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MEDETOMIDINE: A WORSENING ILLICIT SUBSTANCE-USE EPIDEMIC?

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Abstract: *For more than a decade, cities struck with substance-use disorder have experienced the brunt of clandestinely adulterated drugs circulating the streets, culminating in the tragic death of over 107,000 individuals by drug-overdose in the United States in 2022. Recently, those cities, particularly Philadelphia, have witnessed a new "wave" of drug-adulterants entering the illicit drug supply. In May 2024, medetomidine, a non-opioid sedative employed in veterinary medicine, was identified as a new drug-contaminant in Philadelphia, with most identified medetomidine being co-detected with either fentanyl or xylazine. Medetomidine's long-term effects on humans remain unknown, as concerns of a worsening illicit substance-use epidemic grow. Given such fears, this article serves to briefly educate readers on the current pharmacological and medical knowledge of medetomidine and its possible ramifications on the illicit substance-use epidemic, to offer recommendations to combat the early spread of the drug, and to ground our recommendations in ethics.*

Keywords: *Medetomidine, dexmedetomidine, overdose, illicit drugs, adulterants, substance-use disorder, harm reduction, Philadelphia.*

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INTRODUCTION

In 2019, 59.277 million (21.4%) of people ages 12 and above in the United States used illegal drugs or misused prescription drugs while 25.4% of illicit drug users developed a drug disorder.[1] The increased prevalence of illicit substance-use was, in turn, accompanied by a rampant increase in drug overdose deaths nationally, peaking at an estimated 111,029 deaths in 2022, then decreasing to 107,543 and 101,026 deaths in 2023 and 2024, respectively.[2] National reports in 2023 attribute 74,702 deaths to opioid-use, 36,251 deaths to psychostimulant-use, and 29,918 deaths to cocaine-use.[2]

In Philadelphia, Pennsylvania, 1,413 overdose deaths (83% involving opioid-overdose and 34% associated with xylazine-laced substances) were reported in 2022, representing an 11% increase in the city's drug overdose deaths from 2021.[3] In the past 4-5 years, illicit drug markets have experienced increasing trends of drug adulteration, as people who use drugs (PWUD) purchase substances laced clandestinely with more perilous and addictive chemicals (e.g. fentanyl laced with xylazine).[4,5] Furthermore, polysubstance-use has been implicated in many drug overdose deaths, as close to 80% of opioid overdose deaths in 2016 involved simultaneous use of non-opioids.[6,7] Non-opioids may exacerbate opioid drugs' symptoms, hence increasing PWUD's risk of suffering a lethal overdose and further aggravating the illicit substance-use crisis.[8]

Substances commonly detected in trace amounts in the illicit drug supply in Philadelphia include fentanyl (a synthetic opioid) and xylazine (a veterinary tranquilizer), which have brought about media attention and public fright in areas afflicted with substance-use disorder (SUD). On May 13, 2024, the Philadelphia Department of Public Health (PDPH) declared the detection of medetomidine, a non-opioid veterinary sedative, in the illicit drug supply for the first time in the city.[9]

Medetomidine in the Illicit Drug Supply

According to the *Center for Forensic Science Research and Education*, medetomidine was first identified in the illicit drug supply in Maryland in July 2022.[10] Often mixed with fentanyl, medetomidine started appearing more sporadically in toxicology reports on specimens collected from patients presenting with apparent opioid overdoses in California, Colorado, Florida, Maryland, Missouri, North Carolina, Ohio, and Pennsylvania during mid-to-late 2023.[11] In April, 2024, the introduction of medetomidine into illicit drug supplies in Philadelphia, PA led to a large-scale outbreak of non-fatal overdoses over the course of three days, affecting over 100 individuals.[12] Less than a month later, illicit drugs adulterated with medetomidine were detected for the first time in Pittsburgh, PA, and Chicago, IL after a spike in non-fatal overdoses.[12] Researchers are still unsure why medetomidine has made its way into the illicit drug market, but some hypothesize that it may be due to the federal government's heightened regulation of scheduled opioids.[13] It is also unclear whether medetomidine is being illegally diverted from veterinary supplies or drug traffickers are synthesizing their own supplies.[10]

As an uncontrolled substance, medetomidine can be ordered from overseas.[14] Internationally, medetomidine has been detected, alongside other central nervous depressants (e.g. benzodiazepines), in opioids in Canadian provinces such as Ontario and British Columbia.[14] As illicit drug markets continue to prosper, local and national concerns worsen. Residents of areas struck with SUD fear the introduction of new illicit drugs, particularly unregulated synthetic ones that are more potent than xylazine, into open-air drug markets.

Therefore, the purpose of this paper is threefold: first, to provide brief medical and pharmacological insights into medetomidine; second, to recommend local and national interventions to minimize the drug's impact on PWUD; and third, to ethically justify implementing our recommendations, considering the current opioid epidemic.

WHAT IS MEDETOMIDINE?

Medetomidine, a non-opioid alpha-2 adrenergic receptor (AR) agonist belonging to the same class of drugs as clonidine and xylazine, has been detected more frequently in toxicological specimen studies and drug overdose-related incidents throughout the United States.[9,15] Medetomidine, like xylazine, is synthetic but is composed of

two chemical compounds: dexmedetomidine and levomedetomidine. Dexmedetomidine is approved for use in humans and is the active ingredient in Precedex ® – an intravenous sedative often used in emergency departments, intensive care units and operation rooms – and other analgesic medications used in veterinary medicine.[16,17] Levomedetomidine, on the other hand, is not approved for human-use and is considered the pharmacologically inactive enantiomer.[18] Aside from pain relief and sedation, medetomidine-use can induce bradycardia, hypotension, hyperglycemia, and hallucinations. When compared to xylazine, medetomidine is about 200-fold more potent, and its effects are noted to last even longer.[9,13]

CASES IN-POINT

Although this paper's focus is on the ramifications of illicit drugs adulterated with medetomidine on PWUD, detailed clinical encounters with PWUD suffering medetomidine toxicity remain limited. However, there exist clinical cases of patients receiving disproportionately high doses of dexmedetomidine, and subsequently experiencing cardiovascular, metabolic, and neurological symptoms. Such sample cases, albeit limited to clinical settings and managed quickly, underline the harm that PWUD may incur by unknowingly consuming unregulated amounts of medetomidine on the streets.

Case 1: A 68-year-old male accidentally received 200 mcg of dexmedetomidine intravenously. Within minutes, the patient became drowsy but arousable. Shortly after, his speech slurred, and he became unresponsive to stimuli. The procedure was halted, and the patient was transferred to the emergency department for observation. Despite fasting before the procedure, he exhibited hyperglycemia (192.6 mg/dL), likely related to dexmedetomidine's complex effects on glucose metabolism through alpha-2 inhibition and cortisol release. His vital signs remained relatively stable, with his lowest blood pressure of 101/60 mmHg six hours post-infusion and a heart rate of 51 beats per minute.[19]

Case 2: A 29-year-old male (214 kg) with diabetes mellitus, recovering post-surgery, was switched from propofol to dexmedetomidine to facilitate ventilator weaning. The infusion was erroneously set at 0.5 µg/kg/min—60 times higher than intended—resulting in an excess of 1600 µg of dexmedetomidine. The error was discovered the following morning when the patient was unresponsive to sternal rub. Once the infusion rate was corrected, the patient regained consciousness within an hour and was extubated the same day.[20]

Case 3: A 23-month-old (12 kg) male received a dexmedetomidine infusion at 0.2 µg/kg/min, instead of the intended 0.2 µg/kg/hour. The overdose caused a biphasic response, beginning with hypertension (130/84 mmHg) and peaking at 170/100 mmHg and 170 bpm. After the infusion rate was reduced, the patient's vitals stabilized, and upon cessation, blood pressure dropped to 80/30 mmHg.[21]

PHARMACOLOGICAL AND MEDICAL PERSPECTIVES

Alpha-2 Adrenergic Agonists: Brief Description & Mode of Action

Alpha-2 adrenergic agonists are pharmacological agents that have been used in human and veterinary medicines for decades. Common alpha-2 adrenergic agonists include clonidine, tizanidine, medetomidine, xylazine, guanabenz, and guanfacine. In human medicine, some of these agents can be used to treat various indications, including hypertension, long-term substance abuse, pain management, manic episodes, and attention-deficit disorders.[22,23] In veterinary medicine, the most common agents used are xylazine, medetomidine, and dexmedetomidine, all three of which serve the purposes of sedation, analgesia, anxiolysis, and muscle relaxation—most effectively in dogs and cats.[24,25]

In humans, there are three subtypes of alpha-2 adrenoreceptors (α^{2A}, α^{2B}, and α^{2C}) that are distributed throughout various cell types and elicit unique responses respective to their bodily location upon binding of an alpha-2 adrenergic agonist. Each alpha-2 receptor subtype can elicit bodily effects at varying intensities and time periods. Upon its consumption, the medicinal agent will travel to and bind the alpha-2 adrenergic receptor subtypes that it has the strongest affinity for. After binding, a chain reaction takes place as the coupled G-protein signals a response to connecting effector mechanisms. In the case of the alpha-2A receptor, the agent's binding leads to

activation of the L-type calcium channel in the locus coeruleus (a structure in the brainstem), thereby enhancing sympatholytic side-effects.[23]

Pharmacology of Medetomidine & Comparison to Clonidine

Given its popular use in veterinary medicine, much of medetomidine's pharmacokinetics has been understood from veterinary clinical studies. When injected intramuscularly into rats, racemic medetomidine is absorbed fast as peak plasma levels are typically attained in 10-30 minutes. In the blood plasma, 85% of medetomidine is protein-bound. Furthermore, peak medetomidine levels in the brain reached in 15-20 minutes post-administration are five times greater than peak plasma levels. Both "D" and "L" enantiomers are metabolized by hepatic monooxygenases, and the resulting products can be oxidized or conjugated with glucuronic acid, which helps eliminate the drug from the body. About 41% of the drug is eliminated in the urine and 18% in the feces, whereas 5% remains unmetabolized. The half-life of medetomidine is 1.6 hours, and the duration of sedation is 2-3 hours.[13,26] Overall, the quick absorption, distribution, metabolism, and elimination of the drug in animals may mimic the drug's metabolic fate in humans.

Currently, dexmedetomidine and clonidine are the only alpha-2 adrenoreceptor agonists approved for use in humans. Unlike medetomidine, clonidine— an alpha-2 adrenoreceptor agonist— is FDA-approved for use in humans, but only for the treatment of hypertension.[27] Clonidine exhibits an alpha-2/alpha-1 receptor-binding ratio of 220:1 as compared to an alpha-2/alpha-1 receptor-binding ratio of 1,620:1 for medetomidine. Thus, medetomidine has a six-fold stronger affinity to alpha-2/alpha-1 receptors in-vivo and can elicit stronger and longer pharmacological effects in humans than clonidine can.[26] Moreover, medetomidine's sedation effects may be significantly stronger than those of clonidine, hence posing an increased risk of respiratory depression.

Unlike dexmedetomidine, which is FDA-approved for use in both humans and animals, medetomidine is approved for use only in veterinary medicine. With that said, the therapeutic effects of medetomidine-use in humans appear most similar to the more commonly used clonidine and dexmedetomidine.[13,26]

Physiological Effects of Medetomidine-consumption in Humans

Medetomidine has been studied for its physiological effects in humans, primarily through its more commonly used enantiomer, dexmedetomidine. The physiological effects of medetomidine in humans include sedation, cardiovascular changes, and alterations in metabolic parameters.

- Sedation and Analgesia: Medetomidine induces dose-dependent sedation and has been shown to reduce the affective-motivational component of pain without significantly affecting pain thresholds.[28] Dexmedetomidine, the active chemical compound in medetomidine, also produces significant sedation and mild analgesia without causing respiratory depression at clinically relevant doses.[29,30,31]
- Cardiovascular Effects: Medetomidine administration results in a dose-dependent decrease in blood pressure and heart rate.[28] Dexmedetomidine has been shown to cause an initial transient increase, followed by a sustained decrease, in mean arterial blood pressure, along with reductions in heart rate and cardiac output.[32,33] These hemodynamic changes are associated with a decrease in plasma catecholamine levels.[32,33]
- Metabolic Effects: Medetomidine and dexmedetomidine can affect metabolic parameters. Dexmedetomidine has been shown to increase blood glucose levels and alter lipid profiles (e.g. decreasing levels of ketone bodies).[34] Additionally, dexmedetomidine can increase oxygen consumption and decrease carbon dioxide production transiently.[29]
- Respiratory Effects: While medetomidine does not significantly affect respiratory rate or oxygen saturation at sedative doses, higher doses of dexmedetomidine can lead to a decrease in minute ventilation and an increase in PaCO2.[29,31]

Potency & Effects of Medetomidine When Mixed With Opioids or Other Sedatives

Medetomidine, when combined with opioids or other sedatives, exhibits enhanced sedative and analgesic effects, but also poses risks of significant cardiorespiratory interactions.

- Sedative and Analgesic Effects: Combining medetomidine with opioids such as butorphanol or hydromorphone results in more profound and prolonged sedation and analgesia compared to medetomidine alone. For instance, medetomidine-hydromorphone and medetomidine-butorphanol combinations provide longer sedation and better analgesia, as evidenced by studies in dogs.[35] Similarly, medetomidine combined with midazolam or butorphanol enhances sedation, with medetomidine-butorphanol showing superior clinical sedation.[36]
- Metabolic and Neurohormonal Effects: Medetomidine can mitigate stress-related neurohormonal and metabolic changes induced by opioids or ketamine, such as increased plasma epinephrine, cortisol, and glucose concentrations. However, hyperglycemia may still occur.[37]
- Cardiorespiratory Effects: The combination of medetomidine with opioids or other sedatives can lead to significant cardiorespiratory changes. These include increased systemic and pulmonary vascular resistance, elevated pulmonary capillary wedge pressure, and decreased heart rate and cardiac output.[35] Additionally, combinations such as medetomidine-butorphanol or medetomidine-ketamine can result in higher PaCO2 and lower arterial pH and PaO2 compared to medetomidine alone.[38]

Indications of Medetomidine Toxicity

Medetomidine toxicity in humans can manifest through several physiological effects, related primarily to its potent alpha-2 adrenoceptor agonist activity, and which necessitate careful monitoring and appropriate dose adjustments to mitigate the risk of severe adverse outcomes. The key indications of medetomidine toxicity include:

- Bradycardia**:** Medetomidine can cause significant bradycardia, which may be exacerbated by vagal stimuli. This effect is dose-dependent and can be severe, requiring intervention with anticholinergic agents such as glycopyrrolate or atropine.[39]
- Hypotension**:** Hypotension is another common manifestation, particularly in patients with hypovolemia, diabetes mellitus, chronic hypertension, or in elderly patients. Medetomidine-induced hypotension can be more pronounced due to the decreased sympathetic nervous system activity.[39]
- Transient Hypertension**:** An initial transient hypertension may occur due to peripheral vasoconstriction, especially during the loading dose phase.[39]
- Respiratory Depression**:** Although medetomidine typically does not cause significant respiratory depression at therapeutic doses, higher doses or combinations with other sedatives can lead to increased PaCO2 and decreased arterial pH and PaO2, indicating respiratory compromise.[38]
- Sedation**:** Profound sedation is a hallmark of medetomidine toxicity, which can progress to unresponsiveness at higher doses. This sedation is dose-dependent and can last for several hours.[29]
- Cognitive Impairment**:** High doses of medetomidine can impair memory and cognitive function, as evidenced by decreased recall and recognition.[33]
- Hyperglycemia**:** Medetomidine can induce hyperglycemia, which is a common metabolic side-effect due to its impact on glucose metabolism.[39]

Medetomidine's Effects on Wound Care

Provided medetomidine has exceeded xylazine in prevalence in illicit drugs in Philadelphia, many are concerned with how the more potent medetomidine may exacerbate xylazine-induced skin infections, abscesses, and skin ulcers in PWUD. Medical literature indicates that dexmedetomidine decreases skin perfusion even at low doses,[40] which suggests that medetomidine can potentially worsen wound healing due to its vasoconstrictive properties. The decrease in skin perfusion can impair the delivery of oxygen and nutrients to the wound site, thereby delaying the healing process and potentially worsening the wound.

However, there is no direct evidence in the medical literature to suggest that medetomidine or dexmedetomidine causes skin ulcerations. The primary concern with these agents is their impact on perfusion, which can indirectly affect wound healing but does not directly cause ulcerations.

RECOMMENDATIONS

With the current disquieting morbidity rates among PWUD in Philadelphia, a rapid national response to adulterants introduced newly into the illicit drug supply is crucial for abating the severe physical, mental, financial, and social ramifications on PWUD, their respective communities, and local healthcare facilities. In addition to the instructions included in PDPH's public health alert issued in May 2024, the following measures may be implemented or endorsed by city officials.

1. **Promoting research:** Given the veterinary background of medetomidine-use, there's minimal research into the drug's toxicity, metabolism, and physiological effects in humans. However, current evidence suggests that medetomidine's effects may compound when mixed with opioids, as has been detected not only in Philadelphia's illicit drug supply, but also in that of other U.S. cities and even countries. A proper understanding of medetomidine's properties and effects when administered to humans is imperative for adequate local and national responses. One such response may be drug scheduling. Indicated as an analgesic and sedative for small and large animals, medetomidine is currently not a scheduled drug. Per the Drug Enforcement Agency (DEA), a drug must first show potential for abuse, potential for causing dependence, risk to public health, or other characteristics as specified by the DEA before being considered for scheduling.[41] However, the limited knowledge of medetomidine's effects on PWUD and its in-vivo pharmacological properties delay investigations into whether the drug satisfies the criteria for a certain schedule. Therefore, further pharmacological and clinical research into medetomidine's properties is essential to actualizing timely and appropriate national responses.
2. **Educating PWUD and making immunoassay test strips more accessible:** Medetomidine has been introduced as an adulterant, alongside fentanyl and xylazine, into the illicit drug supply. Just as for xylazine and fentanyl, medetomidine may be tested for in a drug sample using immunoassay test strips. Research findings showed that the use of fentanyl test strips among PWUD for drug checking a supply leads to positive drug consumption behavior such as discarding the supply, requesting from a friend to be present during the drug consumption, keeping naloxone at disposal more often, and even offering test strips to friends who are prone to inadvertently consuming fentanyl.[42] Although such findings are yet to be reported for the use of medetomidine test strips, following similar approaches to promoting fentanyl test-strip use (e.g. educating patients adequately and comprehensively on the dangers and side effects of medetomidine-use) may yield similarly effective outcomes as in the case of PWUD using fentanyl-test strips. Alongside education, making medetomidine test strips more accessible or even distributing them at health fairs aimed at serving PWUD may help further educate PWUD on the dangers of consuming medetomidine-adulterated drugs.
3. **Prioritizing wound care**: As a vasoconstrictor, medetomidine may reduce or impair the wound-healing process. Therefore, effective harm-reduction approaches focused on wound management must be endorsed. The availability and accessibility of wound-care services must be given priority. Effective wound-care management prevents bacterial infections and other wound-related complications that may not only harm PWUD but also incur further expenses on the healthcare system. Testimonies from employees at clinics in Kensington suggest that many PWUD are unaware of the locations of wound-care centers or low-barrier clinics close to them. Although such locations have been published on the internet by the PDPH, many PWUD lack access to the internet. Therefore, there is a need for more community-engaged initiatives such as providing PWUD in Kensington with flyers listing the locations of nearby wound-care clinics.
4. **Considering safe injection sites:** A safe injection site (SIS), which is a safe space for PWUD to consume drugs under medical supervision, may also be a viable option for addressing not only the newly witnessed prevalence of medetomidine in the illicit drug supply in Philadelphia, but also possibly mitigating the negative impacts other new adulterants may bring about in the future. *Insite*, an SIS in Vancouver, Canada, and *Onpoint*, an SIS in New York City, United States, are two prime examples of how SISs can reduce overdose risk and drug mortality.[43,44]

ETHICAL PERSPECTIVES

With the above recommendations aimed at empowering the national arsenal against the changes in types of adulterants introduced into illicit drugs, these recommendations serve as bases for continued advocacy for harm reduction approaches. In fact, harm reduction becomes paramount when considering that medetomidine is a continuation of a dynamic drug-adulteration trend that changes in response to drug scheduling and regulatory oversight of synthetic adulterants that have already pervaded the illicit supply.

Harm reduction is an approach focused on minimizing the harms associated with drug abuse and yields both medical and ethical impacts on PWUD and society as a whole.[45,46] Harm reduction approaches accept PWUD as they are, while also tailoring their treatments to fit their needs.[45] 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 PWUD and the communities in which they live to assist them in reducing attendant harm.*
- *Ensures that PWUD 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 PWUD as the primary agents of reducing harms associated with 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*[45]

Within that context, this paper's recommendations fall under harm reduction measures motivated by and intended to safeguard PWUD exposed to medetomidine—a drug whose long-term impacts remain unknown.

Safe Injection Sites as a Harm Reduction Measure

Although this paper's focus is on medetomidine, data collected by PDPH suggests a tendency for medetomidine to be co-laced with xylazine and/or fentanyl for attaining increased drug potency.[30] Therefore, addressing medetomidine would go together with addressing fentanyl and xylazine consumption, requiring similar initiatives. Given current uncertainty about the pharmacological properties and physiological side-effects of medetomidine in humans, especially when mixed clandestinely with other illicit opioids (e.g. fentanyl) and non-opioids (e.g. xylazine), there is a need for harm reduction measures for protecting PWUD against possibly more potent drug mixtures. A safe injection site (SIS) is one such measure.

An SIS can offer people living with substance-use disorder (SUD) a safe environment to inject drugs, thereby potentially serving as a harm reduction agent. Many individuals who overdose on laced substances (e.g. heroin laced with fentanyl, xylazine, and/or medetomidine) do not receive the life-saving medical treatments in time; therefore, increasing PWUD's access to SIS can possibly prevent many evitable deaths. If we, as a society, value human life as sacred, we must work toward preventing such deaths. SIS programs (e.g. *Insite* in Vancouver and *OnPoint* in New York City) that are overseen by trained medical professionals, might function as a viable alternative to address the growing drug addiction epidemic and save thousands of lives.[47,48] In fact, SISs have been shown to decrease drug abuse, disease, and overdose-induced mortality rates in areas in their vicinities.[49]

A proposed SIS would offer fentanyl, xylazine and medetomidine test strips and wound care, in addition to Hepatitis-C/HIV screenings, needle exchange programs, naloxone distribution, and education and counseling on recovery.

a. Medetomidine, Fentanyl, and Xylazine Test-strips:
In 2022, over 80% of overdose deaths in Philadelphia involved opioids, particularly fentanyl.[50] However, a pilot study conducted by researchers at Johns Hopkins Bloomberg School of Public Health and Rhode Island Hospital showed that use of $1 immunoassay fentanyl testing strips may avert overdoses. PWUD whose test strips indicated the presence of fentanyl in the supply were likely to use less, consume slower, and/or ask for other people to stay around as they consume the drugs.[41] As PWUD knew their drugs were adulterated, they became cognizant of the associated dangers and acted relatively more cautiously. Although limited to fentanyl, these findings may translate to the use of medetomidine test strips, as long as PWUD are well-educated on the suspected dangers of medetomidine-use. In other words, increasing medetomidine test strip accessibility may avert preventable overdoses and would align with the abovementioned harm reduction principles.

b. Wound Care:
Given that medetomidine-laced drugs may be injected intravenously, blood-borne diseases and infections (e.g. cellulitis, staphylococcus infections, necrotizing fasciitis, and many more) may be transmitted through or caused by use of unsterile needles, high frequency of injections, and subcutaneous injections.[51] Improper injection techniques may also cause different wounds. Furthermore, current data suggests that medetomidine may impair the healing process of xylazine-associated skin wounds and ulcers, for dexmedetomidine (even at low doses) can decrease skin perfusion, which is necessary for adequate wound healing.[52] The availability of wound-care services, offered by healthcare professionals, would help reduce the spread and progression of secondary infections, thereby sparing PWUD further complications that may require urgent hospitalizations. Increased wound care is also linked to reduced healthcare costs attributed to hospital admissions caused by infected open wounds. In fact, an SIS in Philadelphia is expected to save $1,512,356 – $1,868,205 in healthcare spending.[53]

c. Hepatitis-C/ HIV Screenings:
Given that medetomidine is often found with xylazine and/or fentanyl, which may be injected intravenously or intramuscularly, there is concern about PWUD encountering sexually transmitted diseases, such as Hepatitis C and Human Immunodeficiency virus (HIV), through sharing contaminated needles. In fact, the unsafe sharing of injection needles led to 10% of newly reported HIV infections in the United States in 2018.[54] 382 Philadelphia residents tested positive for HIV in 2022.[55] Moreover, about 25,000 and 53,000 Philadelphia residents suffered Hepatitis B and C infections, respectively, in 2021.[56] However, studies suggest that 75-85% of Hepatitis C infections, which are risk factors for liver cirrhosis, develop into a chronic condition.[57] From a perspective of proper resource allocation, untimely detection of HIV or Hepatitis C may incur significant costs on the healthcare systems. Most recent estimates of lifetime HIV treatment costs for PWUD with an average diagnosis delay of three years range between $420,285 and $1,079,999.[58] Moreover, 12-week Hepatitis C treatment expenses may reach $95,000 in some cases.[59] Therefore, Hepatitis-C and HIV screenings may help with timely diagnosis of either disease, sparing patients preventable pain that may incentivize them to consume more drugs and also saving hundreds of thousands of dollars in healthcare costs.

d. Needle Exchange Programs:
Alongside Hepatitis-C and HIV screenings, needle exchange programs have shown effectiveness in minimizing harms associated with PWUD sharing needles. Unlike a needle distribution program, a needle exchange program (NEP) allows PWUD to exchange/properly dispose of unclean needles in return for sterile ones while receiving education on the risks and complications associated with needle sharing. A study of trends among PWUD participating in a NEP in Philadelphia showed a reduction in the incidences

of HIV transmission through needle sharing from 46% in 1992 to 5.4% in 2014.[60] Furthermore, PWUD who participate regularly in NEPs are about five times more likely to enter SUD treatment and three times more likely to report reductions or stoppage of injections than PWUD who don't resort to NEPs.[61] Thus, incorporating NEPs into SISs would offer PWUD sterile needles, thereby reducing the transmission of blood-borne disease while also potentially guiding participants into rehabilitation.

e. Naloxone Distribution and Education:
Naloxone is an opioid antagonist that reverses respiratory depression, but medetomidine is a non-opioid and thus a medetomidine-induced overdose cannot be reversed using naloxone. The PDPH reported medetomidine being introduced into drug mixtures containing opioids (e.g. fentanyl).[13,62] Fentanyl-induced overdoses can be reverted using naloxone.[63] Therefore, naloxone administration is advised in cases of overdose, considering it is impossible to identify the overdose-inducing substance on the spot.[62] Moreover, Pennsylvania's Act 139, also known as "David's Law", grants first responders, family members and friends access to and authorization to administer naloxone to individuals in an overdose. In return, PA act 139 offers civil, criminal, and professional immunity for the medical professionals who prescribe naloxone and the individuals who administer it.[64] When complemented with instructions on usage, naloxone distribution at SISs would reduce overdose deaths, as one study reported bystanders witnessing 44% of opioid overdose deaths in the United States in 2016.[65] Had they been carrying naloxone, those bystanders may have reversed many preventable overdoses.

On-site cardio-pulmonary resuscitation (CPR) training is also important, given that medetomidine toxicity signs include severe bradycardia that may transition to a pulseless state.[39] In such case, CPR would maintain proper blood flow until emergency medical personnel arrive and appropriate medication(s) (e.g. atropine) is administered. Most importantly, CPR complements naloxone administration. Nasally administered naloxone requires 2-3 minutes to take effect, but a person in severe respiratory depression may have entered cardiac arrest.[66] Therefore, CPR is an attempt to maintain blood flow to the brain until the overdose is reversed.

f. Rehabilitation and Detoxification Counseling by Individuals in Recovery:
Although the prevalence of medetomidine constitutes a public health concern, the root problem remains substance-use disorders. Dedicated educational and counseling services at SISs would connect PWUD interested in rehabilitation with needed resources. The counselors would include healthcare personnel capable of articulating physiological, nutritional, and other medical changes experienced during rehabilitation, and sober individuals capable of offering a personal insight into the rehabilitation journey. Engaging with individuals in recovery may motivate PWUD to pursue rehabilitation. After all, PWUD are likely to view people in recovery as more credible, having lived through similar experiences, and sober individuals can relate to and empathize with PWUD, leading to better counseling. Moreover, counseling services may also drive PWUD wishing to enter recovery away from relapsing.[67]

Overall, the holistic and complementary services offered at SISs have the potential to not only encourage PWUD to seek assistance, thereby minimizing physical harm on PWUD, but also minimize social harms associated with the substance-use epidemic.[68] The minimized physical harms include more positive injection behaviors (e.g. drug filtering, slower injections, and frequency of injections), diminished spread of diseases (e.g. HIV and Hepatitis C) mediated through PWUD sharing contaminated needles, and better treatment of wound complications associated with inadequate access to proper wound care services.[60,61,68] The minimized social harms include, but are not limited to, safer syringe disposals, a decrease in public intravenous drug use and drastic reductions in syringe tips scattered throughout neighborhoods.[68,69,70] Data also suggests that SISs are not associated with increases in public disorder and crime rates.[70,71] Such changes would yield health and safety benefits to both PWUD and people living in the neighborhoods surrounding the SIS.[68] Moreover, SISs may significantly increase PWUD's access to substance-use treatment, which is significant considering the strong emphasis SIS personnel place on educating PWUD on rehabilitation and the hazards of continued substance-use.[70]

Given the mentioned benefits, the proposed SIS would offer comprehensive care that aligns with the principles of harm reduction theory and which may prove effective in minimizing the threats of drug adulterants such as medetomidine that have become part of a years-long trend of drug adulteration—one that may continue to worsen.

Further Research is Imperative for Effective Prevention Strategies

In 2022, over two-thirds (68%) of the reported 107,081 drug overdose deaths in the United States involved synthetic opioids other than methadone, mainly illicit fentanyl.[72] Xylazine, a non-opioid sedative not approved for human use and with no known antidote, has and continues to be detected in illicitly manufactured fentanyl (IMF) in the U.S. drug supply and IMF-laced supplies linked to overdose deaths.[72] Xylazine and fentanyl laced substances have and continue to be problematic, inflicting detrimental harm onto PWUD in Kensington and across the country. Yielding a pronounced sympatholytic effect on PWUD, xylazine further exacerbated the drug epidemic, with its chronic use possibly causing severe withdrawal symptoms (if stopped abruptly) and skin ulcerations.[72] Now, medetomidine, whose potency is about 200 times higher than that of xylazine, raises similar concerns.[44] Medetomidine's pharmacokinetics have been understood only from veterinary clinical studies, but studies suggest that it exhibits enhanced sedative and analgesic effects when combined with opioids or other sedatives, thereby raising the risks of significant cardiorespiratory interactions.[35] Bearing this in mind, further clinical research into medetomidine's toxicity, metabolism, and physiological effects on humans is vital for implementing national prevention strategies that can mitigate the possible harms PWUD may suffer because of uncontrolled medetomidine-consumption.

CONCLUSION

In brief, medetomidine has joined xylazine as a prevalent alpha-2 agonist adulterant circulating in the illicit drug supply in Philadelphia since its first detection in May 2024. With one of its two constituent chemical compounds being approved for use for patient sedation in emergency rooms, medetomidine constitutes a threat to public health and the safety of PWUD. Medetomidine's current pharmacological properties in humans remain understudied and most inferences are derived from veterinary and/or dexmedetomidine studies. Exhibiting higher potency and specificity than xylazine, medetomidine, when consumed in unregulated doses, has been linked to cardiovascular effects such as bradycardia and transient fluctuations in arterial blood pressure, respiratory effects such as higher carbon dioxide pressure, and metabolic effects, namely hyperglycemia, in addition to many more. Although xylazine is most notorious for its resultant ulcerations, the more potent medetomidine has not been shown to directly cause ulcerations but may impair the healing process.

Provided with these facts, harm reduction theory comes into play, supporting the endorsement of approaches that focus on minimizing harm incurred on PWUD by the illicit substance-use epidemic. Therefore, we recommend conducting further research into the pharmacokinetics and pharmacodynamics of medetomidine in humans, educating PWUD, and supporting harm reduction practices such as making medetomidine immunoassay test strips and wound care services more accessible. An SIS is another harm reduction approach that merits consideration given its reported benefits on PWUD and surrounding communities. These recommendations are grounded in an obligation for immediate action to spare PWUD the possible harms of increasingly prevalent medetomidine.

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