths. Deaths associated with xylazine occurred primarily among men (80.9 %) and non-Hispanic whites (74.0 %), and mortality was highest among those aged between 25 to 34 years (28.1 %) [15].

4. Tranq/Zombie drug

The combination of the opioid fentanyl and the tranquilizer xylazine is known as *Tranq/Zombie* in the illicit drug market and is showing exponential growth in use among users in Puerto Rico, the United States, and Canada [1, 9, 16-18]. U.S. Department of Public Health officials are alarmed by the rapid spread of the drug and are concerned about the negative effects of its use. One such adverse effect is the development of hard-to-heal soft tissue injuries that lead to necrotic tissue and culminate in amputation at higher rates than in those who inject other drugs without the xylazine contaminant. Additionally, users may develop a physical dependence on xylazine itself, with some users reporting withdrawal symptoms from xylazine as or more severe than from heroin or methadone; symptoms including sharp chest pains and convulsions. [11, 19]. Xylazine overdoses are difficult to identify in clinical settings because they often appear similar to opioid overdoses and may not be included in routine drug screening tests. Although there is no approved human antidote for xylazine, experts recommend naloxone as an overdose treatment because it is frequently combined with opioids. Unfortunately, naloxone does not reverse the adverse effects of xylazine, but its use can reduce the risk of respiratory depression produced by the opioid in the composition of the drug *Tranq*, an effect sufficient to prevent death [11]. Public Health Departments have issued alerts warning health professionals about the presence of xylazine in the illicit drug supply and have drawn clear guidelines in providing medical care to reduce complications from xylazine drug use [20]. Under current U.S. law, drugs and other substances that are considered controlled substances under the Controlled Substances Act (CSA) are divided into five lists. This placement is based on the substance's accepted medical use, potential for abuse, and liability for safety or addiction. The law also provides a mechanism for substances to be controlled (added to or transferred between lists) or removed from control. Procedures for adding, deleting, or modifying the schedule of a drug or other substance may be initiated by the US Drug Enforcement Administration (DEA), the Department of Health and Human Services (HHS), or by petition of any interested party (drug manufacturer, pharmacy/medical association, citizens, etc.) under section 201 of 21U.S.C. 811 and taking into account the following factors: *(1)* the drug's actual or relative potential for abuse *(2)* scientific evidence of the drug's pharmacological effect, if known, *(3)* the state of current scientific knowledge regarding the substance, *(4)* the history and current pattern of abuse, *(5)* the scope, duration, and significance of the abuse, *(6)* what risk it poses to public health, *(7)* the drug's psychic or physiological dependence liability, and *(8)* whether the substance is an immediate precursor of a substance already controlled [21]. Substances such as fentanyl/fentanyl analogues are included in the controlled lists of the U.S. National Drug Enforcement Agency and are subject to federal trafficking penalties with prison terms (minimum 5 years) and the imposition of fines of maximum values of $5 million U.S. dollars on the first offense and $8 million U.S. dollars for the second offense. Unfortunately, xylazine is not currently listed as a controlled substance under the federal Controlled Substances Act (CSA). Test strips are currently available to identify fentanyl, but they are not able to detect xylazine, thus causing Public

Health Departments to join forces with forensic toxicology laboratories to examine and identify the various substances in the illicit drugs formulation [8].

5. Conclusions

Xylazine low cost and ease of acquiring leads to increased profits for traffickers by making it the main street drug adulterant and rapidly attracting users seeking to experience prolonged effects of the opioids or heroin euphoria. The rapid establishment of physical and mental dependence, the increased risk of death from extended respiratory depression, the occurrence of difficult-to-treat necrotic ulcerations, and the ineffectiveness of naloxone as an antidote should lead to the inclusion of xylazine on the lists of life-threatening substances.

In addition, the lack of tests capable of identifying this substance in illicit drug supplies limits the possibility of public health intervention, the implementation of harm reduction strategies or the development of new treatment strategies.

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