Xylazine, Philadelphia's Silent Killer: Medical, Financial and Ethical Perspectives

V Mehta, P A Clark, C Fang, S Patel, J Szabo, A Fogarty

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Abstract

The opioid epidemic poses a unique and dangerous threat to the United States. What started as overprescription of painkillers like oxycontin and percocet has now spiraled into widespread use of deadly and illicit synthetic drugs like fentanyl. The newest dimension of the opioid epidemic consists of an influx of a veterinary tranquilizer called Xylazine into the drug supply of the Northeastern United States and beyond. Typically cut into a mixture of heroin or fentanyl, Xylazine, or “tranq,” is not an opioid but still increases the risk of death for intravenous drug users. As there are no accepted human medical uses for Xylazine, a number of clinical manifestations, including necrotic skin lesions and severe respiratory depression, complicate the treatment process for a typical opioid overdose. The deadly nature of fentanyl adulterated or associated with xylazine, also known as FAAX, engenders serious medical concerns, but the increased risk of death and overall medical burden presents a number of financial issues as well. This paper aims to examine the clinical, pharmacological, economic, and ethical implications of this new drug in the Philadelphia area and propose a series of recommendations to potentially alleviate some of these issues.

INTRODUCTION

It is no secret that the heroin epidemic has had a death grip on Philadelphia for some time. In recent years, the heroin supply of the northeastern United States has seen an influx in the synthetic opioid fentanyl. With street names like China Girl, Murder 8, and King Ivory, fentanyl is normally used as an anesthetic or analgesic in a hospital setting. However, with a lethal dose smaller than the size of a penny, it is approximately 50 times more potent than normal heroin. [1] Fentanyl can be snorted, smoked, consumed in pill form, or, most commonly, injected along with heroin. This prevalent combination of heroin and fentanyl is so deadly that, in 2021, 82% of Philadelphia’s 1,276 overdose deaths included fentanyl. [2] Since 2020, the decreases that had previously been seen in Philadelphia’s unintentional overdose deaths in 2018 and 2019 have been reversed, and the number of overdose deaths have risen. [2] This increase in the number of fatalities could be accredited to the influx of fentanyl coinciding with the coronavirus pandemic, which hindered or halted many addiction recovery programs.

Both heroin and fentanyl are listed as Schedule I Controlled Substances under the Controlled Substances Act (CSA) of 1970. Such a categorization means they have a high potential for abuse and lack any acceptable medical uses. [3, 4] Schedule I substances are the most highly regulated substances under the purview of the DEA, and such regulation means that only federally approved research studies are permitted to manufacture and possess these chemicals [5] .

Despite the restrictive nature of the CSA Scheduling, some substances have slipped through the cracks and are currently wreaking havoc on Philadelphia's most vulnerable populations.

More recently than the influx of fentanyl, Philadelphia has seen a rise in prevalence of xylazine in its drug supply. As a veterinary tranquilizer, xylazine is readily available for purchase in multiple forms, as it is not regulated under the Controlled Substances Act. [6] Drug traffickers utilize this lack of government oversight to their advantage, cutting their heroin with xylazine (most commonly supplied as a powder) to create a potent cocktail to be sold to unsuspecting addicts. The manner

in which traffickers add xylazine to the traditional heroin/fentanyl combination produces no way for users to distinguish whether or not their batch has been cut with xylazine. Similar to cutting heroin with fentanyl, cutting heroin with xylazine increases the profit for the traffickers, but it also increases risks for the users. Xylazine is not an opioid and, therefore, presents different clinical manifestations than a typical heroin or fentanyl overdose. These differences complicate the treatment process beyond that of a normal opioid overdose, thus adding an unnecessary strain on healthcare systems and causing greater harm to people who inject drugs.

In November of 2022, the DEA issued a warning regarding the use of and exposure to xylazine in humans, stating that xylazine has been "…increasingly detected in the illicit drug supply and in drug overdoses." [7] On April 12, 2023, the White House Office of National Drug Control Policy declared xylazine and "fentanyl adulterated or associated with xylazine (FAAX)" an emerging threat. [8] Termed "tranq-dope" or just "tranq," this fentanyl, heroin, and xylazine combination poses a unique threat to the already deadly drug epidemic impacting the United States. The nickname "Philly dope" is also used to refer to this potent cocktail, but such a name points out a particularly significant dimension of this drug's arrival in the United States.

Philadelphia seems to be the epicenter of the xylazine epidemic, with many of the already afflicted members of Philadelphia's addicted population falling victim to this combination. This paper aims to examine the clinical, economic, and ethical implications of this new drug in the Philadelphia area.

CLINICAL ANALYSIS

One striking clinical manifestation of xylazine use is the development of skin lesions.[9] These necrotic lesions, resulting from vasoconstriction likely mediated by alpha-2 receptor agonism, accentuate xylazine's multifaceted impact on vascular function. [10] Exploring the use of vasodilating agents like hydralazine or minoxidil to promote angiogenesis presents a novel avenue for improving recovery and healing. Additionally, xylazine's history as an anesthetic agent for animals and its failed attempts as a human antihypertensive sheds light on its pharmacological evolution. [9] The constellation of symptoms associated with acute xylazine toxicity, ranging from CNS depression to hypotension and hypothermia, underscores its complex effects on various physiological systems. [11] Given these lesions are often necrotic and may lead to infections caused by agents such as methicillin-resistant Staphylococcus aureus (MRSA), methicillin-sensitive Staphylococcus aureus (MSSA), and Escherichia coli (E. coli), understanding their progression will help to decrease infection and limb amputation rates. [12]

Xylazine, which was initially intended for veterinary use, has emerged with significant implications for human health due to its misuse and associated withdrawal symptoms. [13] Despite being relatively unexplored in humans, xylazine's negative withdrawal effects have yet to lead to the establishment of a standardized protocol for its management. The typical symptoms seen include severe anxiety, dysphoria, and akathisia. [13] A case report published in October 2022 described a 29-year-old female with chronic opioid and xylazine use, highlighting the challenges of managing withdrawal manifestations in a patient with concurrent drug usage. [13] This patient presented to the ICU showing signs of xylazine withdrawal and had numerous lower extremity wounds that were attributed to xylazine injection.[13] Their protocol involving dexmedetomidine, phenobarbital, tizanidine, and clonidine points to an overall approach of alleviating withdrawal symptoms. [13] Symptoms were no longer present after four days, and she was transitioned off dexmedetomidine to buprenorphine prior to being discharged. [13] Notably, the absence of seizures and abnormal vital signs could help differentiate xylazine withdrawal from other substances such as alcohol or benzodiazepines. Further research into withdrawal management offers hope for improving patient outcomes by minimizing distress and lowering the risk of relapse.

A considerable challenge to addressing xylazine withdrawal is the lack of FDA-approved medications. This void in treatment options reflects the need for further research in this area. Broader discussions should encompass the societal impact of xylazine use, potential regulatory measures, and the interplay between medical professionals, researchers, and policymakers in addressing this arising issue. Collaborative efforts are crucial as the medical community navigates the

complexities of xylazine abuse, its effects, and appropriate interventions. By fostering interdisciplinary dialogue between medical professionals, researchers, and policymakers, healthcare providers can better understand and implement effective strategies to tackle the challenges of xylazine misuse.

Figure 1

Xylazine wound [8]

CASE STUDIES

There have been numerous reported cases that highlight the harsh consequences of xylazine use. The first case depicts a patient with extensive ulcerations, suggesting a link between prolonged xylazine use and impaired wound healing, which can lead to severe infections. [14] In general, the cases below underscore the urgent need for heightened awareness and comprehensive research to counteract the detrimental impacts of xylazine misuse.

Case 1

A 37-year-old woman residing in Philadelphia with a history of injecting eight to ten bags of dope every day presented with painful ulcers that extended from her knees to ankles. [14] These ulcers had copious foul-smelling purulent discharge, necrosis of the subcutaneous tissues, and tibial osteomyelitis. [14] Osteomyelitis in particular may cause hospitalization with bacteremia that requires intravenous antibiotics, debridement, and wound care. Due to xylazine's vasoconstrictive effect on regional blood vessels, prolonged use can lead to decreased perfusion and impaired wound healing, leading to higher rates of ulcer infection. [14]

Case 2

A 69-year-old man with a history of daily fentanyl use presented to the primary care clinic with a large irregular ulcer on his left ventral forearm. 12 Upon further evaluation by dermatology, the ulcer had a base of red granulation tissue and a necrotic peripheral crust.12

Biopsy of the region exhibited fibroblasts and collagen bundles, as well as superficial MSSA. 12 Because the patient had difficulty keeping the wound covered, healing was impaired from persistent dryness and eschar formation. 12 A subsequent urine toxicology screen was performed and returned with a positive xylazine level at >200 g/L.12 Unfortunately, the patient returned to fentanyl use despite being in an opioid treatment program between June 2022 to January 2023. 12

Case 3

A 37-year old man with a history of bipolar disorder, PTSD, anxiety, and opioid use disorder (OUD) was admitted to the hospital in November 2022 with bilateral forearm pain from wounds. [12] The patient described that the wounds have become progressively larger and more painful since August 2021 , and reported heroin/fentanyl use ten to fifteen times daily. [12] Dermatology described the wounds as being indurated plaques with overlying irregular eschars and ulcerations and having a peau d'orange presentation. [12] Treatment regimen for this patient included arm elevation, betamethasone 0.05% ointment twice daily for two weeks, and petroleum jelly application to eschars. [12] A follow up serum and urine test for xylazine toxicity came back negative in serum and positive in urine. [12]

Case 4

A 54-year-old woman with a history of IgG deficiency, bipolar disorder, and OUD presented with wounds on her posterior bilateral forearms in February 2021. [12] The wounds appeared to have track marks, and superficial culture grew Enterobacter cloacae and Escherichia coli . [12] After six months of antibiotic use the wounds did not improve, and the patient presented to the hospital with acute bilateral forearm pain. [12] Her WBC count was 16.5 k/L and C-reactive protein was 122.7 mg/L, indicating severe inflammation from infection. [12] X-ray showed subcutaneous gas, which was concerning for necrotizing fasciitis. [12] The patient underwent bilateral debridement and skin grafting, and

a deep wound culture grew S. aureus and Streptococcus Group G. [12] She was prescribed ciprofloxacin, clindamycin, metronidazole, and vancomycin. [12] Her wound management consisted of hypochlorous acid-soaked gauze placement on the wound, and a hydrocolloid dressing.[12] A urine xylazine test in January 2023 was positive and the patient endorsed ongoing fentanyl use to make her pain more tolerable.[12]

PHARMACEUTICAL ANALYSIS

Chemical Overview of Xylazine Hydrochloride

Xylazine is a substance used as an animal tranquilizer in the sedation and relaxation of certain animal species. The U.S. Food and Drug Administration (FDA) has approved products containing xylazine only for veterinary use. However, xylazine was not originally meant to be used in animals. In 1962, xylazine hydrochloride was compounded by Farbenfabriken Bayer as 2-(2,6-dimethyl phenylamine)-4H-5,6-dihydro-1,3-thiazine hydrochloride. The initial aim was to therapeutically use xylazine in humans as an antihypertensive, analgesic, anesthetic, and/or sleeping agent. However, clinical studies within humans identified xylazine as a severe central nervous system depressant with extreme hypotensive effects. Due to these adverse effects, the clinical trials were halted, and the drug was diverted from human use to strictly veterinary use. The FDA has approved xylazine use either on its own or in combination with other veterinary anesthetics. [15,6, 16] It is specifically approved for horses, dogs, cats, deer, and elk. [16]

Despite the strict veterinary use, xylazine has been an emerging abusive agent within the human population. Xylazine use has been observed in cocaine, heroin, and fentanyl abusers either alone or alongside other illicit substances. In the past several years, a rise in the abuse of xylazine has brought attention to the need for classifying xylazine as a controlled substance. Due to the strict veterinary use and the harmful effects of xylazine on humans, there is a lack of data on the pharmacology of the drug within the human body. Several human xylazine overdose cases have been described in healthcare settings that may contribute brief findings to literature thus far. However, there is still much need for a greater understanding of the effects of xylazine within the human population.

Pharmacology

Structure and Mechanism of Action :

Xylazine's structure resembles that of the drug class phenothiazines, tricyclic antidepressants, and clonidine. [16] It is a methyl benzene structure that is lipophilic and acts similarly to clonidine, an alpha-2 agonist. Xylazine is an alpha-2 adrenergic agonist that exhibits various central and peripheral nervous system effects through binding of alpha-2 receptors. The primary effects of xylazine are observed through the impact on central alpha-2 receptors within the central nervous system, specifically the vasomotor center of the medulla oblongata. The central nervous system is made of neurons that are powered by a sympathetic outflow of neurotransmitters. The movement of neurotransmitters between neurons stimulates certain sympathetic responses within the body. Xylazine stimulates the alpha-2 receptors on the neuron ends and decreases the release of neurotransmitters like norepinephrine and dopamine. Xylazine also triggers a negative feedback loop as a result of this decrease in sympathetic outflow, causing the effects of sedation, muscle relaxation, and decreased susceptibility to pain. [16, 17]

Pharmacokinetics :

The pharmacokinetic parameters of xylazine are primarily studied in animal species and not well understood in humans. Xylazine can be administered in humans by various routes including intravenous, intramuscular, inhalation, subcutaneous, or oral. Literature on the specific bioavailability of xylazine in correlation to the dosage route is still scarce. In humans, some case studies have represented rapid absorption of xylazine and a large volume of distribution. Hepatic metabolism is likely to be rapid with nearly 70% of the elimination occurring renally.[17]

Elimination also appears to be rapid with a half-life of 23-50 minutes within the human body. Due to this rapid onset and elimination, the drug may reach toxicity levels quickly after administration and may be difficult to trace after administration due to fast elimination.[7]

Intravenous xylazine administration in rats at a dose of 0.2-1 mg/kg was observed with rapid absorption and rapid distribution within several tissues. There was 70% renal elimination with a half-life of 2-3 hours and 8% unchanged drug.[16] In a combination of animal studies,

rapid absorption and distribution was observed with peak plasma concentration achieved within 12-14 minutes after administration. Rapid hepatic metabolism occurs through cytochrome p450 enzymes. A half-life of 0.5-3 hours was observed with a duration of effect being 3-4 hours. [17,18]

The pharmacokinetics from these animal studies may potentially resemble possible pharmacokinetic parameters within human studies, but more research must be conducted to identify more concrete parameters.

Results from a poison center evaluated the occurrence of adverse events in patients exposed to toxic amounts of xylazine from 2000-2014. About 47.4% of their patients experienced drowsiness/lethargy, 19.7% experienced bradycardia, 10.5% experienced hypotension, 6.6% experienced coma, and 5.3% experienced respiratory depression.[19] Literature shows xylazine doses consumed by humans range from 40 to 2400 mg, but the serum concentrations at which drug toxicity occurs are still not well defined. [20] Moreover, there is not a concrete distinction between non-fatal and fatal doses or serum concentrations of xylazine within humans. [18] Overall, with insufficient literature on the pharmacology of xylazine within human bodies, it is difficult to determine the healthcare outcome of xylazine users along with overdose antidotes.

ECONOMIC ANALYSIS

Along with the rise in overdoses and fatalities, the long standing opioid epidemic has taken an economic toll on society. Although the exact costs cannot be quantified for the overall problem, there have been a number of studies that examine its economic implications in terms of various categories. [21] As estimated by the Council of Economic Advisors (CEA), the United States faced $504 billion in total costs for the opioid epidemic in 2015, with a projection of exponential growth if the problem persisted. During this same year, the per capita costs of the opioid epidemic in Pennsylvania totaled nearly $2,000. As predicted, these figures would rise, and according to the CDC, the cost for opioid overdoses and opioid use disorder in the U.S. in 2017 was approximately $1.02 trillion. [22] Opioid use disorder (OUD), if left untreated, has consequential financial implications on individual people, their loved ones, and society as a whole, and it contributes to increased healthcare spending, criminal justice concerns, and a significant loss of productivity.[23]

A 2021 research study found that overdoses, misuse, and dependence related to opioids accounted for $35 billion in healthcare costs overall, with $1.94 billion being in hospital expenses for opioid overdose. Further, the United States experienced $14.8 billion in criminal justice costs, and $92 billion in lost productivity as a result of the epidemic. The Federal Reserve Bank of Philadelphia made it apparent that the nature of the opioid crisis is intertwined with the declining labor market, as well as the broad state of the U.S. economy. [21] Individuals impacted by the epidemic are less likely to be suitable for professional positions, and the declining demand for low-skilled jobs disvalues their qualifications. Given the average age of an overdose fatality is around 4021 , productivity loss could also be attributed to premature death due to overdose, or opioid related incarceration.[22] Societal organizations have already been overwhelmed by the rise of fentanyl in the opioid market. The crisis continues to pose threats and new costs to the labor force, productivity, the healthcare system, the criminal justice system, and communities overall. Each of these sectors are now working to discover how to withstand the newly introduced threats of xylazine.

The United States healthcare system continues to grapple with the abundant challenges related to the opioid epidemic. Not only are doctors, nurses, administrators, and other healthcare professionals placed on the frontlines of this crisis, but the expenses associated with caring for opioid users have been shown to have a detrimental financial impact on healthcare facilities nationwide. [24] This impact is even greater in areas with prominent addiction rates, and costs continue to rise for hospitals as the opioid epidemic persists. The financial burden tends to stem from emergency room visits, ambulance rides, and the use of naloxone to reverse the overdose. According to data from Premier, a healthcare improvement company, the United States spends more than $95 billion treating OUD in emergency rooms alone each year. [25] Further, a study from the CDC reports that as of 2017, opioid use disorder accounted for $471 billion for the United States, and $480.7 billion was determined to be the value of life lost due to overdose deaths.[22] Especially following the Covid-19 pandemic, the U.S. healthcare system has experienced financial challenges, and opioid-related hospital visits only exacerbate that strain. [24] As

previously stated, the Philadelphia Department of Public Health disclosed that in 2021, the city experienced a total of 1,276 overdose deaths, and 82% of those deaths included fentanyl, [2] which is increasingly related to the use of xylazine.

In March of 2022 , the Philadelphia Department of Public Health released a Health Alert regarding the risks of xylazine use and withdrawal, and provided some guidance and resources for healthcare professionals. [26] This notice made it clear that providers should presume xylazine exposure in individuals who use drugs in Philadelphia, particularly heroin and fentanyl. Given that there are still many unanswered questions about the effect of xylazine in humans, the protocol for withdrawal treatment may be difficult, with longer hospital stays, inpatient monitoring, and a greater use of resources.[27] Xylazine usage often presents in patients similar to opioid overdose, but with the lack of available xylazine testing in most protocols, it is difficult to assess and identify in clinical settings.[6]

Certainty about the presence of xylazine in overdose deaths requires expanded testing, which puts further strain on the healthcare industry economically. According to data from the CDC, the approximate number of overdose related deaths in the United States in which xylazine was identified increased at a rate of 1238% from 2018 to 2021. [8] The number of these deaths grew from 260 to 3480 in 2021, and were most prevalent in Pennsylvania, Maryland, New York and Connecticut.

Due to the relatively new nature of the drug, there is insufficient data regarding the financial implications of treatment. However, this can be assessed based on the cost of treating the individual symptoms associated with xylazine use. Xylazine users face wounds that are increasingly more difficult to treat, thus requiring more resources and exacerbating the financial effect. [28] Data from an NYU study reported that severe cases of pressure ulcers cost an average of $124,327 per patient.[24] Skin ulcerations that result in amputation are estimated to cost nearly $90,000. Given the strong association between xylazine and opioid usage, the majority of patients who experience xylazine withdrawal symptoms are uninsured or on Medicaid in the U.S., leaving the healthcare system to bear the considerable burden and costs of treatment.

Organizations nationwide have been conducting studies to explain the recent increase in xylazine-laced opioids. The Leonard Davis Institute of Health Economics of the University of Pennsylvania reported in August of 2023 that there has been a significant shift in the drug market to illicit synthetic drugs. [29] This classification of drugs is produced in laboratories, making the drug supply more dynamic, as it increases the availability of certain products. Xylazine is easily attainable, and comes at a low cost with low risk for drug dealers due to its lack of governmental oversight. Although xylazine is primarily sold to veterinarians, it is also readily available for purchase on other sites in different forms, often not requiring any legitimacy in the buyer.[6]

Per the Drug Enforcement Administration, the common price of xylazine ranges from $6-$20 per kilogram from supplier sites [6] , meanwhile a similar amount of fentanyl can cost $10,000 to $90,000 [30] . With a significantly cheaper price, cutting opioids with xylazine increases profits for drug traffickers, and allows them to reduce the amount of fentanyl or heroin used in each batch. Further, the veterinary tranquilizer, when combined with fentanyl, produces a longer high, which attracts additional customers. [6] Some epidemiologists postulate that the rise in xylazine was exacerbated by the Covid-19 pandemic, and drug traffickers used it as an "opioid filler" due to the lower supply and high cost of opioids like heroin and fentanyl. [31] Many groups saw this new mixture as an advantage, and it is especially appealing to users in Kensington, a neighborhood in Philadelphia, who can now get a bag of tranq dope for $5, rather than $10 for just heroin.

ETHICAL ANALYSIS

Harm Reduction as Practical Ethical Justification

The driving force for those who advocate for new strategies to deal with individuals using drugs being laced with xylazine is the number of deaths and increased physical harm being done to those with a substance use disorder (SUD). One ethical alternative would be advocating for Safe Injection Sites (SIS) to be made available as a viable option for those with a substance use disorder under the harm reduction theory. Harm reduction is an approach focused on minimizing the negative results that go hand-in-hand with drug abuse. [32, 33] Harm reduction techniques have both a medical and ethical impact on the individual and society as a whole. Harm reduction techniques accept

the individuals as they are, while also tailoring that person's treatment to fit his or her needs.[34] Furthermore, there are certain principles that are quintessential to an understanding of harm reduction, as listed by the Harm Reduction Coalition:

- Accepts, for better and or worse, that licit and illicit drug use is part of our world and chooses to work to minimize its harmful effects rather than simply ignore or condemn them.
- Understands drug use as a complex, multi-faceted phenomenon that encompasses a continuum of behaviors from severe abuse to total abstinence and acknowledges that some ways of using drugs are clearly safer than others.
- Establishes quality of individual and community life and well-being–not necessarily cessation of all drug use–as the criteria for successful interventions and policies.
- Calls for the non-judgmental, non-coercive provision of services and resources to people who use drugs and the communities in which they live in order to assist them in reducing attendant harm.
- Ensures that drug users and those with a history of drug use routinely have a real voice in the creation of programs and policies designed to serve them.
- Affirms drug users themselves as the primary agents of reducing the harms of their drug use and seeks to empower users to share information and support each other in strategies which meet their actual conditions of use.
- Recognizes that the realities of poverty, class, racism, social isolation, past trauma, sex-based discrimination and other social inequalities affect both people's vulnerability to and capacity for effectively dealing with drug-related harm.
- Does not attempt to minimize or ignore the real and tragic harm and danger associated with licit and illicit drug use [35]

The SIS's ability to allow people with substance use disorder to have a safe environment to inject drugs gives itself the potential to be used as a harm reduction agent in and of itself. Furthermore, many individuals who die from opiate overdoses like heroin laced with fentanyl and xylazine did not receive necessary medical treatment in time to save them; allowing these individuals' access to the SIS could possibly save many preventable deaths. If we, as a society, value human life as sacred, we must find a way to prevent these deaths. The SIS program, like Insite in Vancouver, supervised by trained medical personnel as a harm reduction agent could present a viable alternative to address the growing drug addiction epidemic and save thousands of lives.[36] The drug epidemic is growing, fatal overdoses are increasing, and people are becoming more and more frustrated by legal and political barriers to new forms of treatment being put in place to stop this problem. SISs like Insite have been shown to decrease drug abuse, disease, and mortality rates in Canada and Europe. In 2022, provisional data indicated that more than two thirds (68%) of the reported 107,081 drug overdose deaths in the United States involved synthetic opioids other than methadone, principally illicitly manufactured fentanyls (IMFs). Xylazine, a non-opioid sedative not approved for human use and with no known antidote, has been increasingly detected in IMF products in the U.S. drug supply and in IMF-involved overdose deaths. Limited studies suggest xylazine can cause central nervous system depression, respiratory depression, bradycardia, and hypotension in humans; chronic use might lead to severe withdrawal symptoms as well as skin ulcerations.[37] This number of deaths due to overdoses is unacceptable by any standards. Therefore, harm reduction initiatives like SISs must be introduced.

Layout

Logistically speaking, we propose that Philadelphia's SIS will be laid out in a similar format to that of Vancouver's Insite. The SIS will have a reception area in which people with substance abuse disorder will be given a card with an anonymous identification number. In addition to the individual's anonymous identification number, the card will contain the address and phone number of the facility, and the phone numbers of counseling and rehabilitation programs as well as emergency services in the event of an overdose. The staff and SUDs should be reminded that the SIS User ID card does not contain the user's personal information. Rather, the card is to give the users information about the facility and where to contact when emergent situations arise and to collect data to see whether the SIS is efficient in serving the users.

At registration, a SUD individual will be required to give basic information such as how he or she heard about the site, age, gender, ethnicity, and whether the SUD person is interested in rehabilitation, psychiatric services, wound care, and clean needle exchange and additional services later addressed in the paper. This ID card will allow the individual to swipe in and out of the facility so that the facility's traffic can be monitored. If a user does not have a clean needle, one will be provided. At this point, it is pertinent to

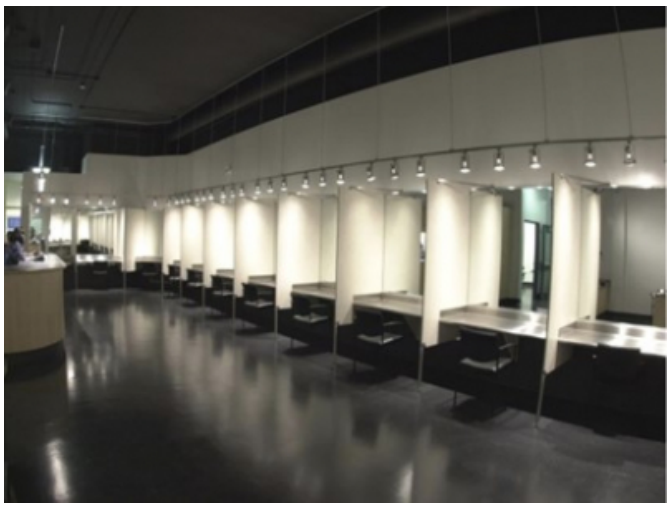
emphasize that the SIS does not provide the drugs for users to inject. Persons with SUD must bring their own drugs for use. Purity testing kits will be made available for those who wish to test if their drugs have been laced with substances like fentanyl and xylazine.

After reception, the SIS will have a large room with numerous benches at which SUD persons can safely inject under the supervision of trained healthcare professionals. SUD persons will be provided with the sterilized supplies or kit needed for substance-use such as syringes, disposable cookers, matches, bottled water, and tourniquet. Spaces at the benches will be partitioned off to create a semi-private space for each individual (See Figure 2). Each bench will have a box in which dirty needles can be safely disposed of. Should an overdose occur, trained medical professionals will be available to administer naloxone to reverse the overdose. Medical students will also be available to care for wounds that result from prolonged IV drug use. Oxygen supplies will be provided if needed.

The injection area is followed by a lounge area in which SUD persons can briefly relax for a designated amount of time (30 minutes). It will be not difficult to gauge if anyone is receptive to the conversation on recovery. Thus, if anyone seems open to the conversation, the time restriction will be set aside as the staff engages in the communication process. It is at this point that educational materials, counseling, and rehabilitation programs will be offered to SUD persons. The goal here is for those staffing the site to build relationships with the individuals from the community. Hopefully, the lounge can be an area that facilitates conversations about rehabilitation and treatment for SUD persons.

Figure 2

CUES Injection Room, Insite Philadelphia[38] (Mayor's Task Force on the Opioid Epidemic)



Services

Due to the effectiveness of Insite in Vancouver, this article seeks to consider SIS as a viable option in response to the severity of the opioid crisis in Philadelphia. In terms of services to be offered, the SIS would be congruent to Vancouver's Insite. But the SIS that this paper suggests incorporates additional services, some of which had not been included in Canada's Insite, namely, more involvement of people in recovery and places a particular emphasis on early education for new and future healthcare professionals. As a result, the following services are to be provided: fentanyl/xylazine screenings, wound care, Hepatitis-C/HIV screenings, a needle exchange program, Narcan distribution and education, counseling for rehabilitation and detoxification done by individuals in recovery, and early education.

Fentanyl/Xylazine Screenings

Fentanyl has become a potent adversary in the Philadelphia crisis. "In 2022, the Philadelphia Department of Public Health recorded 1,413 unintentional overdose deaths. This is an 11% increase from the previous high of 1,276 in 2021... More than 80% of the overdose deaths recorded in 2022 involved opioids, virtually always fentanyl. Stimulants, such as cocaine, were detected in more than 70% of overdose deaths."39 Therefore, the SIS facility would offer fentanyl screenings. The use of fentanyl screenings has been found to change behavior amongst people who

inject drugs. Johns Hopkins and Brown Universities conducted a pilot study investigating the impact of fentanyl testing with SUD persons. Using a simple $1 testing strip dipped in the drugs mixed with water, the study has shown that people who received positive fentanyl results tend to 1) use less, 2) inject with someone around and/or 3) to use more slowly.[40] Upon learning fentanyl was laced in the drugs acquired, SUD persons became more attuned to the severity of their circumstances and became cautious. As individuals with opioid use disorder, proceeded to inject at their own risks but were more cognizant of their safety. Therefore, offering fentanyl testing kits in a SIS would be beneficial in allowing persons with SUDs to become more conscious of their present reality and potentially seek assistance in rehabilitation and detoxification. In addition, we would advocate for "testing the drug samples for xylazine using methodologies such as immunoassay test strips and spectroscopy. In the case of xylazine, knowing of its presence can help people who use drugs make informed decisions guided by harm reduction practices."[41]

Wound Care

Wound care would be another sector within the compartmentalized process of a supervised injection facility as described in Insite. Compounded with the increase blood-borne diseases, other infections arise as a result from injecting intramuscularly and subcutaneously with unsterile needles. Many of these conditions are primarily bacterial infections: staphylococcus infections, abscesses, cellulitis, necrotizing fasciitis, botulism, tetanus, and septic thrombophlebitis.[42] Lacerations and other wounds can be inflicted from the needle itself due to improper technique. Therefore, the SISs would have a wound care service staffed by healthcare personnel such as a physician assistant, nurse practitioner or students in healthcare education to provide immediate care for the wounds at the site, which could minimize the spread and progression of secondary infections. Treating wounds and infections promptly could reduce the future healthcare costs further since the estimated annual savings due to the SISs will range from $1,512,356 to $1,868,205.[43] Additionally, the integration of wound care services with medical education provides an opportunity for students to gain practical medical experience. The wound care service also proactively addresses the systemic issue within the healthcare system by allowing future healthcare personnel to witness the first-hand effects of opioid usage within marginalized populations.

Hepatitis-C/HIV Screenings

Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections are the most prevalent blood-borne diseases that arise from opioid injections. It is estimated that 75-85% of infected cases become chronic through which the virus remains "silent" for decades yet still attacks the body. Prolonged exposure to the hepatitis C virus infection can lead to liver cirrhosis, jaundice, fatigue, fever and muscle aches. Liver cirrhosis often leads to liver failure or even cancer. By the time liver cirrhosis is discovered, treatments entail a 12-week antiviral regimen that are very expensive. The 2021 Annual Report of Hepatitis B and Hepatitis C in Philadelphia shows that over 25,000 residents are positive for hepatitis B and almost 53,000 residents are positive for hepatitis C infections.[44] Additionally, the Philadelphia Health Department recorded 365 new diagnoses of HIV in 2021. This represents a 9% increase in the number of new HIV diagnoses from 2020 but remains 18% lower than the number of HIV diagnoses in 2019. In 2018, newly diagnosed HIV infections among people who inject drugs increased to 17%.45 The human immunodeficiency virus (HIV) infects the body's CD4 cells (T cells) that help the immune system fight off infections. If untreated, the reduction of CD4 cells can lead to further susceptibility to secondary infections or cancers which eventually results in the acquired immune deficiency syndrome (AIDS).[46] No effective cure currently exists, but there are treatment plans which reduce the HIV viral load. The average cost of one drug regimen is $28,688. According to the CDC, the cost for one treatment over a lifetime for an HIV infection is estimated at $379,668 per individual[47] . More often than not, HIV and Hepatitis C are coinfections amongst persons with SUD whom are less likely to afford health insurance. As a result, persons with SUD tend to seek emergency medical attention once the symptoms have progressed to latent stages, costing healthcare systems. Therefore, this article proposes to offer HIV/Hep-C screenings at the SISs. Each comes with its own OraQuick Rapid test that

detects antibodies for the respective viruses via a simple finger stick with results in just 30 minutes.[48] Offering HIV/Hep-C screenings serves as a proactive means for both persons with SUD and healthcare systems by encouraging persons with SUD to seek treatment early and possibly guide them further rehabilitative care because it provides a space and opportunity to be able to test for HIV and HCV infections which could lead to the overall reduction in healthcare costs.

A Needle Exchange Program

The Syringe Exchange Program, also referred to as the needle exchange program, was instituted in Philadelphia in 1992 in an attempt to reduce the number of blood-borne diseases such HIV caused by the reuse and sharing of unclean needles amongst people who inject drugs. At that time, 46% of HIV diagnoses had a strong correlation amongst persons with SUD.[49] The program was created through which unclean needles could be exchanged for sterile ones with the provision of education of risks and implications regarding the sharing of needles. Prevention Point had thus become the largest and only city-sanctioned needle exchange program in Philadelphia.[50] Maurer and her colleagues examined the effectiveness of the needle exchange program over the span of 15 years between 1999 and 2014 and found that the needle exchange program had reduced the number of HIV transmission instances via needle sharing from 46 % in 1992, 22.2% in 2006, 11.1% in 2009 , and 5.4% in 2014.[48] The number of new registrants per year had declined as well from 2168 in 1999 to 1295 in 2014.[48]

Nevertheless, the opioid crisis remains prevalent in Philadelphia today. Maurer and her team note that, even though the number of new registrants per year has decreased, persons with SUD have been utilizing the needle exchanges more than in the past, especially within the younger generation.[48] Therefore, the conjunction of the SISs with a needle exchange program offers sterile needles that may further reduce the transmission of blood-borne diseases while also providing a space that gives education about the risks surrounding opioid usage and offers various opportunities and support that could potentially guide participants into rehabilitation. It is important to emphasize that the needle exchange program would be paired with the SISs as opposed to needle distribution. The needle exchange program with the SISs would also serve as a means to help clean up the area of needles to prevent wounds and infections caused by unsterile needles.

Narcan Distribution and Education

The partnership of the educative Narcan distribution with a SIS could be considered as an attempt to reduce the number of fatal overdoses in Philadelphia. Narcan is the intranasal form of naloxone. Naloxone is an opioid antagonist that acts on the central nervous system to reverse respiratory depression, the main cause of overdose deaths.[51] Naloxone can enact its effects within 5 minutes upon administration. For patients currently taking high doses of opioids as prescribed for pain, individuals misusing prescription opioids, individuals using illicit opioids such as heroin or fentanyl, health care practitioners, family and friends of people who have an opioid use disorder, and community members who come into contact with people at risk for opioid overdose, knowing how use naloxone and keeping it within reach can save a life.[52]

Moreover, Pennsylvania Act 139, known as “David’s Law,”provides first responders, friends and families access to naloxone in hopes to lead an individual toward the substance abuse treatment that they need.[50] In March 2023, the FDA made Narcan available at drug/pharmacy and grocery stores, as well as online retailers with a suggested retail price of $44.99.[53] Given the federal, state, and insurance involvement, the distribution of Narcan complemented with education and training to SIS participants serves as both a precautionary means of saving themselves from overdosing and preventing others from fatally overdosing.

Narcan distribution further encourages persons with SUD to recognize and seek help. The use of Narcan can further reduce the current Philadelphia healthcare cost of $92,408 per hospitalization with an average length of stay of 7-10 days attributed to overdose.[42]

Counseling for Rehabilitation and Detoxification Done by Individuals in Recovery

The information center can provide avenues that can connect participants to different resources. While healthcare personnel will be available to offer their expertise regarding health, nutrition, and safety, the

information center would primarily be run by people in recovery. Having one-to-one interactions with people in recovery facilitate interpersonal relationships to help guide persons with SUD to other resources available to them. For some, the information center could be their only exposure to the various possibilities and opportunities that can be offered to them such as rehabilitation, detoxification, medication-assisted therapies, grooming services, counseling and more. The SISs may serve as a mediator for someone undergoing the journey through rehabilitation by being the "half-way" point, which could prevent overindulgence after an attempt of abstinence. If a person should revert back to substance abuse, the SIS facilitates a space with medical personnel on hand should emergency care be needed. Furthermore, individuals in recovery are also given a sense of purpose in facilitating conversations and providing encouragement for persons with SUD which is an impetus to remain in recovery.

Early Education

Although the government continues to propose and introduce new initiatives focusing on increased early education for new and future healthcare professionals, the nation as a whole continues to fall short of reaching the educational goal. Looking forward, the integration of healthcare students into the SISs would be paramount in buffering the opioid epidemic. The introduction of healthcare professionals into the SISs would be beneficial for all parties involved.

- Healthcare institutions : The SISs would serve as an opportunity for healthcare institutions to show their continued commitment towards the opioid crisis and towards some of the most underserved populations of our country.
- Students : Involvement early on in their career equips them with the necessary practical experience and much needed skills in dealing with the opioid epidemic, in addition to making them more adept with dealing with the underserved populations.
- SIS facilities : In addition to providing voluntary services to the facility from trained healthcare professionals, it will also help destigmatize the public's perceptions of these sites since the SISs could show the fact that they are also focusing on educating our young health professionals early on in their careers.

This model safe injection facility compounded with the additional services suggested makes the SISs a strong viable option for Philadelphia. Fentanyl/Xylazine screening provides a sharp cognizance for safety by showing persons with SUDs the risks of injecting elicited drugs. From the perspective of the healthcare personnel and students training in the healthcare system, the SIS provides first-hand exposure to the opioid epidemic and first-hand experience in attending to persons with SUDs in wound care services and also in counseling. Equipping young healthcare professionals with the necessary skills in dealing with the opioid crisis will be paramount looking forward, as the opioid crisis continues to worsen. Furthermore, offering Hep-C/HIV screenings is a preventative means of encouraging persons with SUDs to seek treatment early before the progression to the viral latent stages. Logistically, the combination of the needle exchange program with the SISs could help clean the area of needles and reduce the number of blood-borne diseases and skin and soft tissue infections. As a result, these measures could effectively reduce the overall healthcare costs. Having healthcare personnel on hand compounded with educative Narcan distribution may reduce the number of fatal overdoses and hospitalizations. Providing an informational center run by people in recovery provides a safe space for people with SUDs to openly discuss their concerns and seek while also giving those in recovery a sense of purpose and impetus to remain in recovery. Thus, the implementation of the SIS offers various dynamics that could curb the ever-increasing opioid crisis in Philadelphia. Ethically, SISs not only have an impact on individuals and society as a whole, but also have the potential to save thousands of lives.

RECOMMENDATIONS

Considering the aforementioned medical and financial implications, it is of paramount importance that effective strategies are devised to lessen the harm associated with xylazine use. Much like other cities in America, xylazine has taken users, clinicians, and public health officials by surprise, and little is currently known about the substance. This lack of knowledge on the substance leads to a lack of effective treatment and management strategies, and in hopes of improving upon these points, we have provided the following recommendations.

1. As discussed in the Ethical Analysis, the creation of a Safe Injection Site will greatly reduce overdose deaths and provide a number of additional services that will improve the quality of life for people who inject drugs

as well as the City of Philadelphia as a whole.

2. As discussed in the pharmacological and clinical analyses, there is limited research on xylazine's effect on the human body. Improving access to the research already published in addition to performing more studies specifically related to xylazine use in intravenous drug users will allow clinicians and public health officials to more effectively combat and treat the many complications associated with xylazine use in humans. Additionally, transient anemia and hyperglycemia after xylazine administration have been seen in animal models, and more research into these two conditions and their symptoms will improve overdose outcomes. [54]

3. The incorporation and encouragement of traditional nursing interventions like padding, laying patients on flat, irritant free surfaces, and rotating the patients reduces the harms associated with immobility in awkward positions. Such interventions can be used on people who inject drugs, including FAAX, that begin to nod in awkward positions to prevent tissue injury or exacerbate any pre-existing xylazine wounds. [54]

4. The use of screening methods on an individual sample basis and on a population level will better inform users, clinicians, and public health officials on the consumption and adulteration trends in the drug supply. Individual test like immunoassay test strips will assist users and clinicians by providing them with a more specific knowledge on what drugs are about to be or already have been consumed. [54] Wastewater screening will provide public health and other city officials with a more accurate composition of the Philadelphia drug supply. [55]

5.Considering the increasingly common incidence of xylazine in drugs like fentanyl, which is a Schedule I drug under the Controlled Substances Act, properly listing xylazine as a controlled substance must occur. Listing xylazine as a Schedule I drug should allow for more regulation by the federal government and make it more difficult for drug traffickers to purchase.

The acceptance of these recommendations by policy makers and public health officials will hopefully provide modest relief from an increasingly threatening dimension of Philadelphia's opioid epidemic.

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Author Information

Vidhi Mehta, M.D.
Mercy Catholic Medical System, PGY-2
Philadelphia, PA

Peter A. Clark, Ph.D.
John McShain Chair in Ethics, Saint Joseph's University; Director of Institute of Clinical Bioethics, Saint Joseph's University
Philadelphia, PA

Christian Fang
Rowan-Virtua School of Osteopathic Medicine, Rowan University
Stratford, NJ

Shikha Patel
Pharm.D. Candidate, 2025, Saint Joseph's University
Philadelphia, PA

Jenna Szabo
Graduate Assistant, Institute of Clinical Bioethics, Saint Joseph's University
Philadelphia, PA

Aidan Fogarty
Senior Research Fellow, Institute of Clinical Bioethics, Saint Joseph's University
Philadelphia, PA