

Yale University

EliScholar – A Digital Platform for Scholarly Publishing at Yale

Public Health Theses

School of Public Health

January 2023

Subcutaneous Lesions And Systemic Infections: A Scoping Review Of The Clinical Implications Of Illicit Xylazine Use

Fatimah Maiga
fatimah.maiga@gmail.com

Follow this and additional works at: <https://elischolar.library.yale.edu/ysphtdl>

Recommended Citation

Maiga, Fatimah, "Subcutaneous Lesions And Systemic Infections: A Scoping Review Of The Clinical Implications Of Illicit Xylazine Use" (2023). *Public Health Theses*. 2301.
<https://elischolar.library.yale.edu/ysphtdl/2301>

This Open Access Thesis is brought to you for free and open access by the School of Public Health at EliScholar – A Digital Platform for Scholarly Publishing at Yale. It has been accepted for inclusion in Public Health Theses by an authorized administrator of EliScholar – A Digital Platform for Scholarly Publishing at Yale. For more information, please contact elischolar@yale.edu.

**Subcutaneous Lesions and Systemic Infections: A Scoping
Review of the Clinical Implications of Illicit Xylazine Use**

Fatimah A. Maiga

A Thesis Submitted in Partial Fulfillment of the
Requirements for the Degree of
Master of Public Health

Epidemiology of Microbial Diseases
Yale School of Public Health
2023

Thesis Advisors:

Robert Heimer, PhD.

Laura Bothwell PhD, MPhil, MA

Abstract

Xylazine, a clonidine analog, is a potent alpha-2 adrenergic agonist used as an analgesic sedative in veterinary medicine. Known to people who inject drugs (PWID) as “tranq”, xylazine has recently infiltrated the U.S. illicit opiate drug supply and has been associated with severe, necrotic lesions, sedation, and respiratory depression. Unlike opiates, xylazine has no human reversal agent or standardized withdrawal treatment protocol and its effects are unclear.

The objective of this study was to conduct a scoping review synthesizing the available clinical research and reporting on xylazine associated subcutaneous lesions and systemic infections. The study also sought to identify gaps in knowledge of the effects of illicit xylazine use and propose opportunities for further research.

While there is limited knowledge and research on xylazine, the selected articles produced insight into some of its effects. The findings from this study reveal that it is probable that the characteristic lesions that are developing in the injection drug use community are attributable to xylazine used in conjunction with an opiate. The development of lesions is not restricted to the site of injection and are more severe at the site of a missed vein. The lesions are also likely a result of chronic xylazine use. Furthermore, an association between illicit xylazine use and the rise in systemic infections is still unclear.

Further research on the topic should focus on the medical cause of the lesions, why they are more severe than typical injection related skin and soft tissues infections, why they appear away from the site of injection, and xylazine’s contribution to an increase in systemic infections.

Table of Contents

INTRODUCTION	4
METHODS.....	10
RESULTS	14
DISCUSSION.....	18
APPENDIX.....	28
FIGURE 1: SEARCH STRATEGY.....	28
FIGURE 2: STUDY SELECTION	30
FIGURE 3: INCLUDED STUDIES.....	31
FIGURE 4: DESCRIPTION OF STUDY SUBJECTS.....	33
FIGURE 5: SUBSTANCES AND INGESTION	34
FIGURE 6: WOUND DESCRIPTION AND SITE.....	35
FIGURE 7: PHOTOS OF SUBCUTANEOUS LESIONS I	36
FIGURE 8: PHOTOS OF SUBCUTANEOUS LESIONS II	36
BIBLIOGRAPHY.....	37

Introduction

Historically, injection drug use has been associated with blood-borne infections, systemic infections, and skin and soft tissue infections (SSTIs) (Ebright & Pieper, 2002; Lambdin et al., 2019). Once a concerning disease amongst people who inject drugs (PWIDs), rates of HIV have drastically decreased overtime, largely attributed to awareness, antiretroviral treatment, and the introduction of syringe exchange programs (Centers for Disease Control and Prevention, 2023a; DES JARLAIS et al., 2016; Kidorf et al., 2011; Ruiz et al., 2019). Transmission through injection drug use now accounts for 7% of new HIV diagnoses (Centers for Disease Control and Prevention, 2023a). Conversely, hepatitis C virus (HCV), SSTIs and systemic infection diagnoses have increased in the last decade. Between 2013 and 2020, HCV incidence rates increased 124%, with most cases amongst PWIDS (Centers for Disease Control and Prevention, 2022a).

Over 50% of PWIDs reported having a history of at least one SSTI (Figgatt et al., 2021).

Cutaneous abscesses and cellulitis are common amongst PWIDs; however, most are able to be managed without hospitalization (Hrycko et al., 2022). Research has shown that these wounds are typically a result of skin popping, where a drug is injected subcutaneously rather than into a vein; repeated skin damage from injecting; and the inflammatory properties of illicit drugs (Chambers, 2021; Freibott et al., 2022; Lloyd-Smith et al., 2008). These wounds typically present at the site or extremity of injection and risk increases after a missed vein (Chambers, 2021; Freibott et al., 2022). Infection can vary depending on the substance injected, but in general, cultures are predominantly positive for *Staphylococcus aureus* (*S aureus*), which is often colonized in PWIDS, with most isolates being methicillin-resistant *staphylococcus aureus*

(MRSA) (Chambers, 2021). Other common organisms amongst PWIDs include beta-hemolytic streptococci (group A and B streptococci) and Candida (Chambers, 2021; Egger et al., 2022; Zhang et al., 2020). Although, historically, there has been a high number of infections among PWIDS, there has recently been a rise in injection-related systemic infections, namely endocarditis, bacteremias, and fungal infections (Hrycko et al., 2022; Parikh et al., 2020; Zhang et al., 2020). This is partially attributed to the introduction of fentanyl as a replacement for heroin in the narco-trafficked opioid supply. Fentanyl's half-life is notably shorter than heroin, leading to an increase in frequency of injecting and, subsequently, needle sharing (Lambdin et al., 2019).

Fentanyl is a synthetic, potent opioid analgesic used for severe pain management (Centers for Disease Control and Prevention, 2015). However, in 2013, illicitly manufactured fentanyl was discovered in illicit opioid supplies across numerous states. This introduction contributed to the severe increase in fatal overdoses, driving the annual number of deaths from less than 50,000 in 2013 to over 100,000 in 2021, 73% of which involved fentanyl (NIDA, 2023; SUDORS Dashboard, 2023). Analogously, while causing the highest number of recorded fatal overdoses, fentanyl has almost replaced heroin in most drug supplies nationwide (Montero et al., 2022). Given the unpredictable nature of the illicit drug supply, it is expected that various new adulterants will appear. While fentanyl is still contributing to unprecedented levels of fatal overdoses, federal officials are creating targeted approaches to controlling the import of the illicitly manufactured drug and fentanyl test strips are widely available (Centers for Disease Control and Prevention, 2023b; The White House, 2023). The novel and most concerning adulterant is now xylazine.

Xylazine, a clonidine analog, is a potent alpha-2 adrenergic agonist used as an analgesic sedative in veterinary medicine (J. Johnson et al., 2021; Korn et al., 2021). It is only authorized for animal use, as severe central nervous system depression and hypotension were reported in human clinical trials (Department of Justice, Drug Enforcement Administration, 2022b; Greene & Thurmon, 1988). Moreover, there are no recommended reversal agents for human use (Food and Drug Administration, 2022). Agents used in veterinary medicine have not been deemed safe for humans. Although bills have recently been proposed to restrict its use, Xylazine is not federally regulated under the U.S. Controlled Substances Act (Catherine Cortez Masto United States Senator for Nevada, 2023; Department of Justice, Drug Enforcement Administration, 2022a). It is, however, a scheduled drug in Florida, Ohio, Pennsylvania, and West Virginia (Levy, 2023). Xylazine has been documented as an illicit drug adulterant since the early 2000s in Puerto Rico, where locals call it 'anestesia de caballo', meaning horse tranquilizer (Montero et al., 2022). In the continental U.S., it is referred to as xylazine, tranq, tranq-fent, or tranq-dope. Toxicology data from the Philadelphia Medical Examiner's office reported xylazine in just 2% of unintentional fatal overdoses between 2010 and 2015 (J. Johnson et al., 2021). However, xylazine-related deaths gradually rose until 2021, when 34% of unintentional fatal overdoses contained xylazine. By year end, over 90% of Philadelphia's "dope" drug samples, a combination of fentanyl, heroin, and other adulterants, contained xylazine (Krotulski et al., 2021). Similarly, in Connecticut, 2019 mortality data detected a xylazine-fentanyl combination in 6% of fatal drug overdoses, but this soared to 24% in 2022 (Connecticut Department of Public Health, 2023). Between 2019 and 2020, of the 146 Connecticut overdose deaths involving xylazine, 99.3% also involved fentanyl (Thangada, 2021). In 2019, 23 states, concentrated in the

Northeast region, reported xylazine-involved fatal overdoses, almost all of which also included fentanyl (99.1%) (Kariisa, 2021). Of these deaths, 64.3% listed xylazine as a cause of death. A recent multicenter study, including 9 emergency departments across California, Michigan, Missouri, New York, New Jersey, Oregon, and Pennsylvania, investigated the presence of xylazine in patients treated for opioid overdoses (Love et al., 2023). Researchers found that of the 90 patients who tested positive for xylazine, which was 38.9% of the sample, 98.9% also tested positive for fentanyl, 25.5% tested positive for heroin, and 32.2% tested positive for fentanyl analogues. Presently, a xylazine-fentanyl combination has been identified in federal drug seizures in 48 states, with concentration in the South and Northeast (Department of Justice, Drug Enforcement Administration, 2022b, 2023).

While most people who use drugs do not intentionally purchase or pursue xylazine (T. A. G. Quijano et al., 2023; Reed et al., 2021; Spadaro et al., 2023), some appreciate its ability to seemingly prolong the euphoric effect of fentanyl (Love et al., 2023; Montero et al., 2022; Spadaro et al., 2023). Moreover, after initiation, some continue to use xylazine because of the severe xylazine withdrawal symptoms unable to be managed with traditional medications for opioid use disorder (MOUD) (Food and Drug Administration, 2022; Spadaro et al., 2023; Torruella, 2011). Interestingly, xylazine's analogue, clonidine, has been known to suppress opiate withdrawal symptoms during detoxification (Kleber et al., 1980). Common side effects of xylazine use are bradycardia, hypotension, loss of consciousness or coma, anxiety, dry mouth, dizziness, respiratory depression, and most notably subcutaneous lesions (Ball et al., 2022).

There has been limited reporting and research on xylazine use and the subsequent lesions. The wounds gained notoriety upon xylazine's swift and severe entrance into the continental United States' illicit drug supplies (J. Johnson et al., 2021; Thangada, 2021). Although uncertain of the clinical cause, multiple researchers in the early 2000s reported the appearance of lesions in people who inject xylazine in Puerto Rican qualitative research studies (Reyes et al., 2012; Torruella, 2011). The wounds were noted to appear after chronic use and described as painful ulcers and abscesses that developed at or away from the injection site (Torruella, 2011). Apart from those studies, there has been no indication of cutaneous wounds or infections because of human xylazine use. However, lesions and necrosis have been reported in animal studies, specifically hamsters and sheep (Gaertner et al., 1987; Poklis et al., 1985).

Clinical publications included in two systematic reviews of xylazine use recorded no wounds or infections during emergency medical treatment of people who ingested xylazine (Ball et al., 2022; Ruiz-Colón et al., 2014). Upon analysis of the articles, most were of single use patients; however, there were three chronic use patients (Ruiz-Colón et al., 2014). Arican, et al's 2014 article presented a case of a 36-year-old patient with a three-month history of injecting xylazine and ketamine (Arican et al., 2004). The author's described ecchymotic wounds, minor bruising from leaking blood vessels, on the patient's arms and upper legs, but attributed them to normal injection site bruising (NIH, 2011) . All other symptoms were consistent with xylazine use including cardiovascular, mental, and gastrointestinal decline. Liu, et al's 2007 article presented a case of a 19-year-old man with a six-month history of inhaling unknown drugs (Liu et al., 2007). Upon presentation, his urine drug screen tested positive for xylazine and sulpiride, while his urine gas chromatography/mass spectrometry revealed ketamine, norketamine,

phenobarbital, and xylazine. This case did not disclose any wounds or infections upon admission, or during his subsequent four-day hospitalization. Finally, Poklis, et al's 1985 study presented a case of a 36-year-old decedent with a history of at least one month of injecting xylazine (Poklis et al., 1985). No wounds were listed in the autopsy report.

Most current research speculates xylazine's vasoconstricting properties and reduced skin perfusion as the catalyst for lesions (Ehrman-Dupre et al., 2022; McNinch et al., 2021; Skrbic & Chiba, 1993). Vasoconstriction decreases blood flow to the skin, resulting in skin and soft tissue necrosis, which is the main concern of xylazine use (Pan, You, et al., 2018). Alternatively, human toxicology data from a fatal xylazine overdose demonstrated high concentrations of xylazine in the urine, lungs, and liver, but relatively low amounts in adipose tissue and blood (Poklis et al., 1985). Animal research has indicated prompt biotransformation of xylazine, resulting in high concentrations in the skeletal muscle and visceral organs. While human skeletal muscle toxicology reports from xylazine exposures are not known to be available, it is hypothesized that further analysis of xylazine poisoned decedents will mirror these animal results. The effect of xylazine on skeletal muscle is also supported by human clinical descriptions of xylazine associated wounds, which have been reported to, in addition to skin and soft tissue, affect skeletal muscle and in some cases bone (Poklis et al., 1985).

In addition to the limited, and mostly anecdotal, clinical information on xylazine associated wounds, substantially increased media attention has heightened the public's concern of xylazine. In response, and to inform the affected community, many jurisdictions and harm reduction organizations frequently release field updates, alerts, and one-pagers. Similarly, as

xylazine affected patients increasingly present in hospital settings for wound care, bacteremia, septicemia, and SSTIs, clinicians and researchers are rapidly publishing case notes and findings (Philadelphia Department of Public Health, 2022a). Thus, this scoping review seeks to synthesize the available clinical research and reporting on xylazine associated wounds and infections.

Methods

Search Overview

The nature of an illicit drug supply, which in recent years has introduced novel additives and adulterants, indicated a scoping review as the most appropriate approach to identifying emerging literature (Munn et al., 2018). Scoping reviews, unlike systematic reviews, can be used to quickly compile all information related to a concept, not necessarily researching for an answer to a specific question. Therefore, seeking to catalog the recent reporting of systemic infections and wounds associated with xylazine use, a scoping review was conducted.

The methods of this review were consistent with the first five stages of Arksey and O'Malley's scoping review framework: identifying the research question, identifying relevant studies, study selection, charting data, and collating, summarizing and reporting results (Daudt et al., 2013).

The primary search strategy followed a traditional database review, utilizing: EMBASE-OVID, PubMed, and Google Scholar, as well as 24 substance use specific journals in PubMed Central and on their dedicated websites. The unprecedented increase of Xylazine in the illicit drug supply has only recently begun to trigger concern and warrant surveillance. Therefore, much of

the most recent and relevant data was published, or in preprint, as case reports, case series, and conference proceedings.

Identifying the research question

The research question used to develop this scoping review was: What is the impact of xylazine adulterated illicit fentanyl use on cutaneous lesions and systemic infections.

Identifying relevant studies

To identify publications with xylazine injection drug use as an exposure and systematic infections or wounds as an outcome, exhaustive key words, exploded searches, and MeSH (Medical Subject Headings) terms were used throughout the search. English, human focused publications between 2000 and 2023 were queried in two databases: EMBASE-OVID and PubMed. The EMBASE-OVID and PubMed databases were selected given their extensive inclusion of social, health, life and physical science journals and publishers. The publication years were determined by preliminary research, which hypothesized a connection between xylazine use and systemic infections dating back to the early 2000s in Puerto Rico (Reyes et al., 2012). Upon title and abstract review, the results did not seem fruitful. Therefore, the search was expanded.

Publications between 2017 and 2023 were queried in Google Scholar and 24 journals using PubMed Central and each journal's website. The journals were selected because they specifically publish substance use related studies. Google Scholar was utilized because it returns unpublished and pre-publication literature not yet available in databases or journals. Learning

that the increase in illicit xylazine use, excluding Puerto Rico, sparked interest and alarm in Philadelphia, around 2016, then Connecticut around 2019, it seemed appropriate to limit the second search to begin in 2017, as city data is not finalized and reported until 2017.

Terms were repeatedly tested and manipulated to finalize the search ([Figure 1](#)). 1,313 articles from EMBASE-OVID, PubMed, PubMed Central, Journal Websites and Google Scholar were imported into the systematic review website platform, Covidence, where 185 duplicates were removed.

Study Selection

Publications were eligible for full text review if (1) the primary or secondary focus described or investigated systemic infections amongst people who injected illicit drugs and/or used fentanyl or xylazine (2) the primary or secondary focus described or investigated any systemic infections, wounds, changing drug supply, or novel discoveries amongst people who use drugs (3) written in English (4) published between 2017 - 2023 (5) human centered. There were no restrictions on study design or country, the later for numerous reasons. As a territory, not a state, Puerto Rico may be excluded from US based studies. Academic research on drug user health and novel diseases is frequently conducted in non-traditional countries. Finally, the Canadian drug market is somewhat supplied through the US illicit drug market, and vice versa, therefore, possibly including illicit xylazine (Department of Justice, Drug Enforcement Administration, 2020). Articles were excluded if their infection focus was HIV or hepatitis, as extensive evidence displays a direct relationship to injection drug use. Publications describing or investigating

clinician administered or sanctioned drug use were also excluded, as this review's focus is illicit drug use.

To account for bias in the initial search strategy, the bibliography of articles included for full text reviews were scanned. This produced 50 more articles, which were then imported into Covidence and screened using the same criteria as their predecessors. 57 of the total 1,157 screened articles were included for full text reviews ([Figure 2](#)).

Charting Data

Articles eligible for full text screening were reviewed with the same inclusion categories as the title and abstract screening. Articles were reviewed by a single researcher; however, for studies in which the researcher expressed doubt on the inclusion of the article, a second researcher assessed the article, generating a joint decision. After review, only nine studies satisfied all the inclusion criteria and were selected for extraction.

The primary researcher utilized the Watkins "RADaR" qualitative data extraction technique (Watkins, 2017). Each article's content extraction included: title, authors, publication year, investigation period, source (journal/ website), study design, location, population and characteristics, infectious disease, wounds, substances, themes, notes, and key findings that may, qualitatively or quantitatively, provide evidence of an association between xylazine and systemic infections or subcutaneous wounds.

Results

The final study selection comprised nine articles ([Figure 3](#)): four case reports (Ehrman-Dupre et al., 2022; Malayala et al., 2022; McNinch et al., 2021; Tkatch et al., 2021), one case series comprising eight patients (Spyres, 2021), and four qualitative research studies (Friedman et al., 2022; Montero et al., 2022; T. A. g. Quijano, 2022; Spadaro et al., 2023). Further, there were two conference proceedings (McNinch et al., 2021; Tkatch et al., 2021), one report (Spyres, 2021), one secondary university published thesis (T. A. g. Quijano, 2022), one article in pre-print (Spadaro et al., 2023), and four peer reviewed journal articles (Ehrman-Dupre et al., 2022; Friedman et al., 2022; Malayala et al., 2022; Montero et al., 2022).

Drug and Ingestion Characteristics ([Figure 4](#))

All the selected studies explicitly listed xylazine in combination with at least one additional substance, most commonly fentanyl (n=6) (Ehrman-Dupre et al., 2022; Malayala et al., 2022; McNinch et al., 2021; Montero et al., 2022; Spyres, 2021; Tkatch et al., 2021) ([Figure 5](#)). Two studies did not list the co-contaminants; however, they were conducted in Philadelphia, Connecticut, and Puerto Rico (Friedman et al., 2022; T. A. g. Quijano, 2022). The Connecticut and Philadelphia drug supplies are xylazine adulterated. Some people who use drugs in Puerto Rico initially reported voluntarily using xylazine as a complement to heroin (Torruella, 2011). They detailed dealers gifting xylazine in a packet attached to heroin, before ultimately selling premixed bags. Therefore, it is unlikely that xylazine was used independent of another substance in those studies, but given the circumstances in Puerto Rico, it is possible. One multi-

subject qualitative research study reported 93% of their sample using an opioid, with 80% using fentanyl in combination with xylazine (Spadaro et al., 2023).

Within the national case report series, there was a single case of xylazine in combination with only cocaine (Spyres, 2021). It was, however, reported in a qualitative interview, without a confirmatory drug screen or purchase location. Drug testing studies have reported that drugs are commonly incorrectly marketed and sold (Krotulski et al., 2022); therefore, it is possible the subject unknowingly ingested opioid adulterated cocaine.

Seven studies listed injection as the only route of exposure (Ehrman-Dupre et al., 2022; Friedman et al., 2022; Malayala et al., 2022; Montero et al., 2022; T. A. g. Quijano, 2022; Tkatch et al., 2021). One study included a subject that used intranasally (Spyres, 2021). The final study included a varied route of exposure: 57% intranasal, 43% injection, 20% smoke, and 3% oral (Spadaro et al., 2023).

Wound Description (Figure 6, Figure 7, Figure 8)

All studies reported wounds on subjects who used xylazine. The description “Ulcer” was used in every study to describe the wound, with eight also using “necrotic” or “necrosis”. Other common descriptive terms included: scabby sores, abscesses, holes, lesions, and craters. Five studies described the wounds as chronic and slow healing (Ehrman-Dupre et al., 2022; Malayala et al., 2022; McNinch et al., 2021; Spadaro et al., 2023; Tkatch et al., 2021). Of the four qualitative research studies, in addition to the case series, three did not report the percentage of participants with wounds (Friedman et al., 2022; Montero et al., 2022; T. A. g. Quijano, 2022;

Spyres, 2021). The fourth qualitative research study reported that 43% of their population, who described adverse side effects, reported wounds (Spadaro et al., 2023).

Three studies confirmed, or alluded to, amputations because of xylazine associated wounds (Friedman et al., 2022; Montero et al., 2022; T. A. g. Quijano, 2022). Six studies listed the location of the xylazine associated lesions: five studies listed bilateral lower extremity wounds (Ehrman-Dupre et al., 2022; Malayala et al., 2022; McNinch et al., 2021; Spadaro et al., 2023; Tkatch et al., 2021); two listed hand lesions (Ehrman-Dupre et al., 2022; Tkatch et al., 2021); one listed neck wounds (Tkatch et al., 2021); and one listed upper extremity wounds (Tkatch et al., 2021). Two studies contrasted xylazine associated wounds and typical injection drug use associated wounds, describing xylazine wounds as more severe, without further comment (Ehrman-Dupre et al., 2022; Friedman et al., 2022).

Wound Site (Figure 5)

Six studies reported wounds at the site of injection (Ehrman-Dupre et al., 2022; Friedman et al., 2022; Malayala et al., 2022; McNinch et al., 2021; T. A. g. Quijano, 2022; Spyres, 2021). Five of these studies emphasized wounds, generally worse and quicker to appear, at the site of a missed vein injection (Friedman et al., 2022; Malayala et al., 2022; McNinch et al., 2021; T. A. g. Quijano, 2022; Spyres, 2021). One of the studies noted wounds at the site of a successful injection (T. A. g. Quijano, 2022). Two studies reported wounds away from the injection site, commonly on the legs (Malayala et al., 2022; T. A. g. Quijano, 2022). Three studies did not provide sufficient information to determine the location of the lesions in relation to the site of injection (Montero et al., 2022; Spadaro et al., 2023; Tkatch et al., 2021).

Infections

Two studies confirmed and detailed infections. Both case's subjects tested positive for *Streptococcus pyogenes* and *Staphylococcus aureus*, among other common pathogens (Malayala et al., 2022; McNinch et al., 2021). Of note, one of the subjects cultured MRSA, which is increasing amongst the PWID population (Malayala et al., 2022). Three studies suggested the presence of infection through the use of antibiotics (Ehrman-Dupre et al., 2022; Spadaro et al., 2023; Tkatch et al., 2021), while the remaining four studies did not indicate infections (Friedman et al., 2022; Montero et al., 2022; T. A. g. Quijano, 2022; Spyres, 2021).

Treatment

Only medical case reviews reported comprehensive wound care, topical care, debridement, and use of antiseptic solutions, all performed during in-patient hospitalizations (Ehrman-Dupre et al., 2022; Malayala et al., 2022; Tkatch et al., 2021). Equally important to the physical treatment of xylazine wounds is withdrawal management. All four case reports described their patient's history of leaving the hospital against medical advice (AMA) while seeking treatment for xylazine wounds (Ehrman-Dupre et al., 2022; Malayala et al., 2022; McNinch et al., 2021; Tkatch et al., 2021). Providers in three of the four studies managed xylazine withdrawal in addition to opioid withdrawal treatment and pain management (Ehrman-Dupre et al., 2022; McNinch et al., 2021; Tkatch et al., 2021).

In Ehrman-Dupre's study, the patient's xylazine withdrawal was initially treated with phenobarbital, dexmedetomidine, and tizanidine (Ehrman-Dupre et al., 2022). However, providers discontinued the use of tizanidine in exchange for clonidine because of the patient's

newly developed dysphoria, rigors, and restlessness. The phenobarbital, dexmedetomidine, and clonidine were used in conjunction for 3 days before discontinuing the phenobarbital and dexmedetomidine and continuing the administration of clonidine for a total of 15 days. Tkatch's patient was treated with benzodiazepines; however, the patient later overdosed from in-hospital injection drug use and left AMA (Tkatch et al., 2021). McNinch's patient was monitored using the Clinical Institute Withdrawal Assessment (CIWA) and treated with clonidine and benzodiazepines (McNinch et al., 2021). There was no mention of xylazine withdrawal treatment in Malayala's study and the patient left AMA during hospitalization (Malayala et al., 2022). However, she returned multiple times over the following months, before completing wound treatment and being discharged to a treatment facility.

Discussion

Impact of chronic versus single use of xylazine

None of the cases included in the previously mentioned systematic reviews discussed wounds or infections, regardless of exposure length. Current research, including the studies included in this review, lack data on length of exposure before the first appearance of wounds. As noted in a human toxicology study, after a single exposure, xylazine concentrated in organs, not in the blood or tissue (Poklis et al., 1985). Similarly, in animal studies, xylazine concentrated in the organs and skeletal muscles. The modest levels of xylazine in the blood and tissue after a single exposure, in conjunction with the absence of lesions, may support the claim that xylazine-related wounds are associated with chronic use. Descriptive language in the studies included in this review suggests all subjects used chronically and experienced multiple lesions in various

places over time. One subject reported that the wounds appeared spontaneously, while others did not denote a timeline (Malayala et al., 2022). Therefore, the length of time between injection and the appearance of a lesion is unclear, as well as the progression of severity. More qualitative research should be conducted to determine frequency and dosage of xylazine use before the onset of lesions. Additionally, studies should examine the role of injection behaviors that may worsen or accelerate wounds, for example repeated injections into the same vicinity of a developing lesion, which is often reported to manage the painful wounds.

Relationship between xylazine exposure and wound location

The results of this study indicate two mechanisms for developing xylazine wounds. Many patients described lesions appearing at the site of injection (Ehrman-Dupre et al., 2022; Friedman et al., 2022; Malayala et al., 2022; T. A. g. Quijano, 2022; Spyrès, 2021), with some reporting worse wounds if the vein was missed during an injection attempt (Friedman et al., 2022; T. A. g. Quijano, 2022). Alternatively, some studies also noted the appearance of wounds away from the site of injection (Malayala et al., 2022; T. A. g. Quijano, 2022), most prevalently on the lower extremities. This is supported by a veterinary sheep study, in which xylazine was found in excess in skeletal muscle distal to the injection site. Although unconfirmed, these wounds may also occur during non-injection ingestion of xylazine, particularly intranasal or inhalation. Together, this suggests wounds may appear because of either systemic accumulation of xylazine or localized exposure, with particular detriment upon direct tissue or muscle exposure. Systemic accumulation resulting in wounds implies that there may be a threshold of consumption for the wounds to develop. However, studies from the previously

mentioned systematic reviews cataloged various doses of ingestion without the presence of wounds. The highest doses were, presumably, amongst fatal overdose decedents. Furthermore, the non-fatal overdose studies were in emergency medical settings and lacked follow-up.

Almost all of this review's studies excluded the concentration of xylazine recorded in urine or blood screens and the dose of xylazine ingested, the latter most likely a result of the uncertain and frequently changing drug supply (Friedman et al., 2022; T. A. g. Quijano, 2022). As demonstrated in drug testing studies and routine analysis, concentrations of xylazine in drug samples almost always vary (Krotulski et al., 2022). More research needs to be conducted to determine why lesions appear outside of injection sites and why they typically occur on the bilateral lower extremities (Ehrman-Dupre et al., 2022; Malayala et al., 2022; McNinch et al., 2021; Spadaro et al., 2023; Tkatch et al., 2021). Additionally, researchers should investigate the varying effects of xylazine, as the drug seems to affect tissue, muscle and veins differently, as supported by toxicology data and the increased severity of wounds when a vein is missed (Friedman et al., 2022; Poklis et al., 1985; T. A. g. Quijano, 2022). Finally, researchers should investigate why the wounds are chronic and difficult to heal (Ehrman-Dupre et al., 2022; Malayala et al., 2022; McNinch et al., 2021; Spadaro et al., 2023; Tkatch et al., 2021). The commonly hypothesized argument of xylazine related skin perfusion may be a predictor of inefficient or slow healing wounds (Pan, Chen, et al., 2018).

Impact of Xylazine in combination with other drugs

Except for one study from the Texas Poison Control Center that included insufficient clinical data, none of the case series or single case reports in the systematic reviews included xylazine

in combination with an opioid or stimulant, most were ingested in the drug's manufactured form or in combination with ketamine. Conversely, all the previously mentioned jurisdictions have recently reported xylazine in combination with fentanyl in almost all drug seizures and xylazine involved overdose deaths. All subjects included in this review developed wounds after reportedly ingesting xylazine in combination with an opioid or were in a geographic area in which xylazine is typically sold with or as an adulterant of an opioid. This suggests that the cutaneous wounds are not the result of the mere presence of xylazine. Instead, the wounds may be a result of a chemical interaction, or the dual presence, of xylazine and opioids.

Ultimately, these factors suggest that the characteristic cutaneous wounds are not solely dependent on the length of use, or the presence of xylazine alone, as previously published. Instead, the presence of the wounds may be a result of the dual presence of both xylazine and opioids, route and location of exposure, and frequency and behaviors of use.

Infections

As previously discussed, illicit drug injection, especially in the absence of a steady supply of sterile syringes, increases the risk of infection. However, xylazine related wounds are characteristically worse than those typically seen in PWIDs (Friedman et al., 2022). These wounds severely affect the muscle and tissue, in some cases extending deeper to affect the bone, and are purulent and necrotic (McNinch et al., 2021; Montero et al., 2022; T. A. g. Quijano, 2022).

Five of the studies in this review described an infection or antibiotic administration (Ehrman-Dupre et al., 2022; Malayala et al., 2022; McNinch et al., 2021; Spadaro et al., 2023; Tkatch et

al., 2021); two of which listed the infections (Malayala et al., 2022; McNinch et al., 2021). Of note, both study's patient cultured methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus pyogenes*. While these organisms are commonly colonized in PWIDS, they are increasing in community circulation (Chambers, 2021; Hrycko et al., 2022). It has also been documented that infection is more prevalent amongst those who use xylazine (J. Johnson et al., 2021). Given that SSTIs among PWIDs are common and typically resolve with limited or no medical treatment, the serious and necrotic nature of the wounds indicates the possibility of more severe systemic infections (Figgatt et al., 2021).

Treatment

The case reports included in this review all provided some form of wound care in a hospital setting and did not give detailed treatments. However, there have been recommendations for treatment of xylazine related cutaneous lesions in non-medical settings. Harm reduction groups and health departments recently began releasing at home or "field" wound care guides for moderate lesions, all relatively providing the same advice (D'Orazio et al., 2023; T. Johnson et al., n.d.; Philadelphia Department of Public Health, 2022b; Shang, 2023; The Everywhere Project, 2023).

After hand sanitizing, and donning gloves, if possible, patients should gently wash the wound with soap and water, not alcohol or hydrogen peroxide. Coat the surrounding healthy skin with an ointment, like A&D and completely cover the wound with non-stick gauze or Xeroform, coated with an antimicrobial ointment, like Neosporin. Finally, wrap the extremity with tape and a wrap, like Coban or an ACE bandage. These steps should be followed frequently, daily, if

possible, to keep the wound bed moist and clean. In the event the wound worsens, or necrosis begins, the patient should seek professional medical treatment. While these are recommended techniques from multiple sources, research should identify a standardized protocol.

In one study, the patient left the hospital before extensive wound care treatment was completed and the wounds did not heal until the patient returned to the hospital (Malayala et al., 2022). While it is likely that the patient left AMA because of insufficient withdrawal treatment, as it is not included in the case report, it cannot be confirmed. There have been many studies investigating the factors contributing to PWIDs leaving AMA, which include stigmatized, negative treatment by staff; isolation; confinement and boredom; and insufficient withdrawal and pain treatment (Pollini et al., 2021).

There are symptomatic differences in xylazine withdrawal compared to opioid withdrawal, which requires additional, focused treatment (Ehrman-Dupre et al., 2022; T. A. g. Quijano, 2022; Spadaro et al., 2023). However, there are also some similarities, particularly dysphoria, restlessness, and anxiety (D’Orazio et al., 2023). Thus, it may be difficult for clinicians to determine the cause of the symptoms for appropriate treatment.

Providers are familiar with opioid overdoses and withdrawal; however, xylazine overdose and withdrawal is reportedly more obscure and severe (T. A. G. Quijano et al., 2023; Spadaro et al., 2023). Ignorance to xylazine overdose and withdrawal can, not only, result in poor withdrawal treatment, but is precipitated by the overuse of naloxone (T. A. G. Quijano et al., 2023). Since naloxone is ineffective at reversing the effects of xylazine, as it is not an opioid, bystanders, and medical professionals over administer naloxone under the impression that previous doses were

inefficient. This results in more severe opioid withdrawal in addition to the inevitable xylazine withdrawal. An additional complication to an expeditious treatment plan is that xylazine cannot be detected on routine toxicology screenings and is quickly dispelled from urine and blood (Food and Drug Administration, 2022).

Given the novelty of xylazine, the FDA has not issued a standardized treatment plan for xylazine withdrawal, nor is there an unofficial recommendation (Food and Drug Administration, 2022).

This is contrary to the multiple MOUD medications available, which do not treat xylazine withdrawal. Instead, providers in this review were resigned to trial-and-error comfort treatment (Ehrman-Dupre et al., 2022; McNinch et al., 2021; Tkatch et al., 2021). A clinical panel at a recent American Society of Addiction Medicine (ASAM) conference presented a list of current practices for treating xylazine withdrawal (D’Orazio et al., 2023). This includes prescribing clonidine, benzodiazepines, antipsychotics, phenobarbital, and gabapentin, as well as dexmedetomidine and ketamine in the intensive care unit. The clinicians also recommended ropinirole and tizanidine, most likely as end of the line options.

Similarly, New York State Department of Health recommended treating with alpha-2 adrenergic agonists and /or benzodiazepines, clonidine, tizanidine, dexmedetomidine, and guanfacine (New York State Department of Health, 2023). The Philadelphia Department of Public Health also recommended clonidine, dexmedetomidine, tizanidine, ketamine, gabapentin, and benzodiazepines, in addition to hydroxyzine, trazadone, quetiapine, guanfacine, mirtazapine, ketorolac, acetaminophen, and NSAIDs (Philadelphia Department of Public Health, 2022b).

At the 2023 Rx and Illicit Drug Summit, providers presented more detailed recommendations (Lynch et al., 2023). They advised using dexmedetomidine if a sedative is needed and choosing between clonidine at 0.1 mg to maximum 1.5 mg per day for extreme withdrawal; guanfacine at 1 mg to maximum 9 mg per day in divided doses; or tizanidine at 2mg to maximum 18 mg per day in divided doses for withdrawal or 24 mg per day if there are other indications. For tizanidine administration, the panel noted that the medication was least likely to decrease blood pressure or heart rate and could mildly prolong QTc.

Importantly, these medications may need to be used in tandem. In a 2016 case report, xylazine withdrawal treatment using only clonidine for one week generated no effect on symptoms, heart rate or blood pressure (Mulders et al., 2016). To standardize care, providers should be encouraged to report successful withdrawal treatment regimens to the FDA and SAMHSA using dedicated reporting forms.

Prevention

Multiple studies have investigated the community's desire for xylazine test strips (T. A. g. Quijano, 2022; Reed et al., 2021). As of March 2023, xylazine test strips were independently evaluated and recommended by a forensic research center (Krotulski et al., 2023), and are available for sale through the BTNX biotechnology company, the same manufacturer as the widely used Rapid Response fentanyl test strips (BTNX, 2023). While xylazine test strips may not be useful for those in jurisdictions with an overwhelming adulteration of xylazine in the opioid supply, they are a national resource for all people who use drugs. They are particularly needed for people who do not inject opioids, as xylazine may follow the pathway of fentanyl and spread

into other drugs like cocaine, crack, and illicitly manufactured pills (Centers for Disease Control and Prevention, 2022b).

Conclusion

The emergence of xylazine as an illicit drug adulterant has been troublesome for people who ingest drugs, and difficult to manage for the harm reduction and medical communities. This is complicated by the limited knowledge about xylazine and its effects, and rapid introduction and entrapment into the illicit drug supply. As xylazine continues to spread across North America, subsequently increasing morbidity and effecting mortality cases, it is critical that more research be conducted. The newly released xylazine test strips are one way to prevent use, but for those who already use xylazine or are accidentally exposed, there are no reversal agents and limited known treatments for the severe withdrawal symptoms.

Clinicians who encounter patients who have used xylazine, especially those with the characteristic lesions, should publish case reports and treatment strategies. Further, expansive prospective case studies are ideal. This will lead to standardized treatment practices, not just in medical settings, but for those who cannot, or will not, seek professional care. As discussed, people who use drugs face substantial stigma in medical settings. A standardized guide to wound care will ensure people can be treated before wounds reach severe states requiring hospitalization and amputation.

Researchers should investigate the cause of the lesions, particularly the role of co-contaminants, and organize clinical trials to identify reversal agents. Studies should be

conducted to determine if lesions will appear because of a one-time use of xylazine in combination with an opiate. This may determine if chronic use is a factor in the development of the wounds. Studying the effect of a combination of xylazine and only a stimulant will reveal if opiates are a requisite factor in the development of the wounds. Studies have already demonstrated that xylazine alone or in combination with ketamine do not result in the lesions.

Qualitative researchers should prioritize interviews with people who ingest xylazine orally, intranasally, or through inhalation. Not only will this determine if the wounds are a result of any type of exposure, but it may also help answer why the lesions appear away from the site of injection. Additionally, there are many known strategies for safer injection that reduce the risk of abscesses and infections; however, as noted in the studies included in this review, those interventions do not seem productive during xylazine injection. Researchers should determine why and suggest alternative strategies.

Finally, legislatures should recognize xylazine's emergence as a harm reduction issue, not criminal, allocate resources to address the root causes of drug use, and invest in substance use treatment expansion. As noted, multiple states have recently designated xylazine as a scheduled substance and federal legislatures have proposed the same. However, given fentanyl's illicit production and the generally steady supply of illicit narcotics, it seems inconsequential. Instead, they should focus on increasing funding for xylazine test strips, research, and treatment.

Appendix

Figure 1: Search strategy

Database	Syntax	Notes
PubMed	((("Xylazine" [Mesh]) OR "xylazine" OR ("fentanyl" [Mesh]) OR "fentanyl") AND ("infections" [Mesh]) (fentanyl OR xylazine) AND (("infections" [Mesh]) OR infection OR wound OR ulcer* OR skin OR necrotic) AND ("Drug Overdose"[MAJR]) OR (People who inject drugs) OR (PWID) OR ("Illicit Drugs"[MAJR]) OR ("Illicit Drugs"[nm])) "Xylazine"	Three separate searches were conducted to maximize output.
EMBASE - OVID	((human and yr="2000 -Current") AND (exp xylazine/ OR exp fentanyl/) AND (exp drug abuse/ or exp intravenous drug abuse/) AND (exp infection/))	
PubMed Central	((("Addict Sci Clin Pract"[Journal]) OR ("Addiction"[Journal]) OR ("Addiction Biology"[Journal]) OR ("Addictive Behaviors"[Journal]) OR ("Alcohol Clin Exp Res"[Journal]) OR ("Am J Drug Alcohol Abuse"[journal]) OR ("Drug and Alcohol Dependence"[Journal]) OR ("Drug and Alcohol Review"[Journal]) OR ("Int J Drug Policy"[Journal]) OR ("Journal of Addiction Medicine"[Journal]) OR ("Journal of Substance Abuse Treatment"[Journal]) OR ("Harm Reduction Journal"[Journal]) OR ("Nicotine Tob Res"[Journal]) OR ("Psychology of Addictive Behaviors"[Journal]) OR ("Am J Addict"[journal]) OR ("Journal of Studies on Alcohol and	<p>In order to use one continuous search syntax, journals were queried in PubMed Central, rather than OVID. To ensure a comprehensive search, journals were also queried on their individual websites. Journals:</p> <ul style="list-style-type: none"> • Addiction Science and Clinical Practice • Addiction • Addiction Biology • Addictive Behaviors • Alcoholism, clinical and experimental research • American Journal of Drug and Alcohol Abuse • Drug and Alcohol Dependence

	<p>Drugs"[Journal]) OR ("Substance Abuse"[Journal]) OR ("Alcohol Alcohol"[journal]) OR ("Alcohol Research: Current Reviews"[Journal]) OR ("International Journal of Mental Health and Addiction"[Journal]) OR ("Subst Use Misuse"[journal]) OR ("Addict Res Theory"[journal]) OR ("Alcohol"[Journal]) OR ("Substance Abuse Treatment, Prevention, and Policy"[Journal]) OR ("J Urban Health"[Journal])) AND ((xylazine OR fentanyl) AND (infection OR wound))</p>	<ul style="list-style-type: none"> • Drug and Alcohol Review • International Journal of Drug Policy • Addiction Medicine • Substance Abuse Treatment • Harm Reduction Journal • Nicotine and Tobacco Research • Psychology of Addictive Behaviors • American Journal on Addictions • Studies on Alcohol and Drugs • Substance Abuse • Alcohol and Alcoholism • Alcohol Research: Current Reviews • International Journal of Mental Health and Addiction • Substance Use and Misuse • Addiction Research and Theory • Alcohol • Substance Abuse Treatment, Prevention, and Policy • Urban Health
<p>Google Scholar</p>	<p>(xylazine infection * adulterant OR fentanyl OR heroin OR PWID OR drugs OR illicit -mice -rabbits -rats -dogs -bears -Anesthesia -pig -pigs -pigeon -pigeons -breed -hamster -experimental -cats -hamsters -assay)</p>	<p>Search terms were selected using the advanced search feature.</p>

Figure 2: Study selection

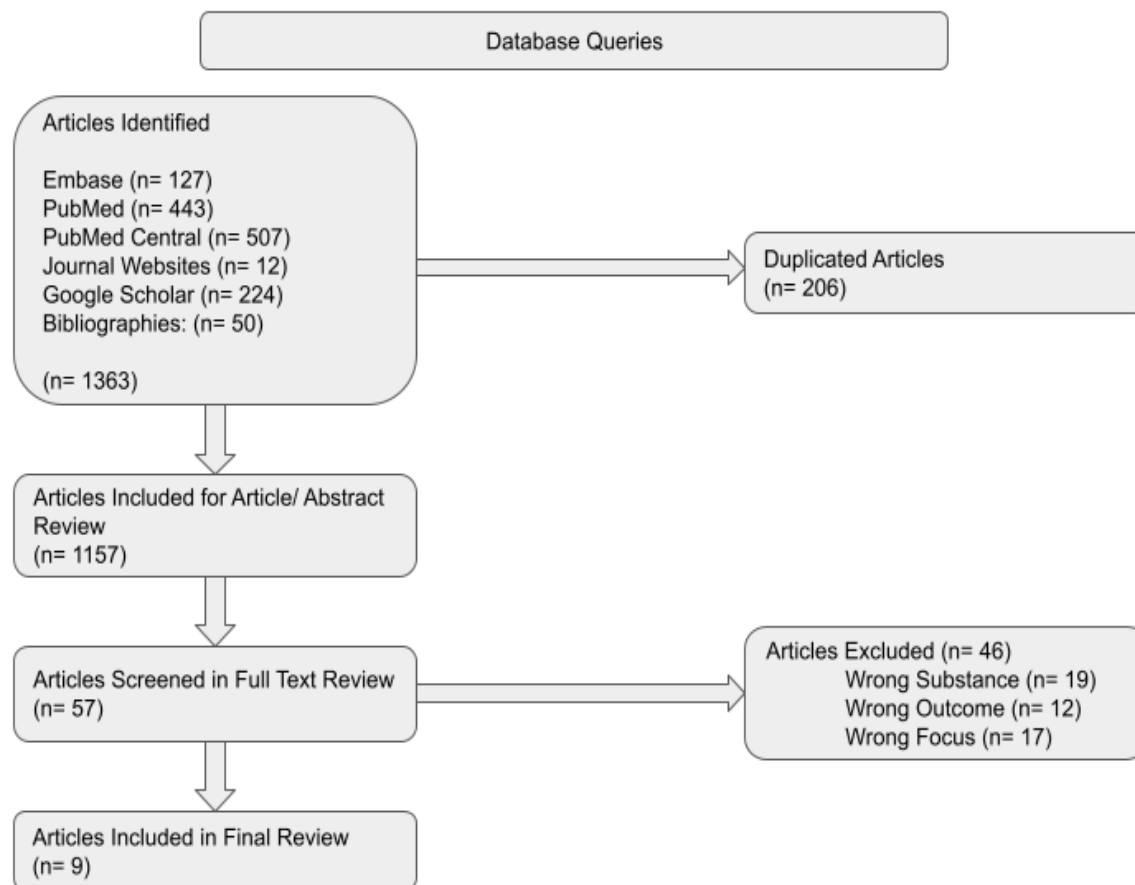


Figure 3: Included Studies

Study Title	Authors	Study Design	Publication	Location	Publication Year
Management of Xylazine Withdrawal in a Hospitalized Patient: A Case Report.	Ehrman-Dupre R; Kaigh C; Salzman M; Haroz R; Peterson LK; Schmidt R	Case Report	Journal: Addict Medicine	Camden, NJ	2022
Xylazine spreads across the US: A growing component of the increasingly synthetic and polysubstance overdose crisis.	Friedman, J; Montero, F; Bourgois, P; Wahbi, R; Dye, D; Goodman-Meza, D; Shover, C	Qualitative Research Study	Journal: Drug & Alcohol Dependence	Philadelphia, PA; Puerto Rico	2022
Xylazine-Induced Skin Ulcers in a Person Who Injects Drugs in Philadelphia, Pennsylvania, USA	Malayala, S; Nagendra Papudesi, B; Bobb, R; Wimbush, A	Case Report	Journal: Cureus	Philadelphia, PA	2022
A Case of Skin Necrosis Caused by Intravenous Xylazine Abuse	McNinch, James; Michael Maguire; Lisa Wallace; Christiana Care	Case Report/Conference	Conference: Society of Hospital Medicine (SHM) 2021	Philadelphia, PA	2021
Potency-Enhancing Synthetics in the Drug Overdose Epidemic: Xylazine (“Tranq”), Fentanyl, Methamphetamine, and the Displacement of Heroin in Philadelphia and Tijuana	Montero, F; Bourgois, P; Friedman, J	Qualitative Research Study	Journal: Illicit Economies and Development	Philadelphia, PA; Puerto Rico	2022
Xylazine in the Drug Supply: Emerging Threat in Connecticut and Lessons Learned from Philadelphia	Quijano, T	Qualitative Research Study	Thesis: Yale School of Public Health	Philadelphia, PA; Connecticut	2022

Self-reported Xylazine Experiences: A Mixed Methods Study of Reddit Subscribers.	Spadaro, A; O'Connor, K; Lakamana, S; Sarker, A; Wightman, R; Love, J; Perrone, J	Qualitative Research Study	Preprint Article: Available through the National Library of Medicine	National	2023, unpublished, preprint
The ToxIC NOSE (Novel Opioid and Stimulant Exposure) Report #5	Spyres, M; Makar, G	Case Series Review	Report: Toxicology investigators consortium report	National, 50% Puerto Rico	2022
Cutaneous Skin Infection Associated with IV Xylazine and Cocaine Use	Tkatch, C; Alvarado, S; Jaeger, J	Case Report/Conference	Conference: Pennsylvania Medicine/ American College of Physicians	Philadelphia, PA	2022

Figure 4: Description of Study Subjects

Characteristic	N¹ (%)
Co-contaminant	
Fentanyl	6 (66.7)
Heroin	3 (33.3)
Xanax Bars	2 (22.2)
Cocaine	2 (22.2)
Methamphetamine	2 (22.2)
Infection²	
Yes	5 (55.6)
No	4 (44.4)
Withdrawal Treatment³	
Clonidine	2 (66.7)
Benzodiazepines	2 (66.7)
Phenobarbital	1 (33.3)
Dexmedetomidine	1 (33.3)
Tizanidine ⁴	1 (33.3)
Ingestion Route	
Injection	9 (100)
Nasal	2 (22.2)
Oral	1 (11.1)
Inhalation	1 (11.1)
Lesion Site	
At Site of Injection	6 (66.7)
Away from Site of Injection	2 (22.2)
Lesion Location	
Lower Extremities	5 (55.6)
Upper Extremities	1 (11.1)
Hands	2 (22.2)
Neck	1 (11.1)

¹Review comprised 9 studies.

²Infection was confirmed in 2 studies and indicated in 3 studies.

³Withdrawal treatment was described in three of four case presentations.

⁴Tizanidine was discontinued because of negative side effects.

Figure 5: Substances and Ingestion

Study	Substances	Xylazine Exposure
Ehrman-Dupre, et al.	Xylazine, Heroin, Fentanyl	Injection
Friedman, et al.	Xylazine and other unlisted drugs	Injection
Malayala, et al.	Xylazine, Fentanyl, Xanax bars	Injection
McNinch, et al.	Xylazine, Fentanyl	Injection
Montero, et al.	Xylazine, Heroin, Meth, Fentanyl, Cocaine	Injection
Quijano, T	Xylazine and other unlisted drugs	Injection
Spadaro, et al.	Xylazine, often in addition to other opioids.	Injection, Snort, Smoke, Oral
Spyres, et al.	Xylazine, Fentanyl, Acetaminophen, Caffeine, Theobromine, Fluoxetine, Olanzapine, Lidocaine, Heroin, Cocaine, Tramadol, Oxycodone, Codeine, Methamphetamine	Injection, Snort
Tkatch, et al.	Xylazine with Fentanyl; Cocaine; Xanax bars	Injection

Figure 6: Wound Description and Site

Study	Clinical Description	Wound in Relation to Injection Sites
Ehrman-Dupre, et al.	Hand and bilateral lower extremity wounds, tissue loss, necrosis.	Wounds at the site of injection.
Friedman, et al.	Craters, black arms, deep/necrotic wounds, scabby sores; alludes to amputations	Emphasis (3 accounts) on wounds at the site of injection after missing a vein.
Malayala, et al.	Necrosis of the subcutaneous tissues, tibial osteomyelitis, abscesses, and ulcers on the anterior bilateral lower extremity.	Abscesses and ulcers away from the injection sites. Ulceration at site of missed vein.
McNinch, et al.	Wounds/ulcers on the anterior surfaces of bilateral lower legs. Necrosis.	Report ulceration at the site of injection after missing a vein.
Montero, et al.	Ulcers/ wounds, scabby sores, abscesses, holes; "body is rotting"; alludes to amputations	No comments
Quijano, T	Ulcers, abscesses, skin infections, lesions, deep craters or cavities; alludes to amputations	Emphasis on wounds away from the injection site. Wounds at sites of successful injection. Worse wounds at site of missed vein injection.
Spadaro, et al.	Ulcers, necrotic wounds, and infections in bilateral lower extremities. 43% of adverse effect respondents reported skin wounds or infections	No comments
Spyres, et al.	Ulcers, holes, abscesses, soft tissue infections	Ulceration at the site of injection after missing a vein.
Tkatch, et al.	Wounds, lesions, ulcers on hands, anterior neck, and upper and lower extremities; necrotic	No comments

Figure 7: Photos of Subcutaneous Lesions I



Adapted from Tkatch, et al. In clockwise order:
Right hand necrotic ulcers.
Necrotic wounds on the bilateral anterior.
Purulent wound on the left lower extremity.
Purulent lesion on the neck, extending to the muscle/fascia.

Figure 8: Photos of Subcutaneous Lesions II



Adapted from Ehrman-Dupre, et al.
Lesions on the lower extremities.

Bibliography

Abuse, N. I. on D. (2023, February 9). Drug Overdose Death Rates. National Institute on Drug

Abuse. <https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates>

Arican, F. O., Okan, T., Badak, O., & Guneri, S. (2004). An unusual presentation from xylazine-ketamine. *Veterinary and Human Toxicology*, 46(6), 324–325.

Ball, N. S., Knable, B. M., Relich, T. A., Smathers, A. N., Gionfriddo, M. R., Nemecek, B. D., Montepara, C. A., Guarascio, A. J., Covvey, J. R., & Zimmerman, D. E. (2022). Xylazine poisoning: A systematic review. *Clinical Toxicology (Philadelphia, Pa.)*, 60(8), 892–901.

<https://doi.org/10.1080/15563650.2022.2063135>

BTNX. (2023). Rapid Response® Xylazine Test Strip.

https://www.btnx.com/files/BTNX_XYL_Flyer_Harm_Reduction.PDF

Catherine Cortez Masto United States Senator for Nevada. (2023). Cortez Masto, Grassley &

Hassan Introduce Legislation to Crack Down on Xylazine | U.S. Senator Catherine Cortez

Masto of Nevada. [https://www.cortezmasto.senate.gov/news/press-releases/cortez-](https://www.cortezmasto.senate.gov/news/press-releases/cortez-masto-grassley-and-hassan-introduce-legislation-to-crack-down-on-xylazine)

[masto-grassley-and-hassan-introduce-legislation-to-crack-down-on-xylazine](https://www.cortezmasto.senate.gov/news/press-releases/cortez-masto-grassley-and-hassan-introduce-legislation-to-crack-down-on-xylazine)

Centers for Disease Control and Prevention. (2015). Increases in Fentanyl Drug Confiscations

and Fentanyl-related Overdose Fatalities. <https://emergency.cdc.gov/han/han00384.asp>

Centers for Disease Control and Prevention. (2022a). 2020 Hepatitis C | Viral Hepatitis

Surveillance Report | CDC.

<https://www.cdc.gov/hepatitis/statistics/2020surveillance/hepatitis-c.htm>

Centers for Disease Control and Prevention. (2022b). Fentanyl Facts.

<https://www.cdc.gov/stopoverdose/fentanyl/index.html>

Centers for Disease Control and Prevention. (2023a, January 31). Volume 33 | HIV Surveillance | Reports | Resource Library | HIV/AIDS | CDC.

<https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-33/index.html>

Centers for Disease Control and Prevention. (2023b, February 16). Fentanyl Test Strips: A Harm Reduction Strategy. <https://www.cdc.gov/stopoverdose/fentanyl/fentanyl-test-strips.html>

Chambers, H. F. (2021). Skin and Soft Tissue Infections in Persons Who Inject Drugs. *Infectious Disease Clinics of North America*, 35(1), 169–181.

<https://doi.org/10.1016/j.idc.2020.10.006>

Connecticut Department of Public Health. (2023). Drug Overdose Monthly Death Reports.

https://www.google.com/url?client=internal-element-cse&cx=004354853108091474482:sp6telu2lxi&q=https://portal.ct.gov/-/media/DPH/Injury-Prevention/Opioid-Overdose-Data/Monthly-Death-Reports/2019-February-2023_Drug-Overdose-Deaths-Monthly-Report_Connecticut_updated-on-3-15-2023_Final.pdf&sa=U&ved=2ahUKEwjen_2A977-AhV1KFkFHYakC_YQFnoEAcQAg&usg=AOvVaw2P2Gr84ablZXhRRIZ3PiP-

Crepet, A., & Sargent, C. (2022). Infections in people who inject drugs on the acute medical take. *Clinical Medicine*, 22(5), 383–386. <https://doi.org/10.7861/clinmed.2022-0364>

Daudt, H. M., van Mossel, C., & Scott, S. J. (2013). Enhancing the scoping study methodology: A large, inter-professional team’s experience with Arksey and O’Malley’s framework. *BMC Medical Research Methodology*, 13(1), 48. <https://doi.org/10.1186/1471-2288-13-48>

Department of Justice, Drug Enforcement Administration. (2020). Fentanyl Flow to the United States (DEA-DCT-DIR-008-20). https://www.dea.gov/sites/default/files/2020-03/DEA_GOV_DIR-008-20%20Fentanyl%20Flow%20in%20the%20United%20States_0.pdf

Department of Justice, Drug Enforcement Administration. (2022a). Xylazine. https://www.deadiversion.usdoj.gov/drug_chem_info/Xylazine.pdf

Department of Justice, Drug Enforcement Administration. (2022b). The Growing Threat of Xylazine and its Mixture with Illicit Drugs [DEA Joint Intelligence Report]. <https://www.dea.gov/sites/default/files/2022-12/The%20Growing%20Threat%20of%20Xylazine%20and%20its%20Mixture%20with%20Illicit%20Drugs.pdf>

Department of Justice, Drug Enforcement Administration. (2023). DEA Reports Widespread Threat of Fentanyl Mixed with Xylazine | DEA.gov. <https://www.dea.gov/alert/dea-reports-widespread-threat-fentanyl-mixed-xylazine>

DES JARLAIS, D. C., KERR, T., CARRIERI, P., FEELEMYER, J., & ARASTEH, K. (2016). HIV Infection among Persons who inject Drugs: Ending Old Epidemics and Addressing New Outbreaks. *AIDS (London, England)*, 30(6), 815–826. <https://doi.org/10.1097/QAD.0000000000001039>

D’Orazio, J., Wightman, R., Schwarz, E., Perrone, J., Laes, J., & Haroz, R. (2023). Wounds, Withdrawals, and Overdose: What to Expect from Xylazine Drug Supply Adulteration. 54th Annual Conference American Society of Addiction Medicine.

Ebright, J. R., & Pieper, B. (2002). Skin and soft tissue infections in injection drug users. *Infectious Disease Clinics of North America*, 16(3), 697–712. [https://doi.org/10.1016/S0891-5520\(02\)00017-X](https://doi.org/10.1016/S0891-5520(02)00017-X)

Egger, N. B., Kainz, K., Schulze, A., Bauer, M. A., Madeo, F., & Carmona-Gutierrez, D. (2022). The rise of *Candida auris*: From unique traits to co-infection potential. *Microbial Cell*, 9(8), 141–144. <https://doi.org/10.15698/mic2022.08.782>

Ehrman-Dupre, R., Kaigh, C., Salzman, M., Haroz, R., Peterson, L.-K., & Schmidt, R. (2022). Management of Xylazine Withdrawal in a Hospitalized Patient: A Case Report. *Journal of Addiction Medicine*, 16(5), 595–598. <https://doi.org/10.1097/ADM.0000000000000955>

Figgatt, M., Salazar, Z., Vincent, L., & Carden-Glenn, D. (2021). Treatment experiences for skin and soft tissue infections among participants of syringe service programs in North Carolina | *Harm Reduction Journal* | Full Text. 18(20).

Food and Drug Administration. (2022). FDA warns about the risk of xylazine exposure in humans. <https://www.fda.gov/media/162981/download>

Freibott, C., Phillips, K., & Bradley, et al. (2022). Under the Skin: The Relationship Between Subcutaneous Injection and Skin Infections Among People Who Inject Drugs. *J Addict Med*, 16(2), 164–168. <https://doi.org/10.1097/ADM.0000000000000844>

Friedman, J., Montero, F., Bourgois, P., Wahbi, R., Dye, D., Goodman-Meza, D., & Shover, C. (2022). Xylazine spreads across the US: A growing component of the increasingly synthetic and polysubstance overdose crisis. *Drug and Alcohol Dependence*, 233, 109380. <https://doi.org/10.1016/j.drugalcdep.2022.109380>

Gaertner, D. J., Boschert, K. R., & Schoeb, T. R. (1987). Muscle necrosis in Syrian hamsters resulting from intramuscular injections of ketamine and xylazine. *Laboratory Animal Science*, 37(1), 80–83.

- Garcia-Villar, R., Toutain, P. L., Alvinerie, M., & Ruckebusch, Y. (1981). The pharmacokinetics of xylazine hydrochloride: An interspecific study. *Journal of Veterinary Pharmacology and Therapeutics*, 4(2), 87–92. <https://doi.org/10.1111/j.1365-2885.1981.tb00715.x>
- Greene, S. A., & Thurmon, J. C. (1988). Xylazine – a review of its pharmacology and use in veterinary medicine. *Journal of Veterinary Pharmacology and Therapeutics*, 11(4), 295–313. <https://doi.org/10.1111/j.1365-2885.1988.tb00189.x>
- Hrycko, A., Mateu-Gelabert, P., Ciervo, C., Linn-Walton, R., & Eckhardt, B. (2022). Severe bacterial infections in people who inject drugs: The role of injection-related tissue damage. *Harm Reduction Journal*, 19(1), 41. <https://doi.org/10.1186/s12954-022-00624-6>
- Johnson, J., Pizzicato, L., Johnson, C., & Viner, K. (2021). Increasing presence of xylazine in heroin and/or fentanyl deaths, Philadelphia, Pennsylvania, 2010–2019. *Injury Prevention: Journal of the International Society for Child and Adolescent Injury Prevention*, 27(4), 395–398. <https://doi.org/10.1136/injuryprev-2020-043968>
- Johnson, T., Zagorksi, C., & Kinkle, B. (n.d.). XYLAZINE WOUND CARE: a guide!
- Kariisa, M. (2021). Notes from the Field: Xylazine Detection and Involvement in Drug Overdose Deaths — United States, 2019. *MMWR. Morbidity and Mortality Weekly Report*, 70. <https://doi.org/10.15585/mmwr.mm7037a4>
- Kidorf, M., King, V. L., Pierce, J., Kolodner, K., & Brooner, R. K. (2011). Benefits of Concurrent Syringe Exchange and Substance Abuse Treatment Participation. *Journal of Substance Abuse Treatment*, 40(3), 265–271. <https://doi.org/10.1016/j.jsat.2010.11.011>
- Kleber, H. D., Gold, M. S., & Riordan, C. E. (1980). The use of clonidine in detoxification from opiates. *Bulletin on Narcotics*, 32(2), 1–10.

- Korn, W. R., Stone, M. D., Haviland, K. L., Toohey, J. M., & Stickle, D. F. (2021). High prevalence of xylazine among fentanyl screen-positive urines from hospitalized patients, Philadelphia, 2021. *Clinica Chimica Acta; International Journal of Clinical Chemistry*, 521, 151–154.
<https://doi.org/10.1016/j.cca.2021.07.010>
- Krotulski, A., Shinefeld, J., & DeBord, J. (2022). Drug Checking Quarterly Report (Q3 2022): Philadelphia, Pennsylvania, USA. Center for Forensic Science Research and Education.
<https://www.cfsre.org/nps-discovery/drug-checking/drug-checking-q3-2022-philadelphia-pennsylvania-usa>
- Krotulski, A., Shinefeld, J., & DeBord, J. (2023). Evaluation of Xylazine Test Strips (BTNX) for Drug Checking Purposes. Center for Forensic Science Research and Education.
<https://www.cfsre.org/nps-discovery/drug-checking/evaluation-of-xylazine-test-strips-btnx-for-drug-checking-purposes>
- Krotulski, A., Shinefeld, J., & Viner, K. (2021). Drug Supply Assessment (Q3 2021): Philadelphia, Pennsylvania, USA. Center for Forensic Science Research and Education.
<https://www.cfsre.org/nps-discovery/drug-checking/drug-supply-assessment-q3-2021-philadelphia-pennsylvania-usa>
- Lambdin, B. H., Bluthenthal, R. N., Zibbell, J. E., Wenger, L., Simpson, K., & Kral, A. H. (2019). Associations between Perceived Illicit Fentanyl Use and Infectious Disease Risks among People who Inject Drugs. *The International Journal on Drug Policy*, 74, 299–304.
<https://doi.org/10.1016/j.drugpo.2019.10.004>

Levy, M. (2023). States restrict “tranq,” animal sedative linked to overdoses. Associated Press.

<https://apnews.com/article/xylazine-fentanyl-tranq-drug-overdose-d21c76be967fbfc82d8e88035fb5d926>

Liu, C.-M., Chiu, M.-J., Fang, C.-C., & Chen, W.-J. (2007). Xylazine abuse: A rare cause of syncope. *Clinical Toxicology (Philadelphia, Pa.)*, 45(3), 309–311.

<https://doi.org/10.1080/15563650601073520>

Lloyd-Smith, E., Wood, E., Zhang, R., Tyndall, M. W., Montaner, J. S. G., & Kerr, T. (2008). Risk factors for developing a cutaneous injection-related infection among injection drug users: A cohort study. *BMC Public Health*, 8, 405. <https://doi.org/10.1186/1471-2458-8-405>

Love, J. S., Levine, M., Aldy, K., Brent, J., Krotulski, A. J., Logan, B. K., Vargas-Torres, C., Walton, S. E., Amaducci, A., Calello, D., Hendrickson, R., Hughes, A., Kurt, A., Judge, B., Pizon, A., Schwarz, E., Shulman, J., Wiegand, T., Wax, P., & Manini, A. F. (2023). Opioid overdoses involving xylazine in emergency department patients: A multicenter study. *Clinical Toxicology*, 61(3), 173–180. <https://doi.org/10.1080/15563650.2022.2159427>

Lynch, W., Chen, G., & Pitotrowski, J. (2023). Xylazine in the Illicit Drug Supply: Making Overdoses Worse and More Difficult to Manage. 2023 Rx and Illicit Drug Summit.

<https://www.eventscribe.com/2015/APP/PresentationSlides/slideShareV3.asp?sfp=MTgxMjZ8MjMxODUzNHw2MTAzMjU1MXwtMQ==&SlidesID=284543>

Malayala, S. V., Papudesi, B. N., Bobb, R., & Wimbush, A. (2022). Xylazine-Induced Skin Ulcers in a Person Who Injects Drugs in Philadelphia, Pennsylvania, USA. *Cureus*, 14(8), e28160.

<https://doi.org/10.7759/cureus.28160>

- McCarthy, N. L., Baggs, J., See, I., Reddy, S. C., Jernigan, J. A., Gokhale, R. H., & Fiore, A. E. (2020). Bacterial Infections Associated With Substance Use Disorders, Large Cohort of United States Hospitals, 2012–2017. *Clinical Infectious Diseases*, 71(7), e37–e44. <https://doi.org/10.1093/cid/ciaa008>
- McNinch, J., Maguire, M., Wallace, L., & Christiana, C. (2021). A Case Of Skin Necrosis Caused By Intravenous Xylazine Abuse. *Journal of Hospital Medicine*. SHM Converge 2021. <https://shmabstracts.org/abstract/a-case-of-skin-necrosis-caused-by-intravenous-xylazine-abuse/>
- Montero, F., Bourgois, P., & Friedman, J. (2022). Potency-Enhancing Synthetics in the Drug Overdose Epidemic: Xylazine (“Tranq”), Fentanyl, Methamphetamine, and the Displacement of Heroin in Philadelphia and Tijuana. *Journal of Illicit Economies and Development*, 4(2), 204–222. <https://doi.org/10.31389/jied.122>
- Mulders, P., van Duijnhoven, V., & Schellekens, A. (2016). Xylazine Dependence and Detoxification: A Case Report. *Psychosomatics*, 57(5), 529–533. <https://doi.org/10.1016/j.psych.2016.05.001>
- Munn, Z., Peters, M. D. J., Stern, C., Tufanaru, C., McArthur, A., & Aromataris, E. (2018). Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Medical Research Methodology*, 18(1), 143. <https://doi.org/10.1186/s12874-018-0611-x>
- Murdoch, D. R., Corey, G. R., Hoen, B., Miró, J. M., Fowler, V. G., Bayer, A. S., Karchmer, A. W., Olaison, L., Pappas, P. A., Moreillon, P., Chambers, S. T., Chu, V. H., Falcó, V., Holland, D. J., Jones, P., Klein, J. L., Raymond, N. J., Read, K. M., Tripodi, M. F., ... International

- Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) Investigators. (2009). Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: The International Collaboration on Endocarditis-Prospective Cohort Study. *Archives of Internal Medicine*, 169(5), 463–473. <https://doi.org/10.1001/archinternmed.2008.603>
- National Cancer Institute at the National Institutes of Health. (2011). Ecchymosis. <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/ecchymosis>
- New York State Department of Health. (2023). Xylazine: What Clinicians Need to Know. <https://www.health.ny.gov/publications/12044.pdf>
- Pan, X., Chen, G., Wu, P., Han, C., & Ho, J. K. (2018). Skin perfusion pressure as a predictor of ischemic wound healing potential. *Biomedical Reports*, 8(4), 330–334. <https://doi.org/10.3892/br.2018.1064>
- Pan, X., You, C., Chen, G., Shao, H., Han, C., & Zhi, L. (2018). Skin perfusion pressure for the prediction of wound healing in critical limb ischemia: A meta-analysis. *Archives of Medical Science : AMS*, 14(3), 481–487. <https://doi.org/10.5114/aoms.2016.62220>
- Parikh, M. P., Octaria, R., & Kainer, M. A. (2020). Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections and Injection Drug Use, Tennessee, USA, 2015-2017. *Emerging Infectious Diseases*, 26(3), 446–453. <https://doi.org/10.3201/eid2603.191408>
- Philadelphia Department of Public Health. (2022a). Division of Substance Use Prevention and Harm Reduction Annual Report, 2021.
- Philadelphia Department of Public Health. (2022b). Health Update: Xylazine (tranq) exposure among people who use substances in Philadelphia. https://hip.phila.gov/document/3154/PDPH-HAN_Update_13_Xylazine_12.08.2022.pdf/

- Poklis, A., Mackell, M. A., & Case, M. E. (1985). Xylazine in human tissue and fluids in a case of fatal drug abuse. *Journal of Analytical Toxicology*, 9(5), 234–236.
<https://doi.org/10.1093/jat/9.5.234>
- Pollini, R. A., Paquette, C. E., Drvar, T., Marshalek, P., Ang-Rabanes, M., Feinberg, J., & Haut, M. W. (2021). A qualitative assessment of discharge against medical advice among patients hospitalized for injection-related bacterial infections in West Virginia. *The International Journal on Drug Policy*, 94, 103206. <https://doi.org/10.1016/j.drugpo.2021.103206>
- Quijano, T. A. g. (2022). Xylazine In The Drug Supply: Emerging Threat In Connecticut And Lesson [Public Health Theses]. <https://elischolar.library.yale.edu/ysphtdl/2191/>
- Quijano, T. A. G., Heimer, R., Crowell, J., Eggert, K., Clark, K., Alexander, M., & Grau, L. (2023). Xylazine in the Drug Supply: Emerging Threats and Lessons Learned in Areas with High Levels of Adulteration.
- Reed, M. K., Roth, A. M., Tabb, L. P., Groves, A. K., & Lankenau, S. E. (2021). “I Probably Got a Minute”: Perceptions of Fentanyl Test Strip Use among People who Use Stimulants. *The International Journal on Drug Policy*, 92, 103147.
<https://doi.org/10.1016/j.drugpo.2021.103147>
- Reyes, J. C., Negrón, J. L., Colón, H. M., Padilla, A. M., Millán, M. Y., Matos, T. D., & Robles, R. R. (2012). The Emerging of Xylazine as a New Drug of Abuse and its Health Consequences among Drug Users in Puerto Rico. *Journal of Urban Health : Bulletin of the New York Academy of Medicine*, 89(3), 519–526. <https://doi.org/10.1007/s11524-011-9662-6>
- Ruiz, M. S., O'Rourke, A., Allen, S. T., Holtgrave, D. R., Metzger, D., Benitez, J., Brady, K. A., Chaulk, C. P., & Wen, L. S. (2019). Using Interrupted Time Series Analysis to Measure the

Impact of Legalized Syringe Exchange on HIV Diagnoses in Baltimore and Philadelphia.
Journal of Acquired Immune Deficiency Syndromes (1999), 82 Suppl 2(2), S148–S154.

<https://doi.org/10.1097/QAI.0000000000002176>

Ruiz-Colón, K., Chavez-Arias, C., Díaz-Alcalá, J. E., & Martínez, M. A. (2014). Xylazine intoxication in humans and its importance as an emerging adulterant in abused drugs: A comprehensive review of the literature. *Forensic Science International*, 240, 1–8.

<https://doi.org/10.1016/j.forsciint.2014.03.015>

Schranz, A., & Barocas, J. A. (2020). Infective endocarditis in persons who use drugs: Epidemiology, current management, and emerging treatments. *Infectious Disease Clinics of North America*, 34(3), 479–493. <https://doi.org/10.1016/j.idc.2020.06.004>

Shang, M. (2023). Xylazine. University of Pittsburgh, Grayken Center for Addiction Training & Technical Assistance.

Skrbic, R., & Chiba, S. (1993). Dominant antagonistic action of alpha 2-adrenoceptor agonists on alpha 1-agonist-induced vasoconstriction. *European Journal of Pharmacology*, 230(2), 131–137. [https://doi.org/10.1016/0014-2999\(93\)90795-j](https://doi.org/10.1016/0014-2999(93)90795-j)

Spadaro, A., Connor, K. O., Lakamana, S., Sarker, A., Wightman, R., Love, J. S., & Perrone, J. (2023). Self-reported Xylazine Experiences: A Mixed Methods Study of Reddit Subscribers. <https://doi.org/10.1101/2023.03.13.23287215>

Spyres, M. (2021). The ToxIC NOSE (Novel Opioid and Stimulant Exposure): Xylazine: A Potentially Deadly Additive to Opioids (No. 5). Banner University Medical Center Phoenix. https://www.acmt.net/wp-content/uploads/2022/09/NOSE_Brief_Report_5_Xylazine_4_29_22.pdf

SUDORS Dashboard: Fatal Overdose Data | Drug Overdose | CDC Injury Center. (2023, April 14).

<https://www.cdc.gov/drugoverdose/fatal/dashboard/index.html>

Thangada, S. (2021). Notes from the Field: Xylazine, a Veterinary Tranquilizer, Identified as an Emerging Novel Substance in Drug Overdose Deaths—Connecticut, 2019–2020 [MMWR]. Centers for Disease Control and Prevention.

<https://www.cdc.gov/mmwr/volumes/70/wr/mm7037a5.htm>

The Everywhere Project. (2023). Tranq Wound Care 101. <https://www.everywhereproject.org>

The White House. (2023, April 11). FACT SHEET: Biden-Harris Administration Announces Strengthened Approach to Crack Down on Illicit Fentanyl Supply Chains. The White House. <https://www.whitehouse.gov/briefing-room/statements-releases/2023/04/11/fact-sheet-biden-harris-administration-announces-strengthened-approach-to-crack-down-on-illicit-fentanyl-supply-chains/>

Tkatch, C. D., Alvarado, S., & Jaeger, J. (2021). Cutaneous Skin Infection Associated with IV Xylazine and Cocaine Use. American College of Physicians - Pennsylvania Chapter.

<https://pa-acp.org/wp-content/uploads/2021/10/Colin-Tkatch-PAS-30-Cutaneous-Skin-Infection-Associated-with-IV-Xylazine-and-Cocaine-Use.pdf>

Torruella, R. A. (2011). Xylazine (veterinary sedative) use in Puerto Rico. Substance Abuse Treatment, Prevention, and Policy, 6, 7. <https://doi.org/10.1186/1747-597X-6-7>

Watkins, D. C. (2017). Rapid and Rigorous Qualitative Data Analysis: The “RADaR” Technique for Applied Research. International Journal of Qualitative Methods, 16(1), 1609406917712131. <https://doi.org/10.1177/1609406917712131>

Zhang, A. Y., Shrum, S., Williams, S., Petnic, S., Nadle, J., Johnston, H., Barter, D., Vonbank, B., Bonner, L., Hollick, R., Marceaux, K., Harrison, L., Schaffner, W., Tesini, B. L., Farley, M. M., Pierce, R. A., Phipps, E., Mody, R. K., Chiller, T. M., ... Vallabhaneni, S. (2020). The Changing Epidemiology of Candidemia in the United States: Injection Drug Use as an Increasingly Common Risk Factor—Active Surveillance in Selected Sites, United States, 2014–2017. *Clinical Infectious Diseases*, 71(7), 1732–1737. <https://doi.org/10.1093/cid/ciz1061>