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Providers' knowledge and perception of xylazine in the unregulated drug supply: a sequential explanatory mixed-methods study

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Abstract

Background Xylazine is increasingly prevalent in the unregulated opioid supply in the United States. Exposure to this adulterant can lead to significant harm, including prolonged sedation and necrotic wounds. In the absence of literature describing healthcare providers' experiences with treating patients who have been exposed to xylazine, we aimed to explore what gaps must be addressed to improve healthcare education and best practices.

Methods From October 2023 to February 2024, we conducted a sequential explanatory mixed-methods study, with (1) a quantitative survey phase utilizing convenience sampling of healthcare providers treating patients in Connecticut and (2) a qualitative semi-structured interview phase utilizing purposive sampling of providers with experience treating patients with xylazine exposure. Summary statistics from the survey were tabulated; interview transcripts were analyzed using thematic analysis.

Results Seventy-eight eligible healthcare providers participated in our survey. Most participants had heard of xylazine (n = 69, 95.8%) and had some knowledge about this adulterant; however, fewer reported seeing one or more patients exposed to xylazine (n = 46, 59.8%). After sampling from this subgroup, we conducted fifteen in-depth interviews. This qualitative phase revealed five themes: (1) while xylazine is novel and of concern, this is not necessarily exceptional (i.e., there are other emerging issues for patients who use drugs); (2) participants perceived that xylazine was increasingly prevalent in the drug supply, even if they were not necessarily seeing more patients with xylazine-related outcomes (XROs); (3) patients primarily presented with non-XROs, making it difficult to know when conversations about xylazine were appropriate; (4) patients with XROs may experience issues accessing healthcare; (5) providers and their patients are learning together about how to minimize XROs and reduce the sense of helplessness in the face of a novel adulterant.

Conclusions Xylazine-specific education for healthcare providers is currently insufficient. Improving this education, as well as resources (e.g., drug checking technologies) and data (e.g., research on prevention and treatment of XROs), is crucial to improve care for patients who use drugs.

Keywords Harm Reduction, Xylazine, Fentanyl

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Background

Across the United States (US), the overdose crisis continues to contribute substantially to premature morbidity and mortality. To exacerbate this crisis, xylazine, a veterinary tranquilizer not approved for use in humans, has emerged as a novel adulterant in the unregulated drug supply and is found almost exclusively in fentanyl [1–7]. As an α-2 adrenergic receptor agonist, xylazine's toxidrome can lead to many serious medical complications, including prolonged sedation, severe hypotension, decreased heart rate, and respiratory depression [2, 4, 8–10]. Further, exposure to xylazine can induce large necrotic wounds that are difficult to manage for people who use drugs (PWUD) and healthcare providers alike [9, 11–14]. In response, the Office of National Drug Control Policy declared xylazine-contaminated fentanyl an emerging threat to the US in April 2023 [15].

Xylazine was first recognized as an adulterant in the unregulated drug supply in the early 2000's in Puerto Rico [4, 8, 16, 17]. After falling off the radar for nearly two decades, xylazine again emerged in post-mortem toxicology and drug seizure data in the Northeastern US before spreading south- and westward [1, 18, 19]. In Connecticut specifically, xylazine is *exclusively* found in combination with fentanyl in overdose mortality data [20]. 2019 marked the first year with more than one reported xylazine and fentanyl combination overdose death (n = 71) in Connecticut [20, 21]. This number has been on the rise; in 2022 alone, almost 25% of overdose deaths involved a combination of xylazine and fentanyl (n = 353) [20].

Given the recent emergence and rise of xylazine prevalence in the drug supply in Connecticut, little information about how to mitigate harms from xylazine exposure is readily available for PWUD and providers [9, 21]. Funded through the Medical Staff Fund at Yale New Haven Hospital, this study was designed to explore Connecticut-based healthcare providers' knowledge and perceptions of xylazine exposure to determine key gaps in education for providers and inform medical best practices as they relate to xylazine exposure and associated complications among patients who use drugs. This information was collected to inform the development of targeted medical education for providers about xylazine and the impacts of xylazine exposure.

Methods

Recruitment procedures, study sample, and human subjects protections

This sequential explanatory mixed-methods study of Connecticut-based healthcare providers was conducted in two phases: a quantitative survey followed by qualitative interviews. Yale's Institutional Review Board deemed this study exempt from human subjects review.

Convenience sampling was utilized to recruit a minimum target of 50 study participants for the quantitative phase. Healthcare providers (e.g., MD, DO, RN, etc.) practicing at hospitals, community healthcare centers, harm reduction organizations, and other care settings around Connecticut were informed of this study through medical listservs, word-of-mouth, and social media. All potential participants were provided with information about this study at the beginning of the survey and completion of the survey was accepted as consent to participate. No compensation was awarded for this quantitative phase.

Subsequently, purposive sampling was utilized to recruit participants for the qualitative phase based on select responses to the survey administered during the quantitative phase, including (a) interest in a follow-up interview, and (b) experience treating patients with confirmed or suspected xylazine exposure. Potential participants were contacted for follow-up over email to verify interest in and availability for the interview. We aimed to interview 15 participants during this phase, based on our previous work, with intent to establish the final sample size through discussion of thematic saturation. Prior to interviews, participants were provided an information sheet and consent form via email; these forms described the purpose and procedures of the study, their rights as participants, confidentiality measures, and potential risk. Participants had the option to have the documents verbally reviewed with them by a member of the study team and were given the opportunity to ask questions. Verbal consent to be interviewed and for recording the interview was obtained prior to beginning the qualitative phase and all participants were advised on their right to terminate participation at any time. Participants received a $30 electronic gift card for their time and expertise upon completion of the interview.

Instrument development and data collection

The quantitative phase of this study utilized REDCap (Research Electronic Data Capture, hosted at Yale University, Version 14.0.27) to facilitate a survey composed of 37 questions (Supplement 1). The survey included questions on (a) providers' medical background, (b) experience treating patients with xylazine exposure, (c) a modified Harm Reduction Acceptability Scale, [22] (d) xylazine knowledge, (e) confidence in medical care for xylazine-related outcomes (XROs), (f) demographic information, and (g) interest in a follow-up interview. The survey was designed to take participants 10–15 min to complete. The qualitative phase comprised one-on-one semi-structured interviews, conducted over the teleconferencing software platform, Zoom, to best accommodate the participants' schedules. The 10-question interview

guide, designed to take approximately 30 min, covered (a) medical experience, (b) xylazine knowledge, (c) perception of xylazine, and (d) education on xylazine (Supplement 2).

Data analysis

For the quantitative phase, summary statistics were tabulated for key demographic information, xylazine knowledge and perception, and harm reduction acceptance. All quantitative data analysis was conducted using Microsoft Excel and R (R Core Team, Version 4.2.2,). For the qualitative phase, interview recordings were transcribed using Trint software and verified for accuracy by the first author (K.H.). Transcripts were entered into NVivo software (QSR International, Version 1.7.1) to facilitate thematic analysis [23]. A codebook with both inductive and deductive codes drawn from the interview guide and existing literature (i.e., "Patient Care Experiences" and "Lack of Supplies") was developed by K.H.. Subsequently, the codebook was discussed among the full study team, improved iteratively, and applied to all transcripts. Themes were discussed with the study team. Pseudonyms for respondents were created for the qualitative analysis presented below to preserve participant confidentiality.

Results

Survey participant characteristics

From October 5, 2023, to January 24, 2024, n = 83 people expressed interest and began the online survey. After screening, n = 78 respondents were eligible to participate. Table 1 provides the frequency and percentage of select characteristics of survey participants. The mean age of providers was 40.6 years (SD = 12.0), and most participants were White (n = 55, 70.5%) and non-Hispanic (n = 66, 94.3%). Seventy-eight percent of providers were medical doctors, with internal medicine (n = 37, 47.4%) and addiction medicine (n = 27, 34.6%) being the most represented specialties. The mean number of years of experience that providers had treating patients with substance use or substance use disorder was 8.2 (SD = 9.4). Based on a modified Harm Reduction Acceptability Scale, [22] most providers who answered these questions expressed favorable attitudes towards harm reduction (n = 70, 97.2%).

Table 1 Select characteristics of providers participating in quantitative survey phase (n = 78)

Characteristics	Frequency	%
Age (n = 66)		
Mean (SD)	40.9	12.0
*Race**		
White	55	70.5
Asian	9	11.5
Other Race	7	9.0
Black or African American	3	3.8
Ethnicity (n = 70)		
Not Hispanic or Latino/a/x	66	94.3
Hispanic or latino/a/x	4	5.7
*Degree**		
Doctor of Medicine (MD)	61	78.2
Nurse Practitioner (NP)	7	9.0
Doctor of Osteopathic Medicine (DO)	5	6.4
Master of Public Health (MPH)	5	6.4
Physician Assistant (PA)	4	5.1
Doctor of Philosophy (PhD)	4	5.1
Registered Nurse (RN)	3	3.8
Master of Science (MS)	3	3.8
*Specialty**		
Internal medicine	37	47.4
Addiction medicine	27	34.6
Emergency medicine	14	18.0
Infectious disease	9	11.5
Psychiatry	7	9.0
Other**	6	7.7
Addiction psychiatry	3	3.8
Dermatology	3	3.8
Pediatrics	2	2.6
Years treating patients with SU/SUD (n = 71)		
Mean (SD)	8.2	9.4
*Harm reduction acceptance (n = 72)****		
Favorable attitude towards harm reduction	70	97.2
Favorable attitude towards abstinence	2	2.8

SU/SUD Substance Use/Substance Use Disorder

*Will not sum to 100%, as providers were able to select multiple choices

**Includes Opthalmology, Rheumatology, Family Medicine, Anesthesia, and HIV

***Our modified Harm Reduction Acceptability scale contained 13 items in which participants indicated their level of agreement for each item on a scale of 1 (strongly agree) to 5 (strong disagree). Some questions are reverse scored. A mean score of less than 3 suggests a favorable attitude toward harm reduction. A mean score greater than three suggests a favorable attitude towards abstinence

Findings from the quantitative phase

Table 2 provides the frequency and percentage of providers' responses to key survey items.

Providers' awareness and knowledge of xylazine and XROs

Most providers had previously heard of xylazine (n = 69, 95.8%) before taking the survey. The majority of respondents knew that (a) xylazine exposure could lead to severe necrotic wounds (n = 68, 94.4%), (b) xylazine is not FDA-approved for use in humans (n = 72, 100%), (c) naloxone cannot reverse a xylazine overdose (n = 69, 95.8%), and (d) xylazine is added to fentanyl to prolong the prolong the opioid/narcotic effect of the fentanyl (n = 67, 93.1%). A smaller proportion of providers believed that xylazine

Table 2 Providers' awareness of and knowledge about xylazine and treating xylazine- related complications (n = 78)

Characteristics	Frequency	%
Xylazine awareness (n = 72)		
Has heard of xylazine	69	95.8
Xylazine knowledge (n = 72)		
Knows xylazine is not a novel central-acting opioid (n = 71)	51	71.8
Knows xylazine exposure may lead to wounds	68	94.4
Knows xylazine is not FDA-approved for use in humans	72	100.0
Knows naloxone cannot reverse a xylazine overdose	69	95.8
Knows xylazine is almost exclusively found with fentanyl	55	76.5
Knows xylazine is added to fentanyl to prolong the high	67	93.1
Number of patients seen with known/expected xylazine exposure (n = 77)		
0	13	16.9
1–5	25	32.5
6–10	10	13.0
11 +	11	14.3
I don't know	18	23.4
Frequency patients have discussed xylazine with provider		
Often	8	10.3
Sometimes	20	25.6
Rarely	23	29.6
Never	27	34.6
Confidence recognizing xylazine complications in patients (n = 71)		
Extremely confident	5	7.0
Confident	18	25.4
Some confidence	27	38.0
Little confidence	15	21.1
Not at all confident	6	8.5
Confidence Treating Xylazine Complications in Patients (n = 71)		
Extremely confident	4	5.6
Confident	11	15.5
Some confidence	22	31.0
Little confidence	22	31.0
Not at all confident	12	16.9
Confidence Counseling Patients on the Prevention of Xylazine Complications (n = 71)		
Extremely confident	8	11.3
Confident	19	26.8
Some confidence	16	22.5
Little confidence	17	23.9
Not at all confident	11	15.5

was not a central-acting opioid (n = 51, 71.8%) and that xylazine is almost exclusively found as an adulterant in fentanyl (n = 55, 76.5%).

Providers' experience with patients exposed to xylazine

Over half (n = 46, 59.8%) of providers reported seeing one or more patients who have been exposed to xylazine, while 18 providers (23.4%) did not know how many patients they had seen with a known or expected xylazine exposure. Most providers (n = 43, 55.2%) sometimes or rarely had their patients discuss xylazine with them.

Providers' confidence with care related to xylazine

Few providers reported feeling confident (n = 18, 25.4%) or extremely confident (n = 5, 7.0%) in *recognizing* XROs in their patients. Instead, most providers only felt some confidence in this ability (n = 27, 38.0%). When reporting confidence in their ability to *treat* patients with XROs,

many providers indicated they had some (n = 22, 31.0%), little (n = 22, 31.0%), or no confidence (n = 12, 16.9%). However, for confidence in *counseling* patients on how to *prevent* XROs, more providers felt some confidence (n = 16, 22.5%), confident (n = 19, 26.8%), or extremely confident (n = 8, 11.3%) in their abilities.

Interview participant characteristics

From November 30, 2023, to February 9, 2024, trained members of the study team conducted one-on-one semi-structured interviews with providers via Zoom. After the a priori goal of n = 15 interviews was met, theoretical saturation was discussed by the study team and deemed to be sufficient (i.e., no new themes emerged over the course of the last few interviews conducted; additional interviews were not likely to reveal new themes). The average duration of the interviews was 24.7 min. Participant characteristics for the qualitative phase are detailed in Table 3.

Findings from the qualitative phase

Theme 1: "the top of a mountain of sad data points"

While all providers described the many ways xylazine is troublesome for PWUD, most participants asserted that this adulterant is accompanied by other troublesome issues for this patient population. Dr. Rivera, a physician in internal medicine at a federally qualified health center, stated that the potential for xylazine exposure among PWUD is "just an additional sad data point at the top of a mountain of sad data points that these folks have collected about their situation." In this way, xylazine was non-uniquely unique; while a novel concern for the healthcare of PWUD, it was one more addition to the list of concerns that was already quite crowded. Ultimately, participants identified xylazine exposure as a distinctive harm for many reasons (e.g., necrotic wounds, marked sedation). Further, Dr. Ford, an addiction medicine physician at a community health center, explained:

> *"Well, [xylazine] is odd… it can cause these scary complications. It doesn't neatly fit into the opioid category… [Clinicians] like to 'bucket' things. There is sort of a fentanyl / heroin bucket. We know what to do about that. Xylazine is in its own bucket. It's hard to kind of conceptualize what it is and how best to combat it."*

Here, xylazine's novelty can be largely attributed to healthcare providers not feeling as though they have experience with substances that have a similar mechanism of action (i.e., a 'bucket') currently being used for medical care or on the streets. Without this direct comparator in their metaphorical toolbox, many providers gauged xylazine's impact on care by using fentanyl as a benchmark or point-of-reference.

Despite the unique mechanism and impact of xylazine as a street drug, providers often cautioned against xylazine exceptionalism, explaining that *many* issues are unique when it comes to treating the various needs of PWUD. Dr. Bennet, an infectious disease physician at an urban hospital system, stated:

> *"The opioid epidemic now has been just kind of crushing for ten years… When I was first a resident, it was pretty much just straight heroin. And then we got fentanyl. And then, occasionally, you'll see people who are skin popping, which has a kind of a similar effect in terms of the necrosis, though not as bad as xylazine. And now [xylazine] on top of it? It's just kind of grim. But I don't know if it really changes my attitude much from where it's been. It's been kind of grim for a while."*

Xylazine was described with this level of nuance by many providers—xylazine was perceived as one of many potential harms PWUD face daily.

Theme 2: "we see it every day whether we recognize it or not"

Many providers described a strong desire for access to rapid xylazine testing at the point-of-care (POC) to provide immediate results to patients. In the absence of sufficient POC testing, providers were left making educated

Table 3 Select characteristics of providers participating in qualitative semi-structured interview phase (n = 15)

Characteristics	Frequency	%
Age		
Mean (SD)	42.4	14.2
Race/ethnicity		
Non-hispanic white	13	86.7
Non-hispanic black or African American	1	6.7
Non-hispanic Asian	1	6.7
*Degree**		
Doctor of Medicine (MD)	13	86.7
Nurse Practitioner (NP)	2	13.3
Registered Nurse (RN)	1	6.7
Master of Science (MS)	3	20.0
*Specialty**		
Internal Medicine	9	60.0
Addiction Medicine	8	53.3
Infectious Disease	4	26.7
Emergency Medicine	1	6.7
Pediatrics	1	6.7
Psychiatry	1	6.7

*Will not sum to n = 15 or 100%, as providers could select multiple options

guesses as to the magnitude of xylazine's prevalence in the unregulated drug supply and, accordingly, the impact of this adulterant on their patient population. Dr. Campbell, an addiction and emergency medicine physician at a large academic medical center, stated "we see it every day whether we recognize it or not. [That's] my strong suspicion based on what we see in our overdose death data." In this way, many providers recognized that they do not diagnose, treat, or discuss XROs with a number of patients that is congruous with what might be suggested by overdose death data. For example, if approximately 25% of overdose deaths in Connecticut test positive for xylazine, providers might expect about a quarter of their patients to present with XROs, not just a few. Thus, without adequate POC testing, providers are left piecing together whether or not xylazine may be involved in their current patient cases. Dr. Roberts, an addiction medicine physician at a medically supervised withdrawal program, stated:

> *"The large, crater type wounds? Those we can definitely say are related to xylazine. The rest is often conjecture where somebody just appears to be having a much harder time… It's really only a suspicion. Unfortunately, at this stage, there's no reliable test that we have access to that will give us an answer. I understand there are some in development and I think there's one that's available, but it's a 'send up' test… 48 hours later, you get your answer. Which isn't really much help."*

Here, not only did Dr. Roberts believe that the lack of POC testing interfered with what they considered to be patient care best practices, but they also expressed frustration with the temporal delays in receiving information about xylazine exposure.

Even in the face of insufficient testing, most providers perceived that xylazine prevalence is growing in the unregulated drug supply—even if they had personally only seen one or two patients with certain XROs. Dr. Sullivan, an internal medicine physician working at an addiction medicine clinic, explained:

> *"I think that it's more widespread than we're giving it credit for. I've only seen a very small number of patients with 'for sure' complications of it. But I think that it is way more widespread than we know and that our patients know as well."*

Many providers shared Dr. Sullivan's suspicion that xylazine was more prevalent than currently described. In this way, the available data sources for evaluating xylazine exposure among PWUD (e.g., overdose death data) are temporally delayed at best, but also potentially erroneous or misleading (e.g., counted deaths are just the tip of the iceberg).

Theme 3: "focus on what they are there for"

Participants also described their role in discussing xylazine's potential harms with their patients. Some providers explained that the initiation of such a conversation was influenced by the reasons a patient sought care, noting that XROs were infrequently the primary reason PWUD sought care and that this can introduce challenges with starting a conversation. For instance, despite perceiving xylazine exposure to be widespread, Dr. Sullivan described how it is difficult to talk to patients about xylazine; they stated "when I bring [xylazine] up, [patients] just want to focus on what they are there for… We know there's cocaine and we know there's fentanyl. They address that rather than something that I can't test for." Providers described feeling ill-equipped to discuss this novel adulterant—especially in the absence of proper tools to diagnose and treat xylazine exposure. Further, providers described how it was difficult to know when it was appropriate or necessary to discuss this novel adulterant with patients, particularly in the face of competing priorities. For instance, Dr. Rivera explained:

> *"If I have a patient that's coming in who has very severe heart failure, and they are clearly having an exacerbation right in front of me, and I need to send them to the emergency room? That's something that I have to address right away. And it's not helpful to them for me to also sort of screen them for xylazine exposure. And it's very rare for me to just have a visit where there aren't acute issues happening or something very serious that needs to be addressed that wouldn't be more threatening to their life than their xylazine exposure, as hard as that might be to believe."*

Thus, despite the seriousness of potential xylazine exposure, PWUD often have more pressing health concerns that must be addressed during medical care. Due to this limitation, providers in high acuity settings may not always serve as the best primary point of education for PWUD on xylazine; in fact, some providers urged the importance of harm reduction organizations and word-of-mouth among networks of PWUD for this information dissemination.

However, some providers did report initiating xylazine-specific conversations with their patients when it was deemed relevant and important. Dr. Baker, an addiction and internal medicine physician employed at an addiction treatment clinic, explained one recent case in which they spurred conversation with a patient:

"We approached her about [her positive xylazine result] and just said, 'hey, I know that you're still using fentanyl and we're just trying to help to give you some extra ammunition for reasons to abstain. And here's one of them,' and we showed her some pictures, actually, on the internet of some of these xylazine associated wounds."

Here, Dr. Baker utilized a positive screen on a send out test as a conversation starter to introduce xylazine and its related harms to a patient. While this was seen as an opportunity to educate the patient, Dr. Baker additionally considered xylazine to be a lever that could help motivate specific care goals. In this way, some providers perceived that the presence of xylazine in the drug supply might influence drug use behaviors (e.g., reducing drug intake) among specific patients. However, other providers perceived that the discussion of xylazine—in the absence of specific tools or robust information to provide patients—might reinforce stigma, induce fear, and be potentially harmful for patient care, as discussed below.

Theme 4: "afraid to go to the hospital"

Multiple providers lamented that XROs are likely to impact healthcare seeking, healthcare access, and the quality of care for patients who use drugs; further, some providers explained that these impacts may be exacerbated by preexisting stigma around drug use in many medical care settings. One way that xylazine was described to impact patient care was in the context of accessing medical care for wounds and fear around receiving poor management of their substance use disorder. Alex, a nurse practitioner at a behavioral health organization, described:

"Recently, I had a patient with xylazine wounds and abscesses. He was very sick, febrile, and needed to go to the hospital. He was coming into the clinic knowing that he was really sick and knowing he couldn't manage his wounds himself. But also, he was afraid to go to the hospital first because he didn't want to be sick and didn't want to not have that methadone in place before going. That was someone that we initiated on methadone and then sent immediately to the hospital for care."

In this way, the provider explained how a patient seeking care for wounds might in turn be worried they would receive inadequate treatment for withdrawal symptoms. Here, while a patient may have previously been able to avoid care settings where their substance use was poorly managed, XROs—especially wounds—made it difficult for PWUD to avoid acute care or other medical settings where they may experience fear, stigma, shame, or other negative feelings around their drug use.

Additionally, many providers discussed that PWUD exposed to xylazine might not get proper follow-up for their XROs, largely depending on where they seek care. For instance, Dr. Bennet, who provides inpatient infectious disease consultations, described one patient case where this discontinuity in care was especially relevant:

"Unfortunately, [this patient] would come into the ER when she was very sick, get some antibiotics, and then usually leave the ER not too long after. But she had the worst scarring I'd ever seen. And it was really getting to the point where a good proportion of her upper and lower limbs are now all pretty fairly scarred… and unfortunately, I didn't get much of a chance to build a rapport with her because like I said, I saw her in the ER and by the time I came back the next morning, she was already gone."

While this patient was accessing some level of care in the emergency department, Dr. Bennet describes that it was unclear whether or how this patient was managing her extensive xylazine-related wounds. Ultimately, numerous providers described a similar pattern wherein patients with XROs were leaving care settings without adequate care plans in place and/or against medical advice; however, the exact mechanism behind this is not yet fully understood (e.g., fear, stigma, pain, etc.). Additionally, in the quote above, Dr. Bennet explains that this abbreviated interaction with the patient also interfered with building a strong patient-provider relationship. In the context of drug use, and xylazine specifically, this building of "rapport" is crucial, as stigma and fear could interfere with their relationships with providers. For example, Dr. Blackwood, an infectious disease physician in an inpatient hospital setting, described a recent patient consultation in which they believed the patient was not being fully truthful about their drug use:

"[This patient] had very extensive wounds on the dorsal aspect of his hands that were kind of red and beefy and had a granulation tissue and raised border around them. He wasn't entirely straightforward about his drug use history but said that he had injected in the past. But not recently… He had tested positive for xylazine on the send-out test… But he was like, 'oh, [this wound] was an allergic reaction to a glove that I had. It wasn't related to any recent injection drug use.'"

In this case, having a pre-existing rapport might have eased the patient's fear and ameliorated stigma in ways that encouraged the patient to disclose their drug use behaviors to their provider.

Even if PWUD have an established care continuum and established rapport with their providers, it is still imperative to try to balance any existing power differentials. For instance, Dr. Baker—who used pictures of xylazine wounds to try to get their patient to abstain from fentanyl—further described that they believed:

> *"Stigma and shame associated with having these very grotesque wounds [might lead patients to] hide from their providers because they're ashamed of them… If a patient comes in and they're hiding things under their sleeves, so to speak, really make sure that you visualize – with patient consent – their arms and legs… And [my patient] that I was taking care of last summer with all these wounds? She was reporting severe pain all the time. You have to decide how much of that one wanted to believe… she looked quite comfortable."*

Thus, while providers can try to comprehend the impact stigma and shame have on their patients who use drugs, they must also be open to actively dismantling environments in which patients feel stigmatized and shamed. Without access to settings that meet people where they are, patients may delay seeking care. Such delays worsen outcomes that can include loss of limb function and amputation. Further, even once in care, PWUD may not feel comfortable disclosing information about their drug use, showing their wounds, or revealing their true pain levels—especially if they have previously been exposed to care settings where they are marginalized and systematically not believed.

Theme 5: "we are all learning together"

All of the participants, in some aspect, described how they did not always feel as though they had the information or tools necessary to provide high-quality care or counseling for patients with XROs or those at risk for xylazine exposure. As Dr. Rivera stated, "I think there's just a lot that [providers] don't know and, certainly, I think a lot that the folks that we take care of who use intravenous drugs don't. We're all learning together." Many other participants recognized that patients who use drugs might have more knowledge about this adulterant than they do as providers. This creates a learning opportunity for providers; while providers may have asymmetric information about current medical care best practices and proposed mechanisms of action, patients may have asymmetric information as well as it relates to street-based medicine and recognizing if xylazine is in their drug supply. Dr. Ford explained that:

> *"This is one of those examples in medical care where I think patients know more about it than we do. And so, whereas about maybe a year ago there were more like, 'Doc, what the heck is this?' types of conversations, now, oftentimes, I am learning from my patients about xylazine."*

Learning about novel adulterants like xylazine from patients who use drugs could inform best medical best practices over time and develop community-informed research questions. Providers might be encouraged to be open to this learning opportunity from patients, as Drs. Ford and Rivera were.

Without all of the knowledge and tools providers need and want, xylazine's evolving medical landscape has created a sense of helplessness among providers. Many participants indicated that xylazine's presence in the unregulated drug supply led to feelings of worry and fear both on (a) behalf of their patients and (b) for their own ability to provide care. Gabrielle, a nurse practitioner at a methadone clinic, stated that xylazine has "definitely changed the game of addiction… it's worrisome." To mitigate such feelings of worry and to ensure quality care, providers not only looked to patients for closing information gaps, but also leaned on the specific expertise of other medical specialties to fill information or resource gaps in patient care. Dr. Thompson, an infectious disease and internal medicine physician, explained some of the resources available at their healthcare setting:

> *"We have excellent plastic surgeons who have been really good partners in kind of debriding the wounds as needed. And then if there is a wound, in addition to a general infectious disease follow up, we have a wound care center. And the nursing staff there is really meticulous. And there's a plastic surgeon in that clinic, there's a nurse practitioner who specializes in wound care. And then, of course, we have addiction medicine, so we really do have wraparound services to manage that."*

Here, the participant was able to utilize referrals and collaboration with a multidisciplinary team to ensure the best treatment for their patients with xylazine exposure. Ultimately, many providers described how having multiple specialties and areas of expertise involved in patient care reduced their feelings of helplessness and worry.

Discussion

Our mixed-methods study to explore healthcare providers' knowledge and perception of xylazine in the unregulated drug supply highlighted the need for targeted research and purposeful information dissemination to

fill crucial gaps as they relate to xylazine exposure among PWUD. The quantitative phase revealed that although our sample of Connecticut-based healthcare providers had some baseline knowledge on xylazine, this knowledge did not necessarily translate into confidence in recognizing, treating, or counseling patients with XROs. The qualitative phase of our study, focusing on providers who perceived they had pre-existing knowledgeable and experience with xylazine and XROs, elucidated the possible mechanisms behind this, as providers highlighted the need for (a) continuing medical education on xylazine and XROs, (b) improved resources for managing XROs, such as more rapid xylazine testing at the POC and (c) access to quality data and research on the prevalence of xylazine in the local drug supply, and (d) information of the best evidence-based practices for treating XROs. Our study also found that healthcare providers who serve PWUD are not solely or uniquely concerned with xylazine, as other pressing health issues and even other adulterants are also of growing concern.

This study highlighted key areas where further medical education is needed, even among providers with high acceptability of harm reduction principles and general familiarity with xylazine as an adulterant. For instance, while providers noted that they felt xylazine was unique in terms of its mechanism of action and they did not have experience with similar substances, medical education could point to similar α-2 agonists they likely have experience with medically, such as clonidine [24]. However, not only did providers point to a need for more information about xylazine's mechanism of action and impacts on health for themselves and their patients, they also called for improved data sources and research for understanding xylazine in the context of their patient population. Unfortunately, providers are currently left relying on delayed or biased data sources (e.g., overdose death data, drug seizure data) to establish the prevalence of xylazine and its potential for exposure in their patient populations [18, 25, 26]. To overcome this, one potential solution would be to improve funding for community-based drug checking programs that would provide more rapid and accurate results for patients.

It is important to elucidate if, and how, xylazine impacts perceived and experienced stigma among PWUD. While there are numerous ways drug use and bodily markings related to drug use have been shown to contribute to stigma among PWUD, it is crucial to understand how XROs—especially wounds—may novelly impact patient care and healthcare seeking among PWUD [27–30]. In lieu of specific research aimed at understanding XRO-associated stigma, providers should continuously strive to create safe environments for their patients who use drugs. This is especially critical given that PWUD may wait until their condition becomes serious before seeking medical care [29, 31, 32]. For instance, patients with necrotic wounds may have waited a significant period of time before presenting for care; while it is still unclear how painful xylazine wounds are at the various stages of development and healing, providers should heed caution and make every effort to ensure patients are able to access a continuity of care.

On a more positive note, we found that providers reported working with PWUD to build knowledge and practice bases to address xylazine and XROs. Certainly, this finding is likely influenced by our sample of providers who were mostly harm reduction-oriented; regardless, future efforts to build knowledge around xylazine and XROs should be collaborative with opportunities for information exchange with a wide range of providers and community members. For instance, people with lived experience should be incorporated into—and compensated for—medical training for providers who serve PWUD. Additionally, providers could explore how existing social networks of PWUD might be harnessed to encourage information dissemination about XROs and prevention of unwanted xylazine exposure.

Ultimately, without addressing these key information and practice gaps, providers may continue to feel fear, worry, and helplessness when it comes to serving patients with XROs. Funding training programs for medical providers and others who serve PWUD with XROs (e.g., harm reduction outreach workers) could serve as a key intervention for improving patient care and limiting the harms caused by xylazine in the unregulated drug supply.

Limitations

While our study fills a research gap and responds to the urgent need for more research on xylazine, some limitations should be mentioned. First, our study was not designed to be representative of all healthcare providers and should not be interpreted this way; instead, our goal was to examine a diversity of provider experiences, not make population-level generalizations. For instance, those with some baseline knowledge of xylazine were more likely to self-select for participation (i.e., most providers in our sample had previously heard of xylazine). It is very likely that providers in geographic regions with a lower prevalence of xylazine in the drug supply and specialties not represented here may be unaware of xylazine and its impact. However, our study shows that even amongst those with some xylazine knowledge, providers still lack confidence and knowledge in certain areas of patient care related to xylazine.

Further, most providers we surveyed and subsequently interviewed expressed attitudes favorable towards harm reduction (as opposed to abstinence-focused approaches); this almost certainly influenced how providers perceived xylazine and measures to address XROs. Accordingly, providers without such attitudes would likely perceive of xylazine and XROs differently. It is worth exploring in future studies how providers with an abstinence-focused mindset, and those simply unfamiliar with the philosophy and practice of harm reduction, might perceive of xylazine in the unregulated supply.

Additionally, our study utilized self-reported information about xylazine knowledge and perceptions, so resulting information may be misclassified if participants experienced poor recall or other errors. Lastly, due to the cross-sectional and provider-focused nature of our study design, we cannot make any temporal conclusions (e.g., about how certain areas of provider knowledge impacts patient outcomes, etc.).

Conclusion

There are key knowledge and practice gaps related to xylazine for healthcare providers, even if they have experience serving PWUD who have been exposed to this adulterant. Future research should focus on mechanisms to improve care for PWUD, including informing harm reduction and medical care best practices to limit the harms associated with xylazine exposure (i.e., prolonged sedation, overdose, wounds). Additionally, policy and funding should support evidence-based harm reduction strategies that can mitigate XROs (e.g., wound care supply provision, etc.). Without filling such research gaps and providing PWUD access to harm reduction resources, providers will likely continue to feel powerless in the face of this pressing health issue.

Supplementary Information

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Supplement 1.

Supplement 2.

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Author contributions
KH, KLS, and RH conceived of the project idea. KH led quantitative and qualitative instrument development, and all authors provided feedback on instruments. KH organized the quantitative phase in REDCap. KH, RM-R, and EB conducted qualitative interviews. KH conducted quantitative data analysis and qualitative thematic analysis and led manuscript creation. All authors contributed to the final version of the manuscript.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available to protect participant privacy and confidentiality.

Declarations

Ethics approval and consent to participate
Yale's Institutional Review Board deemed this study exempt from human subjects review. All potential participants in the quantitative phase were provided with information about this study at the beginning of the survey and completion of the survey was accepted as consent to participate. Prior to interviews in the qualitative phase, participants were provided an information sheet and consent form via email; these forms described the purpose and procedures of the study, their rights as participants, confidentiality measures, and potential risk. Participants had the option to have the documents verbally reviewed with them by a member of the study team and were given the opportunity to ask questions. Verbal consent to be interviewed and for recording the interview was obtained prior to beginning the qualitative phase and all participants were advised on their right to terminate participation at any time.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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