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Review Article

# Xylazine intoxication in humans and its importance as an emerging adulterant in abused drugs: A comprehensive review of the literature

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ABSTRACT

Xylazine is not a controlled substance; it is marketed as a veterinary drug and used as a sedative, analgesic and muscle relaxant. In humans, it could cause central nervous system depression, respiratory depression, bradycardia, hypotension, and even death. There have been publications of 43 cases of xylazine intoxication in humans, in which 21 (49%) were non-fatal scenarios and 22 (51%) resulted in fatalities. Most of the non-fatal cases required medical intervention. Over recent years xylazine has emerged as an adulterant in recreational drugs, such as heroin or speedball (a cocaine and heroin mixture). From the 43 reported cases, 17 (40%) were associated with the use of xylazine as an adulterant of drugs of abuse. Its chronic use is reported to be associated with physical deterioration and skin ulceration. Literature shows some similar pharmacologic effects between xylazine and heroin in humans. These similar pharmacologic effects may create synergistic toxic effects in humans. Therefore, fatalities among drug users may increase due to the use of xylazine as an adulterant. Xylazine alone has proven harmful to humans and even more when it is combined with drugs of abuse. A comprehensive review of the literature of non-fatal and fatal xylazine intoxication cases including those in which the substance was used as adulterant is presented, in order to increase the awareness in the forensic community, law enforcement, and public health agencies.

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**Contents**



## 1. Introduction

Xylazine is a non-narcotic drug synthesized in 1962 by Bayer (Leverkusen, Germany), used as a sedative, analgesic, and muscle relaxant in animals [1]. According to the Food and Drug Administration (FDA), xylazine is used exclusively in veterinary medicine, marketed as Rompun®, Anased®, Sedazine™, and

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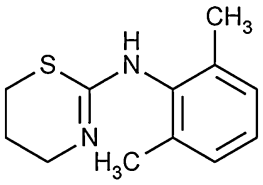


**Fig. 1.** Structure of xylazine.

Chanazine®. It is approved for use in dogs, cats, horses, fallow deer (dama dama), mule deer (odocoileus hemionus), sika deer (cervus nippon), white-tailed deer (odocoileus virginianus), and elk (cervus canadensis) [2]. Its chemical structure closely resembles the phenothiazines, tricyclic antidepressants, and clonidine (Fig. 1) [1]. Xylazine is a potent $\alpha_2$-adrenergic agonist that mediates via stimulation of central $\alpha_2$-receptors. The $\alpha_2$ stimulation decreases the release of norepinephrine and dopamine in the central nervous system resulting in sedation, muscle relaxation, and decreased perception of painful stimuli. Its actions may also involve cholinergic, serotonergic, dopaminergic, α-1-adrenergic, histaminergic, or opiate mechanisms [3]. Acknowledged side effects in animals include transient hypertension, hypotension, and respiratory depression. [1,4].

The routes of administration in animals include intravenous, intramuscular and, subcutaneous. The dosage form and amount are available in liquid solution equivalent to 20, 100 and 300 milligrams of xylazine. The dose varies with animals ranging from 0.25 to 4 milligrams per pound intramuscularly or 0.5 milligrams per pound intravenously [2]. The ranges of these doses provide analgesia for 15–30 min, but the sedative effect may continue for 1–2 h [5].

Xylazine pharmacokinetic parameters are well-established in different animal species, but not in humans. Briefly described, xylazine is absorbed, metabolized and eliminated extremely rapid [4,6]. After intravenous administration in animals, xylazine rapidly distributes, concentrating in the kidney and the central nervous system. The duration of effects begins within a few minutes and last up to 4 h. [4,7,8]. The pharmacokinetics of xylazine have been studied in the dog, sheep, horse, and cattle [9]. Pharmacokinetic parameters do not vary greatly between species following intravenous administration. In all four species after intravenous administration, the distribution half-life ($t_{1/2\alpha}$) was very short (1.21–5.97 min) and the elimination half-life ($t_{1/2\beta}$) varied from 23.11 to 49.51 min. These values indicate that the xylazine concentration would decrease to an undetectable level within a few hours. Xylazine has a large volume of distribution (1.9–2.5 for horse, cattle, sheep and dog) suggesting that xylazine, as expected for the lipophilic nature of the compound, diffuses extensively. Xylazine bioavailability (intramuscular to intravenous) ranges from 52 to 90% in the dog, 17 to 73% in sheep, and 40 to 48% in the horse [9]. Peak plasma concentrations are reached in 12–14 min in all species. The LD50 for dogs and horses is 47 and 60–70 mg/kg intramuscularly, respectively [10].

There is limited information on the metabolism of xylazine. In rats, using radio-labeled xylazine, after intravenous (i.v) injection (0.2–1.0 mg/kg) the drug was rapidly distributed to different tissues and 70% of the radio-activity was eliminated in urine with a half-life of about 2–3 h, only 8% of the activity corresponded to the unchanged form of the drug [9]. In the urine of cattle, 1% unchanged xylazine was eliminated during the first 2 h, with apparent half-life of 40 min. [9]. Total drug elimination after a therapeutic dose occurs over 10–15 h in the animal model [4,8]. The rapid elimination of xylazine is attributed to extensive metabolism, and not to rapid renal excretion of unchanged xylazine. Several metabolites have been identified in horses, rats and cattle [6,11–13]. Recently, a study on human metabolism in urine was investigated by Meyer and Maurer. Xylazine was N-dealkylated and S-dealkylated, oxidized, and/or hydroxylated to 12 phase I metabolites. The phenolic metabolites were partly excreted as glucuronides or sulfates. All phase I and phase II metabolites identified in rat urine were also detected in human urine. In rat urine after a low dose as well as in human urine after an overdose, mainly the hydroxy metabolites were detected using the authors' standard urine screening approaches by GC–MS and LC–MSn [14].

Illicit drugs, such as cocaine and heroin, are often adulterated with other agents to increase bulk and enhance or mimic the illicit drug's effects. In Puerto Rico, heroin is commonly adulterated with xylazine [15,16]. Also, it is frequently found in speedball (a cocaine and heroin mixture) [15,17]. It has also been reported to be misused as a horse doping agent, a drug of abuse, a drug for attempted sexual assault, and as source of accidental or intended poisonings [14]. From human reported cases, central nervous system depression, respiratory depression, bradycardia, hypotension, and hyperglycemia were observed. [16]. Literature shows some similar pharmacologic effects between xylazine and heroin in humans. Both drugs cause bradycardia, hypotension, central nervous system depression and respiratory depression [16,18–21]. Because of these similar pharmacologic effects, synergistic effects may occur in humans when xylazine is use as an adulterant of heroin. Therefore, fatalities among drug users may increase due to the use of xylazine as an adulterant, especially due to the potentiation of the respiratory depressant effects of heroin. Authorities must be on alert about the use of xylazine as an adulterant, but also of others $\alpha_2$-adrenergic agonists. For example, dexmedetomidine is approved in humans by the FDA, produce sedation, analgesia, anxiolysis, and sympatholysis with less respiratory depression than others $\alpha_2$-adrenergic agonist such as xylazine [22]. To the best of our knowledge, dexmedetomidine has not been found as an adulterant of illicit drugs, however due to its FDA legal usage in humans and increase availability at this time, it may also encounter as a drug of abuse or possible adulterant in future.

A comprehensive review of the literature regarding non-fatal and fatal xylazine intoxication cases including those in which the substance was used as adulterant of drugs of abuse is presented and discussed in order to increase the awareness in the forensic community, law enforcement, and public health agencies.

## 2. Search strategy

A literature review was performed with PubMed using the keywords "xylazine", "xylazine and poisoning", "xylazine and humans", "xylazine and adulterant", "xylazine and cocaine", xylazine and morphine", and "xylazine interaction". Articles were also identified through searches of the authors' own manuscripts and relevant publications. Only papers published in English language were reviewed.

## 3. Results

Forty-three intoxication cases (43) in humans were identified from the years 1966 to 2013 [1,3,4,8,10,16,23–38]. A brief history, general effects, supportive care, drug used during the treatment, uses, route/mode of administration, dose, toxicological results and analytical technique are presented in Table 1 for the non-fatal cases. A summary of a brief history, uses, route, toxicological results and analytical technique are described in Table 2 for the fatal cases.

**Table 1**
Literature review of xylazine intoxication in non-fatal cases (21 cases).

| History | General effects | Supportive care and drugs used | Uses[a] | Route/mode of administration[b] | Dose (mg) | Toxicological results/ analytical technique(for xylazine quantification) | References |
|---|---|---|---|---|---|---|---|
| Human volunteer | Anesthesia<br>Bradycardia | na | frp | iv | 7 | na | [24] |
| A 34 y/o male was found unconscious within 30 min of retiring to bed. Beside him lay a syringe and an empty Rompun® (xylazine) bottle which had been earlier noted to contain about 10 mL of a 100 mg/mL solution of xylazine hydrochloride. He had easy access to supplies of xylazine and was well aware of its restriction to veterinary use and its sedative properties. He admitted to having successfully treated five or six episodes of insomnia with small intramuscular injection | CNS and respiratory depression, tachycardia, multifocal premature ventricular contractions (PVC), nonspecific electrocardiographic st-t segment changes, hyperglycemia | Endrotracheal intubation, ventilation with a bird respirator, intravenous fluid therapy, bladder catheterization, and central venous pressure monitoring<br>Lidocaine | mi | im/sa | 1000<br>(15 mg/kg bw) | na | [10] |
| A 20 y/o female horse trainer with history of chronic depression and two previous suicidal attempts drank 4 mL (400 mg) of xylazine (Rompun®) after argument with her boyfriend | CNS and respiratory depression, mild hypotension, bradycardia, unifocal PVC, hyperglycemia, incontinence of urine, miosis | Endrotracheal intubation, ventilaton, gastric lavage, activated charcoal, and saline cathartics<br>Lidocaine and naloxone | s | oa/sa | 400 | Plasma: neg.<br>Urine: pos.<br>GC–MS | [8] |
| A 39 y/o veterinary surgeon's wife with history of alcohol abuse had some bruising and puncture marks on the buttocks. She admitted to taking xylazine because of her painful hand, but she did not admit to injecting herself with the drug | CNS depression bradycardia | No endrotracheal intubation | mp | im | na | Serum: 0.03 mg/L<br>Urine: 1.67 mg/L<br>na | [24] |
| A 29 y/o woman injected 1 mL (40 mg) of xylazine intramuscularly | CNS and respiratory depression, hypotension, bradycardia, miosis | No endrotracheal intubation | pns | im/sa | 40<br>(0.73 mg/kg bw) | na | [23] |
| A 37 y/o female with history of depression self-injected 24 mL (2400 mg) of Rompun® (xylazine) intramuscularly in a suicide attempt | CNS and respiratory depression, hypertension, hyperglycemia, ecchymosis at the injection site | Endotracheal intubation and oxygen<br>Naloxone | s | sc/sa | 2400<br>(22 mg/kg bw) | na | [23] |
| A 29 y/o female injected an undetermined amount of xylazine intravenously | CNS and respiratory depression, bradycardia | Endotracheal intubation and ventilation<br>Naloxone | pns | iv/sa | na | na | [23] |
| A farmer inadvertently placed a needle cover in his mouth. The needle cover had been on a dart that had misfired. Presumably some of the drug had leaked into the plastic cover. Within minutes he felt "woozy". His face went numb and began to feel heavy. His legs and arms began to feel heavy. As he lost control of his limbs, even when he was down on the floor he was aware of conversations, but quite unable to take part or move. As he was moved to the truck he was able to talk again and began to brighten up. He soon felt drowsy again as the truck moved along | CNS depression | No endrotracheal intubation | ai | oa | na | na | [25] |
| A veterinarian accidentally self-administered a small dose subcutaneously when a horse reared and hit him. He soon became very sleepy and was taken to hospital by the owner of the horse | CNS depression | No endrotracheal intubation | ai | sc | na | na | [25] |
| *Two* people ate an elk, sedated with xylazine before being slaughtered | CNS depression | na | ai | oa | na | na | [25] |

**Table 1** (*Continued*)

| History | General effects | Supportive care and drugs used | Uses[a] | Route/mode of administration[b] | Dose (mg) | Toxicological results/ analytical technique(for xylazine quantification) | References |
|---|---|---|---|---|---|---|---|
| A 19 y/o male veterinary nurse, in the process of his routine work, accidentally injected himself subcutaneously with 2 mL (100 mg/mL) of xylazine. There was no past medical or psychiatric history of note | CNS and respiratory depression, hypotension, bradycardia, hyperglycemia, and miosis | Endotracheal intubation, intravenous fluids, and ventilation Naloxone | ai | sc | 200 (3 mg/kg bw) | na | [26] |
| A 16 y/o old son of a horse breeder came home stumbling and stuporous. He admitted to drying an amount of xylazine on a compact disk case, scraping the powder into a bag, snorting the drug, and feeling euphoric shortly thereafter | CNS and respiratory depression, bradycardia, miosis, hypotonia, and dry mouth | Endotracheal intubation, ventilation, activated charcoal and IV fluids Thiamine, naloxone lorazepam and vecuronium | r | ih/sa | na | Urine: positive to benzodiacepines. Blood: 0.54 mg/L GLC | [27] |
| A 27 y/o male farmer attempted to commit suicide by self-administration of about 75 mL 2% aqueous solution xylazine by intramuscular injection as a consequence of a conflict situation in his family | CNS and respiratory depression, hypertension followed by hypotension, bradycardia, hyperglycemia, and miosis | Endotracheal intubation, ventilation, gastric lavage, activated charcoal, cathartics, intravenous fluid therapy and urinary, gastric, and central venous catheters Etomidate, propofol orciprenaline, metoclopramide, ranitidine | s | im/sa | 1500 (13 mg/kg bw) | Serum: 4.6 mg/L Urine: 194 mg/L Stomach: 446 mg/L HPLC, GC–MS | [3] |
| A 23 y/o old male was found by the highway patrol passed out in the center median of a freeway with his pickup truck in gear. He admitted injecting himself twice while in his pickup with 1.5 and 3 mL of xylazine (Xyla-Ject®, 100 mg/mL injectable) | CNS and respiratory depression and bradycardia | No endotracheal intubation | pns | im/sa | 450 | Blood: Xylazine 0.57 mg/L Paroxetine 0.02 mg/L GC–MS | [1] |
| A 18 y/o male with antecedents of drug abuse with various substances (cocaine and amphetamines) inhaled xylazine | CNS depression, hypotension, and bradycardia | Intravenous fluids, no endotraceheal intubation | r | ih/sa | na | na | [28] |
| A 36 y/o veterinarian, who self-injected himself with 15 mL xylazine (from a 50 mL vial with 100 mg xylazine/mL) and 10 mL ketamine (from a 10 mL vial with 100 mg ketamine/mL. He had been injecting himself with ketamine for 5 years. Because of tolerance to ketamine's effect, he had been using the xylazine + ketamine combination for the last 3 month | CNS depression, hypertension, tachycardia, hyperglycemia, ecchymotic areas on his arms and upper legs, miosis, vomiting, hypersalivation, and constipation | Intravenous fluids and monitored for high blood pressure and ECG changes, no endotraceheal intubation Metoprolol succinate | r | im/sa | 1500 xylazine and 1000 ketamine | na | [29] |
| A 38 y/o male who works in a veterinary clinic had an accidental irrigation of both eyes with approximately 800 mg of xylazine (8 mL of the 100 mg/mL solution) | CNS depression, hypotension, and bradycardia | No endotraceheal intubation, copious irrigation of both eyes with normal saline (NS) | ai | oe | 800 | na | [4] |
| A 44 y/o male veterinarian helper was chasing an ox, the loaded gun containing 20 mg/mL solution fired accidentally, and the anesthetic dart hit him in his right foot. He had diabetes mellitus and had been medicated subcutaneously | CNS depression, bradycardia, and hyperglycemia | No endotraceheal intubation Atropine, enoxiparin, flucloxacilin, and insulin | ai | sc | na | Blood: 1.5 mg/L GC/MS | [30] |
| A 19 y/o male with history of chronic use of antacids and sulpiride for chronic epigastric pain admitted to inhale unknown powder and began to suffer from repeated episodes of syncope. He admitted to drug abuse over the previous six months | CNS depression, bradycardia, and, orthostatic hypotension | Intravenous saline No endotraceheal intubation | ai | ih/sa | na | Urine: Ketamine: 582 mg/L, Norketamine: 448 mgL, Phenobarbital: 745 mg/L, and Xylazine: 762 mg/L GC-MS | [31] |
| A 14-year-old male accidentally injected the narcosis arrow in his left thigh while doing some cleaning work in the deer park. The arrow, containing xylazine and ketamine, was incompletely injected | CNS depression, bradycardia, nightmares, nausea, vomiting | Endotraceheal intubation and ventilation Midazolam etomidate | ai | sc | na | Plasma: Xylazine 0.3 mg/L Ketamine 0.1 mg/L LC–MS | [32] |

[a] Accidental intoxication (ai), for research purpose (frp), misused to treat insomnia (mi), misused to treat pain (mp), purpose not specified (pns), recreational (r), suicide attempt (s).
[b] Inhaled (ih), intramuscular (im), intravenous (iv), ocular exposure (oe), oral admistration (oa), subcutaneous (sc), self administration (sa), no data available (na).

**Table 2**
Literature review of xylazine intoxication in fatal cases (22 cases).

| History | Uses[a] | Route[b] | Toxicological results | Analytical technique (for xylazine quantification) | References |
|---|---|---|---|---|---|
| A 36 y/o male veterinarian, with history of alcohol abuse, was found dead on the kitchen floor with two syringes and a 50 mL vial of xylazine. On the evening prior to death he was drinking alcohol to excess before retiring to bed at midnight. He was a psychiatric patient and was known to have been self-administering xylazine for at least one month prior to death. The death was attributed to the combined depressant effects of alcohol, nordiazepam, and xylazine. | ai | iv | Xylazine:<br>Blood, 0.2 mg/L<br>Brain, 0.4 mg/kg<br>Kidney, 0.6 mg/kg<br>Liver, 0.9 mg/kg<br>Lung, 1.1 mg/kg<br>Adipose, 0.05 mg/kg<br>Urine, 7 mg/L<br>Ethanol:<br>Blood, 380 mg/dL<br>Nordiazepam:<br>Blood, 2.5 mg/L | GC | [35] |
| A white 59 y/o female with history of alcohol abuse, was found dead lying in her bed in the locked bedroom. Some empty packages of Ludiomil® (maprotiline), Temestra® (lorazepam), Halcion® (triazolam), and Tenormin® (atenolol) were found on a little rack in the bedroom. She was working in a company trading in veterinary products. The cause of death was a massive intoxication with xylazine *per os* with suicidal intent. | s | na | Xylazine:<br>Blood, 16 mg/L<br>Urine, 30 mg/L<br>Stomach, large amount<br>Ethanol: Blood, 0.78 g/kg | GC–NPD | [36] |
| The decomposed torsos of a *33 y/o male* and 23 y/o female were found each within their respective 55 gallon drum dumped in a Dade County waterway. Approximately one month later, the severely decomposed heads were found in $3_{1/2}$ gallon buckets in a remote location. At the crime scene, there was a 50 mL vial of xylazine (100 mg/mL) with 32 mL of solution remaining. In addition, police recovered syringe and hypodermic-dart gun. | h | im | Xylazine:<br>Brain, 0.16 mg/kg<br>Kidney, 0.15 mg/kg<br>Liver, 0.26 mg/kg<br>Ethanol:<br>Brain, 0.04 g/dL<br>Liver, 0.08 g/dL | GC–MS<br>GC–NPD | [37] |
| The decomposed torsos of a 33 y/o male *and 23 y/o female* were found each within their respective 55 gallon drum dumped in a Dade County waterway. Approximately one month later, the severely decomposed heads were found in 31/2 gallon buckets in a remote location. At the crime scene, there was a 50 mL vial of xylazine (100 mg/mL) with 32 mL of solution remaining. In addition, police recovered syringe and hypodermic-dart gun. | h | im | Xylazine:<br>Brain, 19 mg/kg<br>Kidney, 28 mg/kg<br>Liver, 42 mg/kg<br>Ethanol:<br>Brain, 0.01 g/dL<br>Liver, <0.01 g/dL | GC–MS<br>GC–NPD | [37] |
| A 42 y/o male was found hanging from a tree just inside the tree line near an abandoned gravel quarry. A used 3-cc syringe, clamps, and a tourniquet were found on the ground below the body. He was a practicing veterinarian and had a history of depression. His wife founded a suicide note. | s | iv | Xylazine:<br>Heart blood, 2.3 mg/L<br>Peripheral blood, 2.9 mg/L<br>Bile, 6.3 mg/L<br>Liver, 6.1 mg/kg<br>Kidney, 7.8 mg/kg<br>Urine, 0.01 mg/L | GC–NPD | [38] |
| Seven postmortem cases associated with drug of abuse and xylazine as an adulterant. Four were males and in three cases the sex was unknown. | ai | na | Blood: From trace to 130 ng/mL | GC–MS | [33] |
| Nine postmortem cases associated with drug of abuse and xylazine as an adulterant. Five were males and four were females whose ages ranged from 23 to 70 years. Xylazine was associated with the cause of death in all of these cases. | ai | na | Blood: 0.29–5.00 mg/L | LC–MS | [34] |
| A male, drug user, was found dead. Case associated with drug of abuse and xylazine as an adulterant. | ai | na | Xylazine:<br>Heart blood, 0.461 mg/L<br>Free morphine<br>Heart blood, 0.743 mg/L<br>Codeine<br>Heart blood, 0.024 mg/L<br>6-AM<br>Heart blood, less than 0.01 mg/L | UPLC–MS–MS | [16] |

[a] Accidental intoxication (ai), suicide attempt (s), homicide (h).
[b] Intravenous (iv), intramuscular (im), no data available (na).

## 4. Discussion

### 4.1. Xylazine and humans

Xylazine is not approved by the FDA for human use. It was investigated in humans as a sedative-hypnotic, analgesic and anesthetic drug, but it was rejected because of its frequent association with severe hypotension and central nervous system depression [7,23]. From all the reported cases (43), 21 (49%) were non-fatal scenarios in which most required medical intervention and 22 (51%) resulted in fatalities. According to the history described in both tables, 14 (33%) of the individuals had easy access to supplies of xylazine, due to their type of job (veterinarian, veterinarian assistant, farmer, horse trainer or related field). From

**Table 3**
Purpose of consumption in 43 cases.

| Purpose of consumption | # non-fatal cases | # fatal cases | # total of case |
|---|---|---|---|
| Accidental/xylazine as an adulterant | – | 17 (77%) | 17 (40%) |
| Accidental intoxication | 9 (43%) | 1 (5%) | 10 (23%) |
| Suicide attempt | 3 (14%) | 2 (9%) | 5 (12%) |
| Recreational | 3 (14%) | – | 3 (7%) |
| Purpose not specified | 3 (14%) | – | 3 (7%) |
| Homicide | – | 2 (9%) | 2 (5%) |
| Misused to treat pain | 1 (5%) | – | 1 (2%) |
| Misused to treat insomnia | 1 (5%) | – | 1 (2%) |
| For research purpose | 1 (5%) | – | 1 (2%) |
| Total of cases | 21 | 22 | 43 |

all cases, 26 (60%) were males, 11 (26%) were females and in 6 cases (14%) the gender was unknown with ages ranging from 14 to 70 years with a mean age of 34 years and a median of 33 years. As shown in Table 3, from 22 fatal cases, xylazine consumption was suicidal in 2 cases (9%), homicidal in 2 cases (9%) and accidental in 18 cases (82%). Xylazine was used as an adulterant in 17 out of 18 accidental cases. From the non fatal cases (21), xylazine consumption was accidental in 9 (43%), for suicidal purpose in 3 cases (14%), for recreational purpose in 3 cases (14%) and it was also misused to treat insomnia or pain. The routes of administration were mostly parenteral (intravenous, intramuscular, subcutaneous), but other routes such as oral, ocular exposure and inhalation have been reported.

The general toxidrome for xylazine is illustrated in Fig. 2. In the case of an overdose (Table 1), patients present central nervous system symptoms (areflexia, asthenia, ataxia, blurred vision, disorientation, dizziness, drowsiness, dysarthria, dysmetria, faintness, feeling "woozy", hyporeflexia, slurred speech, somnolence, staggering, tiredness, coma), respiratory depression (apnea or shallow breathing), cardiovascular effects (hypotension, bradycardia, tachycardia, premature ventricular contractions (PVC)), endocrine symptoms (hyperglycemia) and additional symptoms (miosis). Rarely, hypotonia, dry mouth, urine incontinences and nonspecific electrocardiographic st-t segment changes were observed [1,3,4,8,10,23–32]. The typical duration of effects in animals last up to 4 h. Prolonged duration of effects from 8 to 72 h was noted in reported cases of human overdose [4].

The treatment after a xylazine exposure should be directed at maintaining respiratory function and blood pressure. Supportive care is probably much more important in treating xylazine overdose [28]. Supportive treatment should include endotracheal intubation, ventilation, intravenous fluid infusion, gastric lavage, activated charcoal, bladder catheterization, electrocardiographic (ECG) and hyperglycemia monitoring. The predicted large volume of distribution suggests that hemodialysis would be an ineffective means of enhancing elimination [4]. So far, no antidote exists for xylazine intoxication in humans. Alpha-adrenergic antagonists such as phentolamine, yohimbine, and tolazoline have been proposed as antidotes for xylazine, but have not undergone testing in humans [27,28]. Although no antidote exits for xylazine intoxication, multiple drugs were used as supportive therapeutic intervention such as: lidocaine, naloxone, thiamine, lorazepam, vecuronium, etomidate, propofol, orciprenaline, metoclopramide, ranitidine, metoprolol, atropine, enoxiparin, flucloxacilin, insulin, and copious irrigation of both eyes with normal saline. In several cases of naloxone administration, a drug used to counteract the effects of opiate overdose, there were no apparent clinical effects.

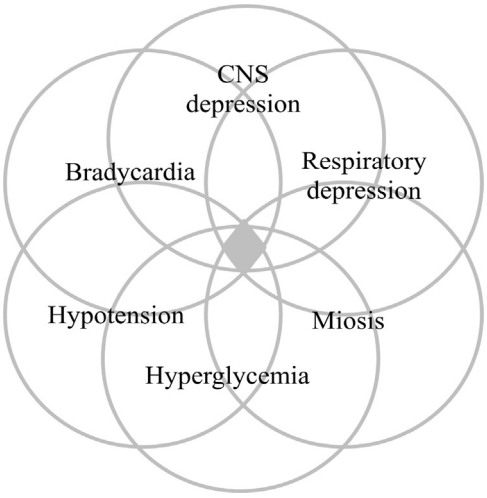


**Fig. 2.** General toxidrome for xylazine.

From the 22 fatal cases (Table 2), xylazine was related to drug abuse in 17 cases (77%). In 7 of the 17 cases xylazine was detected along with fentanyl (a synthetic opioid) at the Philadelphia Medical Examiner's Office. Of those 7 there were 5 cases in which xylazine was detected along with fentanyl, heroin metabolites, and cocaine and/or its metabolites. In the remainder 2 postmortem cases, xylazine was also detected along with fentanyl and heroin metabolites [33]. In addition, xylazine was found in combination with one or more compounds such as free morphine and 6-AM, codeine, cocaine and BE in 9 postmortem cases between 2003 and 2007 at the Puerto Rico Institute of Forensic Sciences (PRIFS). Xylazine was associated with the cause of death in all of these cases [16,34]. The last case, related to a drug user, was presented in our previous study [16].

According to the literature, the known doses of xylazine to produce toxicity and fatality in humans vary from 40 to 2400 mg. Small doses may produce toxicity and larger doses may be survived with medical help. Non-fatal blood or plasma concentrations range from 0.03 to 4.6 mg/L. In fatalities the blood concentrations of xylazine range from trace to 16 mg/L. It is evident that there is significant overlap between the non-fatal concentration and postmortem blood concentration of xylazine, which means there is no defined safe, toxic or fatal concentration.

Screening methods for the detection of xylazine in biological fluids in humans includes thin layer chromatography (TLC), gas chromatography with nitrogen-phosphorus detector (GC–NPD), gas chromatography mass spectrometry (GC–MS), Remedi HS Bio-Rad Laboratories, and liquid chromatography mass spectrometry (LC–MS). To the bets of our knowledge, the screening method by immunoassay used by most clinical and forensic laboratories has not been developed for the detection of xylazine and/or its metabolites. Therefore, the prevalence of xylazine could be underestimating unless a different screening method other than immunoassay is used. Analytical techniques reported for the confirmation and/or quantification of xylazine in biological fluid in humans include GC–NPD, GC–MS, high-performance liquid chromatography (HPLC), LC–MS, ultra performance liquid chro-

matography–tandem mass spectrometry (UPLC–MS–MS) with electrospray ionization (ESI). Those methods require isolation of the drug from biological matrices using different types of extractions e.g. liquid-liquid extraction (LLE), solid-phase extraction (SPE) and protein precipitation (PP) [1,3,4,8,10,16,23–38].

### 4.2. Xylazine as an adulterant

To the best of our knowledge, there are five published studies that discuss the use of xylazine as an adulterant, four studies in Puerto Rico and one from Philadelphia [15–17,33,39]. Xylazine is commonly known as "anestesia de caballo" (horse anesthetic) on the streets of Puerto Rico [15,16]. Xylazine as an adulterant of speedball was first identified in Puerto Rico in 2008 by Rodríguez in a syringe content [17]. It was also found in street heroin in our previous study [16]. Xylazine detection in the street heroin samples in year 2007 (36%) was similar to year 2006 (36%), showing a recurrence of xylazine as the major adulterant of heroin in Puerto Rico [16].

Rodríguez [17] concluded that xylazine users were more likely to be in poorer health than non-users. This is consistent with the results obtained by Reyes [39] in 2012, which established that xylazine chronic use is associated with physical deterioration and skin ulcerations which could be considered the primary health concern. Torruella [15] provided information on xylazine use and its associated harm through a semi-structured interview of a Puerto Rican drug user. The interviewee indicated that xylazine is sold in packages together, but not mixed with heroin, as well as in premixed form. Another non-mixed packaging form is called "el combito" (the small combo), a combination of heroin and xylazine mixed with cocaine. Pre-mixed with heroin or not, xylazine users claim that chronic use of this substance creates open skin ulcers. Apparently, drug users who develop skin ulcers due to xylazine use are relocated from Puerto Rico to the state-side for better treatment. Healthcare professionals need to be aware of this issue, so the patients can be treated in an effective, timely manner especially in places with high prevalence of this drug as an adulterant.

Heroin abusers report feeling a surge of euphoria or "rush" followed by a twilight state of sleep and wakefulness. However, apparently among users, the combination of heroin and xylazine will give a better high, probably due to their similar pharmacologic effects in humans [16,18–21]. An interviewee from Torruella [15] described the first time he used the combination of xylazine and heroin, he fell asleep and woke up five hours later sick (withdrawing). After this event, he expressed that only heroin will not give the same high. According to Torruella [15] the users demand to the addition of cocaine in a non-mixed packaging form, to balance the "down" of both heroin and xylazine.

Heroin, cocaine and xylazine have different pharmacological modes of action. As mentioned above, xylazine is a potent $\alpha_2$-adrenergic agonist, resulting in sedation, muscle relaxation, nervous system depression, respiratory depression, cardiovascular effects (hypotension, bradycardia, tachycardia, premature ventricular contractions (PVC)) and hyperglycemia [3]. Also, it is not known if xylazine may cause addiction in humans. The intoxicating effects of heroin are most closely associated with action at opioid receptors. Heroin by itself has little affinity for the opiate receptors and it is believed that its metabolites (6-AM and morphine) account for all or most of the narcotic activity of heroin [40,41]. Its metabolites bind to the body's three major opioid receptors [kappa ($\kappa$), delta ($\delta$), mu ($\mu$)], but they primarily interact with $\mu$ opioid receptors [42]. The $\mu$-receptor is responsible for analgesia, sedation, euphoria, nervous system depression, respiratory depression, constipation and physical dependence [18,20,21]. Acute exposure to heroin appears to affect measures of noradrenergic signaling, but it is unclear if chronic use is suppressing or enhancing this signaling [43]. In horses, the xylazine-morphine sequence produced reliable and predictable analgesia without any drug failure or adverse reaction. Maximum analgesia usually lasts 30–45 min and begins to dissipate rapidly after one hour. For dogs, the drugs were used in sequence with great clinical satisfaction. The dog becomes recumbent but not unconscious and is ambulatory within two to three hours [44]. Administration of xylazine decreases the anesthetic requirement for halothane in horses. Concurrent morphine administration to anesthetized horses does not alter the anesthetic sparing effect of xylazine or its plasma concentration-time profile [45]. Results from Keegan [46] study indicated that epidural administration morphine and xylazine is not associated with significant cardiovascular side effects during isoflurane-maintained anesthesia in dogs. In humans, xylazine and heroin in combination may potentiate the desire effect of sedation as well as the adverse effects of respiratory depression, bradycardia, hypotension. Xylazine-morphine sequence to obtain analgesia in the horse and dog.

Cocaine is a reuptake inhibitor of dopamine (DA), norepinephrine (NE), and serotonin (5-HT) at pre-synaptic nerve terminals in the CNS, resulting in stimulant effects [47]. It also blocks voltage-dependent sodium channels, an action that is responsible for the topical anesthetic effects of this drug [48]. Adverse effects of cocaine use include CNS stimulation, tachycardia, arrhythmia, thrombosis, tachypnea, chest pain, seizures [49]. The analgesic interaction of cocaine and xylazine was studied utilizing the mouse writing test in which abdominal contortions were evoked by a 0.6% acetic acid solution. Cocaine and xylazine gave a higher reduction of contortions (77%) compared with cocaine (39%) and xylazine (43%) alone. Also the two drugs in combination reduced the $ED_{50}$ from 0.42 to 0.13 mg/kg [50]. Assuming similar analgesic interaction in humans as in mouse, cocaine and xilazine in combination may potentiate the desire effect of analgesia. However, cocaine adverse effects may be added with the adverse effect of xylazine. The first appearance of agitation or sedation will depend on which drugs got exposed more and the pharmacokinetic interaction of both drugs in humans.

Cocaine alone increased the rating of "stimulated", whereas morphine (from heroin) alone increased the rating of "sedated". According to Rhodes [51], the simultaneous administration of cocaine and opiates does not induce a novel set of subjective effects; rather, it induces, simultaneously, effects that are typical to both drugs. Speedball users report an improved euphoria because of the combination, and there is evidence of an interaction, because cocaine reduces the signs of opiate withdrawal, and heroin may reduce the irritability seen in chronic cocaine users [41]. Due to the difference in half-life, cocaine effects predominate and then within an hour the narcotic effects of morphine from heroin predominate, when they are taken in combination [47]. The set of effects when xylazine is present in combination with cocaine and heroin are unknown. In general, classic or expected toxidrome of a known single exposure may be vary depending which drugs are involved and at what concentration. Pharmacokinetics/pharmacodynamic drug interaction between xylazine, heroin and cocaine in humans is difficult to assess due to the lack of research in this area. However, the concomitant use of these drugs may potentiate or attenuate the effects of these drugs, which can lead to toxic effects. The health care provider must be more vigilant and cautious in this scenario for a better outcome.

One study about the prevalence of xylazine in postmortem cases related to heroin and/or cocaine intoxication were reported in a research study exhibited at the American College of Medical Toxicology Annual Scientific Meeting in San Juan, Puerto Rico in 2013 by Ruiz-Colón [52]. This study was conducted at the PRIFS and retrospectively studied 75 cases submitted to the laboratory from 2008 to 2010, re-analyzing them for xylazine by UPLC–MS–MS. The cases were selected based on positive immunoassay

results for cocaine and opiates and the circumstances of death. In 36 out of 75 postmortem cases (48%), xylazine was found in combination with heroin metabolites and/or cocaine metabolites. More details of this work, including autopsy findings, will be published in the future.

## 5. Conclusion

In conclusion, xylazine is a potentially hazardous drug in humans. From 43 xylazine published intoxication cases in humans, 21 cases (49%) occurred in non-fatal scenarios and most required medical intervention; 22 cases (51%) resulted in fatalities. 14 (33%) out of 43 of the individuals had easy access to supplies of xylazine, due to their type of job (veterinarian, veterinarian assistant, farmer, horse trainer or related field). From the total reported, 17 cases (40%) were associated with the use of xylazine as an adulterant of drugs of abuse. Its chronic use is reported to be associated with physical deterioration and skin ulceration. Concomitant use of xylazine in combination with speedball may potentiate or attenuate the effects of these drugs, which can lead to toxic effects. This combination may increase the fatality rate among drug users. The use of xylazine as an adulterant of drugs of abuse has not only been reported in Puerto Rico. Therefore the goal of this review is to alert other laboratories to use analytical methods which allow the investigation of the possible presence of this adulterant. In addition, we emphasize the need for an awareness of the pharmacological effects of xylazine in humans, especially because of its widespread availability in veterinary medicine and prevalence in street drugs. Further studies are suggested to increase the knowledge and understanding of this drug combination in humans.

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