Overdoses Involving Xylazine Mixed with Fentanyl: Clinical and Public Health Implications

Good afternoon. I'm Captain Ibad Khan and I'm representing the Clinician Outreach and Communication Activity, COCA, with the Office of Emergency Risk Communication at the Centers for Disease Control and Prevention. I'd like to welcome you to today's COCA call; Overdoses Involving Xylazine mixed with Fentanyl: Clinical and Public Health Implications. All participants joining us today are in listen only mode.

Free continuing education is offered for this webinar and instructions on how to earn continuing education will be provided at the end of the call.

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At the conclusion of today's session, participants will be able to accomplish the following: discuss the history and epidemiology of xylazine in the drug supply and among overdoses; describe the current understanding of adverse health effects from exposure to xylazine mixed with fentanyl, and acute overdose treatment strategies; list laboratory testing options and harm reduction activities to minimize disease and death from overdoses involving xylazine mixed with fentanyl; and identify opportunities for public health and clinical partnerships to improve communication, outreach and outcomes in people exposed to xylazine mixed with fentanyl.

After the presentation, there will be a Q and A session. You may submit questions at any time during today's presentation. To ask a question using Zoom, click the Q and A button at the bottom of your screen and type your question in the Q and A box. Please note we receive many more questions than we can answer during our webinars. If you're a patient, please refer your questions to your healthcare provider, if you're a member of the media, please contact CDC Media Relations at 404-639-3286, or send an email to media@cdc.gov.

I would now like to welcome our presenters for today's COCA call. We're pleased to have with us Captain Josh Schier, who is a senior medical officer in the Health Systems and Research Branch in the National Center for Injury Prevention and Control at CDC. Dr. Lewis Nelson, who's the chair of the Department of Emergency Medicine and director of the Division of Medical Toxicology and Addiction Medicine at Rutgers New Jersey Medical School. And Dr. Rachel Wightman, who's an associate professor of emergency medicine and epidemiology at Brown University's Alpert Medical School and consultant medical director for the Rhode Island Department of Health.

Before we begin the presentations, it is my pleasure to welcome Dr. Allison Arwady, who's the director of CDC's National Center for Injury Prevention and Control. Dr. Arwady will provide opening remarks and a brief situational update. Please note the slides will not advance during Dr. Arwady's presentation. Dr. Arwady, please proceed.

Thank you so much. I want to welcome all of you to this call, the National Center for Injury Prevention and Control at the CDC oversees a lot of complicated responses. It's our responsibility to prevent and control overdoses, violence, suicide, and other unintentional injuries and in all of these partnerships between public health and clinicians are absolutely critical. Especially in the overdose space, where the threats continue to emerge and change really with every passing month, we really count on our clinician partners to alert us when we are seeing changes and to participate with public health in these kinds of educational activities. I am a practicing provider myself, I'm a primary care physician trained in med peds, and I know how much time it takes to ensure that you're staying up to date on all of the critical public health related activities.

This is one we've been getting a lot of questions on, and again, we've got excellent nationally known presenters, I thank them for their time, and I especially thank all of the clinicians who are staying up to date as we try to stay ahead of the continuing changes in the overdose crisis. And with that, I'm pleased to pass it to Dr. Josh Schier.

Thank you, Dr. Arwady. Next slide.

Good afternoon everyone, and thank you for joining this call on the clinical and public health implications of overdoses involving xylazine mixed with fentanyl. My name is Captain Josh Schier, and I am EM trained and med tox trained physician with the CDC's National Center for Injury Prevention and Controls Division of Overdose Prevention. I will be providing a brief overview of what xylazine is, how it became a public health concern, and what is known about the epidemiology of overdoses involving xylazine mixed with fentanyl. Next slide.

The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Next slide.

My overarching learning objectives for this presentation include providing you with information that will help you understand what xylazine is and how it entered the illicit drug supply, the rationale for this COCA call, and what is known about the epidemiology of overdoses involving xylazine mixed with fentanyl. Next slide.

So xylazine, what is it? Well, the drug that we currently know as xylazine today was first developed in the 1960s as a possible anti-hypertensive agent. The drug was ultimately abandoned for use in humans because of its strong sedative properties. However, it's sedating, analgesic, and muscle relaxing properties supported its use in veterinary medicine for animals and is still used today. The benefits of its use in veterinary medicine include its sedative properties across multiple species with minimal respiratory depression at therapeutic doses. Next slide.

Xylazine has a similar mechanism of action to another hypertensive drug still commonly used today in humans known as clonidine. There are a number of street names used for xylazine, the most common one of which is probably Tranq. When combined with opioids such as fentanyl is it often referred to as Tranq dope. There are other terms used, but less frequently so, such as Zombie and even Anestesia de caballo. Next slide.

Xylazine was first reported in drug samples from Puerto Rico in the early 2000s, since 2006 it has been found in postmortem toxicology testing results and in actual drug samples seized by the U. S. Drug Enforcement Administration. Xylazine is sometimes referred to as being a contaminate or an adulterant in the media and literature. Adulterants are additives that increase the bulk volume of the combined substances or physical, chemical, biological, or other substances that are chemically created in the lab with an intent to mimic another drug such as marijuana, cocaine, or morphine.

Historical examples of drugs used as adulterants include ones such as xylazine, diphenhydramine, and quinine. The risk of adverse health effects from an adulterant depends on several factors, including but not limited to type of chemical, dose, concentration, and route of exposure. It is unclear as to why xylazine is being mixed with fentanyl and some investigators have hypothesized that perhaps it causes a synergistic psychoactive affect or possibly prolongs the short acting effects of illicitly manufactured fentanyl. However, the true rationale for its inclusion is not known.

There are many historical examples of adulterant associated outbreaks of illness from illicit drugs with severe effects, one of which that occurred from levamisole adulterated cocaine back in 2009. The increasing appearance of xylazine in fentanyl samples and in fentanyl related overdoses has generated a lot of concern among public health authorities and in the media which has driven the need for a public health response. Next slide.

This is a screenshot from an article published in the New York Times that illustrates the depth of media attention this issue has been getting recently. It goes on to describe some of the dermatological changes such as chronic, nonhealing wounds described in some patients who were exposed to xylazine mixed with fentanyl. I will leave further discussion of this to our later speakers, but suffice it to say, it has generated lots of concern and numbers questions about the scope, extent, and depth of any potential public health threat. Next slide.

On April 12, 2023, Dr. Rahul Gupta, director of the Office of National Drug Control Policy, formally designated xylazine mixed with fentanyl as an emerging drug threat. This designation triggers a number of follow-on federal actions that are outlined in explicit detail in the report pictured here.

This plan provides overarching guidance for public health agencies to develop activities and achieve progress towards measurable goals in a number of areas, including laboratory testing, epidemiology, evidence-based prevention, harm reduction, and treatment implementation of capacity building, source and supply information, and intelligence and supply reduction actions, regulatory control and monitoring options, and basic and applied research. And if you're interested in reading more, the link is provided. Next slide.

So what factors limit the ability to accurately and completely describe overdoses involving xylazine mixed with fentanyl? Well, there is a lack of inexpensive and readily available testing options for detecting xylazine in biological fluids, such as urine or blood, which can be used to help identify xylazine exposures in suspected or known fentanyl overdoses. This is a major limiting factor in the ability to fully characterize its epidemiology.

There are some specialty laboratories that can do this testing in biological fluids but it can be expensive and is usually not needed for clinical decision making. Xylazine test strips and other methodologies for detecting xylazine in drug samples exist and can be used for identification, but drug samples are not always available for testing and may not be done in cases where the opioid is considered the most local causative factor. Therefore, monitoring and following trends in descriptive epidemiology can be challenging. Since the presence or absence of xylazine mixed with fentanyl often does not really change clinical management decision making, there may be a lower likelihood that healthcare professionals would use them since persons that overdose on xylazine mixed with fentanyl or other opioids, present clinically as opioid overdoses, the treatment still primarily revolves around the use of opioid antagonist drugs such as naloxone and of course good, old fashioned, symptomatic and supportive care.

[No dialog] Next slide, please.

Presented here are three screenshots showing where xylazine was detected in overdose deaths as reported out by CDC's State Unintentional Drug Overdose Reporting System, or SUDORS, from 2020 to 2022. As you can see, there is a general trend towards increase in overdose deaths where xylazine was detected following testing during those years. Next slide.

This report uses data from SUDORS to describe illicitly manufactured fentanyl involved overdose deaths with and without xylazine detected that occurred during January 2019 to June 2022. The article this graph came from reports that among 21 jurisdictions, the monthly percentage of illicitly manufactured fentanyl involved deaths with xylazine detected increased 276 percent from January 2019 to June 2022. During the same period, xylazine was detected in a higher percentage of illicitly manufactured fentanyl involved deaths in the Northeast U. S. Census Bureau Region, among 32 jurisdictions.

Now, the listing of xylazine as the cause of death was variable across jurisdictions, but the figure shown on the screen shows the number and percentage of drug overdose deaths involving illicitly manufactured fentanyl by month and by xylazine detection or co-involvement. As you can see, the overall number of IMF, or illicitly manufactured fentanyl involved deaths, where xylazine was detected or co-involved, has increased of the last three years. In addition, the percentages of illicitly manufactured fentanyl involved deaths where xylazine was detected has generally increased across the reporting period as well. Next slide.

There are a number of studies published that look at xylazine involvement in opioid overdoses in limited geographical settings, such as cities or communities as well. The first graph shows an increasing number and percentage of heroin and fentanyl overdose deaths that involved xylazine in Philadelphia. The second shows a similar trend among poly drug seizures involving fentanyl and heroin where xylazine was detected. These figures came from a study of medical examiner

cases from Miami Dade County in Florida, where biological sample testing for xylazine exposure was performed as part of the postmortem evaluation.

As you can see, there is a rise in xylazine positive biological sample testing results starting around 2016, peaking in 2021, and then plateauing somewhat in 2022. The second graph shows the relationship between fentanyl positive cases and xylazine positive cases over several years and demonstrates a similar trend. Next slide.

To date, the available, albeit limited, evidence suggests that the presence of xylazine in drug samples and among testing results in overdose deaths is increasing, however, the numbers are relatively small compared to data on opioid overdose deaths and therefore it's difficult to accurately determine and predict future trends.

The National Forensic Laboratory Information System, or NFLIS, was established in 1997 as a DEA led program. It's systematically collects drug identification results and associated information from drug cases submitted to, and analyzed by, participating federal, state, and local forensic laboratories. It's yet another source of data that can be used for monitoring trends and drug samples where xylazine is detected. Interestingly, in the September 2023 report, picture here, there appears to be a down tick in xylazine reports but this data is not separated out by region and truthfully, this could represent many things, including a transient drop for some unclear reason, could be due to reporting delays, or possibly a new trend. Unfortunately, only time will tell. Next slide.

Maryland's Rapid Analysis of Drugs Program is reporting a recent drop in the prevalence of xylazine among all drug samples tested, not just fentanyl. In addition, there appears to be wide variation in the number of drug samples testing positive for xylazine and range from 20-80 percent and seems to be highly dependent on jurisdiction as well. Next slide.

The first graph, picture here on Figure 13, illustrates how often xylazine was detected among samples tested by the NFLIS in a six-month period during 2023. As you can see, it appears that at least in this dataset, it is being detected in fentanyl about 22 percent of the time. However and ultimately, it appears that the presence of xylazine in drug samples is dependent on several factors, including at least geography and type of drug. Next slide.

And for our self-knowledge check, commonly reported effects of xylazine include which of the following? Sedation, hypertension, seizures, or ulcers. Next slide.

The answer is A, sedation. Xylazine is a drug that depresses the central nervous system, so options B and C are incorrect. Ulcers are not a commonly reported effect of xylazine. Thank you very much for your time, and I'd like to turn the presentation now over to Dr. Lewis Nelson.

Thank you, Dr. Schier, and thanks for inviting me to talk about this so very important topic. Next slide, please.

So I'm not going to read this, and I'm going to let everybody read the learning objectives on their own, but to summarize what I'm going to speak about is a little bit about the pharmacology and a

little bit more depth than Dr. Schier just did, and a lot about the clinical effects, both what the drug potentially does to people and how we manage some of these adverse and somewhat unexpected effects. Next slide, please.

Just a shameless plug if you don't mind, there are two resources I would recommend that people look at if they are interested in learning more about this, the recent webinar that we held on, that was part of the NIDA, will be coming out in a synopsis form in the Annals for Emergency Medicine in the near future, and it'll summarize the findings or the discussions that occur between a group of physicians and scientists who are interested in studying the effects of xylazine in humans and a recent review article written by Dr. Wightman, another speaker here, and some of her colleagues down in the Philadelphia and Camden area, that was published earlier, late last year on this exact topic, so both of those I think might provide some information to supplement what we discuss here. Next slide, please.

I think it's always worth going back to the basics and the pharmacology of xylazine is very important. As you've heard, xylazine is not approved for use in humans so a lot of the information we get comes either from an understanding of how the drug works at a pharmacological level, and understanding how it affects animals, largely through its use in clinical management, largely sedation for procedures through veterinarians.

Xylazine is an alpha-2 agonist, often people link the alpha-2 receptor in the brain and the imidazoline receptor in the brain, both because they co-locate in certain parts of the brain but probably more importantly that they both control sympathetic outflow. Remember, sympathetic activity is essentially the fight or flight response that we're used to talking about. Alpha-2 receptor agonists decrease sympathetic outflow, leading to sedation. They don't typically have a lot of effects on the conventional vital signs like blood pressure and pulse, whereas the imidazoline agonists exemplified by clonidine, typically decrease sympathetic outflow in regions of the brain responsible for lowering your heart rate and blood pressure.

Clonidine and xylazine are structurally similar as you can see on the right of the screen, but importantly dexmedetomidine is an alpha-2 agonist that we have use data for in humans and is probably the best example of the xylazine replicant that we have that we could utilize to understand the effects that xylazine might have in humans. Dexmedetomidine is known as Precedex, it's used for sedation of people, typically in the ICU who are on sedation for days and it is used in place of or in addition to other conventional sedatives. The implications of the pharmacology that was very important, because xylazine lacks significant imidazoline activity, it doesn't really produce much in the way of vital sign abnormalities, it doesn't produce bradycardia or hypotension, low heart rate or blood pressure, and it lacks significant respiratory depression, at least at conventional doses.

And that's important because when we see people die from opioid overdoses, whether it contains xylazine or not, respiratory depression is a key driver of death. Right, and that comes back later when we talk about treatment as Dr. Schier said, providing respiratory support is generally all that's needed for most people. We like to use other agents like naloxone, but if you just support their breathing, the fentanyl or the xylazine should ultimately have limited negative outcome on the patient. The drug is very rapid in onset when given IV.

We know that from animal models and some human use, as we'll talk about shortly, we don't know very much about the intranasal pharmacokinetics of xylazine, so it's very hard to comment on what it would do in humans. The animals, the animal use suggests that the drug lasts up to about four hours but it's usually significantly less than that. Again, we don't have any data specifically on its effects in humans, but there's really no reason to suggest that it would be significantly different from the animals used in veterinary practice. Next slide, please.

The limited data we do have on humans is interesting, because it tends to be in the form of case reports and there's a handful of them in the published literature, this is just a report of three separate cases of xylazine overdose with self-harm in people who had gotten access to veterinary xylazine. And I'll just quickly detail the three cases because I think they're pretty demonstrative.

The first patient came in after an overdose injecting xylazine with some mild bradycardia and hypotension which is exactly what you would expect to see, was a little disoriented but awake and was breathing. The second patient came in with a little high blood pressure which, again, is not uncommon in people who take drugs like this, it's usually short-lived and it fairly quickly goes to normal or low build pressures in this case. This patient developed apnea, requiring intubation but it didn't occur for two hours after arrival in the emergency department, which makes it very suspect to actually be the xylazine, because as you talked about earlier, xylazine has a very rapid onset to sedation when given IV. So, there may have been a secondary exposure that we weren't aware of at the time, or that the authors weren't aware of at the time.

And the third patient came in with a low heart rate, and low blood pressure, and required intubation what appears to be fairly immediately, suggesting apnea, not breathing at the time. Whether that was due to xylazine or not is unclear but the intubation, the respiratory depression lasted about 18 hours, which would also be fairly unexpected from xylazine, again, implying potentially that there's a secondary exposure. No drug testing was done in any of these patients, so it's unclear if there were co-intoxicants at the time. You know, the sum of this really suggests that xylazine probably doesn't have tremendous respiratory depressant effects in humans, again, this is case based data, it's certainly not systematic, but at least it's what we have to understand the clinical effects in humans. Next slide, please.

Jen Love and her team at Mount Sinai looked at 321 patients who'd come in with fentanyl or an opioid xylazine combination overdose or at least a perceived combination overdose, and they tried to look at the clinical comparison between the two groups, the group that had xylazine in their opioid, and the group that did not have xylazine, and you'll see that that substantially more did not have xylazine, but the percentage is about right for what we expect to see in our community samples. You'll note if you go down the columns, that the two groups are essentially identical, if anything, the severity of affect is a little bit lower in the xylazine containing opioid group than in the group which did not have xylazine.

The two that were, were near statistical significance were the need for CPR, implying cardiac arrest, it was again small numbers but at least the statistics show and the trend is in the direction that perhaps xylazine may even reduce the risk of cardiac arrest and we may ask why that happens. The data is early and may be incomplete at this point, but suggestion is that the addition of xylazine to a fentanyl product lowers the amount of fentanyl that's in that product, actually

reducing the risk of adverse outcome. It's unlikely that xylazine protective per se, but rather an epiphenomenon that occurs due to the addition of xylazine. And you'll also see that coma within four hours was nearing significance, again, whether that's just an aberration of statistics or whether there's something is unclear, but all of the other parameters for the most part suggested that the two groups were essentially identical. Which isn't really surprising, because it's unclear that other than sedation, xylazine has a lot of relevant clinical effect to humans. Next slide, please.

So as Dr. Schier mentioned, although naloxone, which is an opioid antagonist, does not reverse the effects of xylazine, which is not unexpected because xylazine is and to an opioid, it does remain the drug of choice. And the reason is spelled out fairly nicely in these tables, next slide, or next click if you would.

You'll see that of samples analyzed by the New Jersey State Police Analysis Laboratory, of all of the samples, whether they're submissions per se or the components of the submission with glassine envelopes, regardless of how you broke the data down, about half of the fentanyl or opioid straight heroin samples they analyzed contained xylazine, so it's an extremely prevalent drug in our street bought opioid.

And if you click once more, you'll see that virtually none of the street bought opioid contained only xylazine. It all contained fentanyl or a combination of fentanyl and a fentanyl derivative, suggesting that the majority of the adverse effect is due if not completely due to the opioid, usually fentanyl component. Which is why naloxone is the drug of choice and is typically so effective. Next slide.

So, one of the questions that's often raised is what is the optimal dosing strategy of naloxone in these situations? And if we go next slide - remember, we're really not treating the xylazine here, but rather we're treating the opioid. So is there such a thing as a naloxone resistant overdose, you read about this, that xylazine is making opioid overdoses more difficult to reverse. The answer is rarely, if you click to the next slide.

But not for the reasons you think. Naloxone is very good at reversing fentanyl, it's often said that fentanyl's very potent so naloxone doesn't work, but remember, potency is a dose phenomenon, so it's how many milligrams per kilogram or equivalent of a drug does it take to have a given effect? You can always give more drug in order to have more effect. The real question is affinity, so the question is naloxone more, does it have a higher affinity than fentanyl, and the answer is yes. Does it have a higher affinity than almost all other fentanyl analogs, we know the answer is yes. So, naloxone should have no problem reversing any of the fentanyl analogs. It will not reverse xylazine of course, which is why patients may appear to be naloxone resistant.

There are other reasons, people who take opioids get hypoxic, they get hypercarbic, their blood carbon dioxides rise, so blood oxygen levels fall. That may take a little time to recover after reversal. They may also have massive doses of fentanyl and again, because it's a dose related thing, it's possible that they may not respond to a small dose of naloxone, but more naloxone will reverse even a massive fentanyl overdose. The next question is, what is the clinical endpoint for reversal, I think this is going to be a very important question. And the answer is breathing,

because the idea that people have to wake up to be successful is a bit of a misunderstanding. We don't really need people to wake up, we need them to breathe, and if they have a xylazine fentanyl combination overdose and they don't wake up, that may be the xylazine that's causing sedation, but if they're breathing, they're going to do fine.

Can too much naloxone be administered? And the answer is next, yes it can be, we know that precipitate opioid withdrawal is a problem, that raises concerns for me with, as we start seeing escalating doses of naloxone being used in commercial preparations, some of the higher affinity or longer acting opioid antagonists but just Nalmefene and Naltrexone might lead to some adverse outcomes. Again, the data is not quite in on these yet, but precipitate opioid withdrawal is a problem. Now it's better than dying, of course, but most of these people don't die. And particularly if we're concerned about somebody not waking up because we're looking at a wakefulness as an endpoint and not breathing, it can lead to adverse outcomes. And then is there an alternative for xylazine reversal? The answer of course is technically but not really, if you go to the next slide, please.

There is an FDA approved so to speak, antidote for awakening or reversing xylazine in veterinary practice. It's not approved for use in humans, and it's probably not needed because again, we're sort of, we're confusing xylazine sedating affect with its lethal affect. And atipamezole, which is a fine drug if you're trying to reverse somebody who's taken xylazine alone, probably isn't necessary for someone who's taken this combination because naloxone seems to work fairly well and is probably not a need to invest a lot of resources to develop this drug for humans. Next slide.

I know Dr. Schier showed some of this, but I just want to highlight that while the public health response is very important and we have done messages, we just have to be careful how we message them, you know, some of the messaging that came out after the MMWR piece that Josh showed in the, in his presentation, that showed a correlation between increasing prevalence of xylazine in decedents, and the fact that xylazine is leading to those deaths, led to some mis-messaging such as you see in this Bloomberg piece here, linking the two, when in reality, they're probably just co-relative, or correlated and not causal in nature.

So, while messaging is important, and I think getting the word out, what we say is important. We deal with a problem that is already highly stigmatized and there's a fear of engagement by rescuers and potential rescuers to get near the--to give the naloxone, and again, how we use our limited resources to address these things is very important. So, we need to make sure that we use the funds to look at harm reduction and treatment and other aspects of care for this population, you know, rather than focus on drug development or some things and may not have as much value going forward. Next slide.

People ask a lot about xylazine withdrawal and it's very unclear that xylazine withdrawal exists as a dependent syndrome, but rather, it looks a lot like opioid withdrawal and maybe it tweaks a little bit of what opioid withdrawal looks like but it's not clear in and of itself that it's a unique withdrawal syndrome, we have essentially no data in humans and we don't give it to animals long enough to induce a dependency state that would lead to withdrawal. What we do know that with dexmedetomidine, remember Precedex which is given for days, there doesn't really seem to

be withdrawal syndrome, there is some patients and some reports you read about withdrawal, but these are people getting poly pharmacy, very complicated and ill patients, and whether it is withdrawal syndrome, it remains to truly be determined. Next slide.

One thing that does appear to be real are the development of wounds and this is some data from Pennsylvania, probably the Philadelphia area, that shows that over time with the increasing prevalence of xylazine, the number of wounds which can be quite impressive and I'll show you a photo in a moment, of what these wounds look like if you haven't seen them, it has really paralleled one another, and when you start asking about correlation versus causation, you have to start asking about alternative reasons and biological bases and things like that, and there's not a lot of great explanations for why this is occurring, other than the addition of xylazine to the drugs. Next slide.

We do know that we've seen wounds, skin wounds, horrible skin wounds in people for decades, both heroin and black tar heroin, and Krokodil from a couple years ago, so it's possible that this is not related to xylazine at all, and rather related to the heroin or some other addition to the product, another adulterant as Dr. Schier brought up earlier. There are some potential causes of why xylazine may be associated with wounds, and some of them could be cytotoxic effects of the drug, some could be pharmacologic affects and the xylazine might have just localized vasoconstriction, might induce subtle hypoxia, could be an epiphenomenon, such as compression of the extremities as you're laying on it. But the wounds are fairly impressive and fairly unique, leading to some significant consequences such as health risks, of course, from infection, long-term need for healthcare, but also the inability to get into shelters or into treatment programs and others because these wounds are just so extensive and difficult to see. There are not animal models of injections that I know of and certainly we wouldn't expect to see it in the veterinary population, given the short use of the drug in that population. Next slide.

And finally just to say, this is what a wound would typically look like, thank you to Joe D'Orazio from Camden, for sharing these images with me. You know, and there's a number of ways to address them, I think most have recognized that it becomes largely a treatment of supportive care, of hygiene and keeping the wounds clean. Surgical debridement and skin flaps and other things don't really seem to be widely used or very helpful. Next slide.

With some good treatment though, you can see resolution, it's slow, and it may take, you know, weeks or months before they get better, of course continuation of injection is probably most relevant. It's worth noting that these wounds don't only occur at injection sites, and they don't only occur in injection drug users, it's been repeated in people who use this drug intranasal. What's also interesting is that I live in New York, New Jersey, or work in New York, New Jersey, which is only about 80 miles away from Philadelphia and we see very little wounds up here, and we see injection drug use and we see intranasal drug use. So, why the wounds are so prevalent down in the Philadelphia, Camden area and not up in the rest of the state of New Jersey is a little bit unclear to me, but it's clearly a phenomena that we see happening. Next slide.

And I'll just let you read through these, I don't have to read through them for you, I think you can read faster than I speak.

But I think, I've raised a few thoughts, hopefully that people can think through as we do forward. Next slide.

So, in the absence of naloxone, after calling 911, what should be done to help a patient with a xylazine fentanyl overdose? Should they inject epinephrine? Provide rescue breathing? Stimulate with cold and hot water? Or give sublingual buprenorphine? Next slide.

And I think you recognize that this is a problem probably with the fentanyl and rescue breathing would be the correct answer. Thank you.

I'd like to turn it over now to Dr. Rachel Wightman, going to take it over and continue.

Thanks so much, Dr. Nelson. I'm going to present now on managing xylazine mixed with fentanyl in the community. Next slide.

Here are the objectives; first, we're going to discuss testing options to evaluate xylazine in the community and I'll provide an example of a project we did in Rhode Island. Second, I'm going to walk you through the processes we took, including working as a multidisciplinary team to take action steps to disseminate information around xylazine in our state. And finally, I'm going to provide some concrete examples of harm reduction initiatives led by community partners to address xylazine given, as Dr. Nelson just pointed out, that lack of clinical knowledge in humans. I think that part of this is especially important. Next slide, please.

So, let's start out with testing. I know many of you are well-aware of these data sources but I do think it's important to take a moment and talk through some nuances. There are a number of programs that do community drug checking across the country. Most often they use handheld devices such as an FTIR in combination with fentanyl and/or substance test strips. They're able to test drug samples in the field and provide real-time results back to clients. Depending on things like funding and capacity, often a portion of samples are sent out for comprehensive testing and this is done to ensure that what's being detected on those handheld devices continues to match up with evolution of changes in the drug supply.

The ability to stand up community drug checking is going to depend on drug checking laws in your state as well as local attitudes, things such as local testing capacity and resources. Non-fatal overdose testing in hospitals and emergency departments is often used for surveillance, however, you're only going to detect what you test for. Xylazine isn't detected on the standard urine drug screen amino assay, which is the standard of testing across hospitals and office space settings. Even when states or academic researchers are running comprehensive bio surveillance testing, it's really essential to understand that testing scope.

So, this is the methods and the limitations. As an example, Rhode Island has the leading state-run bio surveillance program. Initially it had a focus on fentanyl and fentanyl analogs, which was the main concern. But given that focus, adulterants like xylazine were detected. And that's since changed and testing's been expanded but I think it's a good example to keep in mind as some programs or hospitals are investing in adding xylazine testing alone.

Similarly, with fatal overdose testing, we see a lot of those same issues. Testing and reporting is delayed. Different municipalities have different testing algorithms and scope and those also change over time. And details around really what's being testing and when are often left out of reports or academic papers which really does challenge the interpretation of those results, and can potentially be misleading. And seizure data, this can be a really useful data source, but public health really isn't a customer for that type of testing. And when testing is done at the state level or lower, sometimes only substances that are scheduled in that state are reported out.

So, this can really limit reporting of novel or new substances if and when they're detected. Further, as you all know, this testing is often not widely shared. There are other methods like for example, waste water surveillance, but if you're testing xylazine via waste water, it's a veterinary tranquilizer, so if you find it, it may just mean that you have horses in your area. So, when it comes to interpreting any testing, and especially testing for things like xylazine or new substances, that context really, really matters when interpreting results. Next slide, please.

I want to highlight some additional testing considerations and I'm going to run through these pretty quickly. Xylazine testing landscape right now is rapidly evolving. In the data that I'm going to present, I'm going to show you that we were testing only for parent compound xylazine, this is overall the current state of most xylazine testing. Some institutions for example, CSFRE in Pennsylvania, are making progress to characterize the metabolites for xylazine in humans and they're working to determine that window of detection, not only for the parent compound, but also for metabolites. This plays into the clinical utility and testing. Because we don't understand the pharmacokinetics in humans, it really limits clinical application and interpretation of testing.

To give you an example, so from our state seizure data, I know that about 40 percent of counterfeit M30 pills in Rhode Island contain xylazine. I have a patient who's snorting a number of M30 pills per day, and he comes to me in withdrawal, requesting substance use treatment after not using for a couple days. I decide to send a comprehensive urine drug screen that contains xylazine and it comes negative. And so, the question is, what does that negative test mean?

Just because he doesn't test positive for xylazine, it doesn't necessarily mean that he was not exposed to xylazine. We're still trying to figure out over what time you'd really expect xylazine to be detected in either urine or blood after an exposure and how that would be different with a single, acute exposure versus a chronic exposure. And chronic exposures are really what we're seeing more often in clinical practice. Similarly, we're learning about false positives and false negatives, for example with xylazine test strips. Some reports lidocaine has thrown false positives. And finally, I think it's great that we're seeing a lot more quantitative testing, but messaging around that has to be really careful. These are not pharmaceutical grade homogeneous products. People have different levels of tolerance, different comorbidities, use patterns, and it's particularly important to think about this given the high levels of poly substance use and/or exposure. Next slide, please.

So, here's an example of a project that I led with Dr. Alexandra Collins in Rhode Island, in collaboration with the Rhode Island Department of Health, and local harm reduction partners. It was very simple, we collected drug samples and combined comprehensive testing results with qualitative interviews and field work with people who use drugs. This way we could see how the

drug supply chain was changing and at the same time, learn how those changes were impacting people using substances in our community. All the testing was done by Dr. Adina Badea, using untargeted comprehensive testing via LC-QTOF-MS at her clinical lab at Rhode Island Hospital. Next slide, please.

Here you can see a testing snapshot that was focused on xylazine. You can see we tested paraphernalia, product, refuse. Obviously testing equipment and refuse you expect cross contamination. Also, samples are sometimes donated for a reason and aren't necessarily representative of the overall supply. And the real punch line though is that it was clear that xylazine was prevalent in our state fentanyl supply. And I do want to know, we only found xylazine with fentanyl, and we'll get to this later, but these findings, these early findings aligned with seizure data and non-fatal overdose data that was collected over that same time period. Next slide, please.

So given the lack of clinical data in humans, understanding that experiences of people who use drugs in combination with testing results is especially important when it comes to things like novel substances and new adulterants in the supply. And here you'll see some anecdotes of observed drug supply changes during our testing period. And these line up a bit with the reported clinical effects that Dr. Nelson was outlining. So, things such as new onset incontinence, compression wounds, unexpected deep sedation, and you can see the quotes below, so that idea of feeling drowsy or sleep walking. Next slide, please.

So, how did this match up with non-fatal overdose testing? And our findings did align with comprehensive testing I was doing as part of a different study in the Emergency Department. So, for the study participants were consented, post-overdose, and blood and urine samples were obtained during their ED visit and tested at Rhode Island Hospital, again, by Dr. Adina Badea, comprehensive LC-QTOF screen. Because of that lack of pharmacokinetic knowledge that I mentioned before, these results are a little bit challenging to interpret but the takeaway for me with this study was that we found xylazine in 37 percent of urine samples where fentanyl was detected, so we were not only seeing xylazine in community drug supply testing, but we were also seeing it associated with non-fatal overdose. The urine in the study was generally collected about four and a half hours after triage. Next slide, please.

And finally, to give you a more complete picture, here's an idea of seizure data over that same time period. And you can see xylazine was detected in about 35-50 percent of fentanyl incidence in Rhode Island between the third quarter of 2021 and the second quarter of 2023. Again, this data aligns with what we saw on post-overdose and community testing. Again, I want to mention that xylazine was always detected with fentanyl and in this dataset there was one exception of a counterfeit Xanax that had xylazine without fentanyl. Next slide, please.

So, the key thing is what was done with this information? We had a new finding of xylazine and fentanyl that was confirmed by three different data sources and one of the things that was great about the testRI study is that it was done in collaboration with the Rhode Island Department of Health and community partners. We really wanted to be sure that testing wasn't siloed in a vacuum and so we were already sharing this data. And from here, the Rhode Island Department of Health was able to convene a multidisciplinary group, and this didn't just include public health

officials and health professionals and MDS, but also leaders in the community on the ground, in outreach, and out of these sessions a few focus points came out. And some of which were obvious, but others were a little bit more nuanced.

First, the importance of messaging that's accessible to multiple different audiences. Second, the need for honesty about the lack of knowledge about xylazine in humans. And this wasn't to scare people but to really level set the uncertainty we are dealing with. And three, the need to emphasize that in our state, so far on testing xylazine was found almost universally with fentanyl. And further highlight that importance of administering naloxone in suspected overdose. So these newly developed communication materials and trainings allows for a base from which to disseminate information, that xylazine was here and fairly prevalent in the drug supply. Next slide.

So here are some examples of those outputs. On the left you'll see a ZINE on xylazine, that was an output from our testRI study, and the ZINE was really led by Claire Macon, you'll see it was Tweeted here by the Rhode Island Department of Health next to a picture of the governor signing something. Unfortunately, I don't think it was a xylazine. On the right you'll see just one of many outputs, this one was a pocket card that was developed by the Rhode Island Department of Health in collaboration with community partners that highlighted concerns about xylazine including wounds, excess sedation, and further promoting that importance of naloxone for overdose reversal. Next slide, please.

This example is actually related to nitazenes but we were able to leverage the Rhode Island Department of Health listserv and distribution channels to message every healthcare provider in the state to provide updates about new supply findings. And letting this workforce know about novel substances is helpful for getting everyone on the same page. But it also sets that expectation that providers should know about changes in the drug supply. And I think this is a good example again, of testing results not being stuck in one or two lanes, but really casting that wider net. Next slide, please.

So, to finish up, I want to pivot to actual outreach initiatives, and I'm going to highlight three things and spend most of the time talking about the last one. First, that continued emphasis on the importance of naloxone and again, xylazine mixed with fentanyl making naloxone critically important. Second, distribution of xylazine test strips. In Rhode Island there have been years of distribution of fentanyl test strips, so when xylazine test strips became available, people wanted to use them, and they were released into the community with the assumption that the best way to really figure out if they'd be useful would be to provide them.

And anecdotally, the feedback I've heard is that the combined test strips are not as useful and people really preferred the simplicity of a single result. And part of that may be due to the fact that we're in an almost 100 percent fentanyl market, so testing your fentanyl for fentanyl really may not make a lot of sense to folks. And finally, I want to end talking about wounds and wound care. When individuals come to the Emergency Department with wounds, they've often progressed. So, requiring admission for IV antibiotics, sometimes they've developed sepsis, or deep space infections, but when I'm practicing out in the community, I often see wounds end earlier stages where early intervention or proper wound care, that individual where with early

intervention and proper wound care, that individual may be able to avoid an Emergency Department visit and that more complicated course.

Unfortunately, the limited availability of wound care for people who use drugs is a known entity and this is happening with or without xylazine involvement, it's an issue. With an increased number of wounds this became more pressing and to address this made Rhode Island, namely EOHHS provided funding to get a wound care nurse on outreach with community teams. And the idea is to meet ongoing wound care needs. So, this includes things such as triage and monitoring wounds, as well as providing appropriate wound care supplies and developing treatment plans. And it also created wound care specific beds at medical respite units. And these beds were available to individuals who needed a safe place to stay while receiving wound care and while wounds were healing.

This is a really great first step, however, I routinely have patients denied access to nursing facilities, shelters, inpatient substance use treatment, rehab, because of the presence of wounds. Public health officials and government are trying but this is really a larger systems-based issue where a lot of work still needs to be done. And frankly, I think hospital systems and other service providers need to be more responsive to the need. This can't fall solely on the shoulders of harm reduction or community organizations, given the levels of funding and if wounds progress, the potential complexity of treatment. Next slide, please.

So, in summary, testing data, testing and data cannot be siloed. As we see increased drug checking programs develop, it's essential to have those collaborations with public health to ensure broader dissemination. The importance of multidisciplinary teams, not just in implementation but in decision making. Your local approach to testing is going to be influenced by a number of factors and this may include things such as xylazine market saturation, testing resources, state and local laws and attitudes, but I hope with presenting this data, that I showed you that there's more than one way to do this testing and gather drug supply data in a timely fashion. And finally, that continued emphasis on naloxone, things change but right now on testing, we're seeing xylazine with fentanyl and can't lose that focus. Next slide.

Alright, it brings us to a self-knowledge check question; xylazine test strips can potentially result in false positives, true or false? Okay, and so the answer is xylazine test strips have been shown to have false positives and this has been specifically reported out with lidocaine which is a common cut in drugs, namely cocaine most often. Next slide, please.

And I'm going to go ahead and hand it back over to Ibad. Thank you.

Presenters, thank you so much for sharing this timely information with our audience. We will now go into our Q and A session and joining our presenters for the Q and A session, is subject matter export Lieutenant Commander Julie O'Donnell. Lieutenant Commander O'Donnell is the team lead for the Overdose Mortality Team, with the National Center for Injury Prevention and Control at CDC.

Our first question asks, does xylazine increase the central nervous system depression effects of fentanyl and if so, does this compound the risk of immediate overdose and death compared to fentanyl alone?

I mean, it's Lewis Nelson, and I could probably address that. You know, you have to differentiate these, differentiate sedation from respiratory depression, and there's nothing to truly suggest that xylazine increases the risk of overdose death due to respiratory depression, it probably does increase the sedating effect of the fentanyl, but that's fairly inconsequential because you don't really die from sedation per se, you die from respiratory depression. So, if I'm understanding the question, there doesn't appear to be any data to truly support a causal link with death from xylazine.

Thank you very much. Another question asks; have you seen similar international cases of xylazine being mixed with fentanyl or is this mostly a U.S. situation?

I can address that. So, from the data I've looked at, most of the xylazine testing and contamination has been in the U.S., most notably initially in Puerto Rico and then also extending up into Canada have been the places I've seen it most commonly reported.

Thank you very much. Our next question asks if naloxone does not counteract the effects of xylazine, is there an antagonist for the tranquilizer effects of xylazine that you would recommend, such as an alpha-2 antagonist?

It's Lewis Nelson, yeah I did comment on atipamezole, which is available for use in animals or veterinary practice, there is a, there's an agent called yohimbine, which is technically available, not something that we would recommend but the key issue here is that there's probably not a lot of benefit in reversing the sedating effect of xylazine, unless you're trying to wake the person up specifically. But since sedation doesn't cause harm, and respiratory depression does, the true answer is either provide respiratory support by breathing for the person one of many ways, or using naloxone. So, while conceptually there is an antidote for xylazine, it's probably not clinically relevant and not worth spending a lot of time investigating.

Thank you very much. We do have a few questions regarding the skin wounds information that you shared and the questions essentially boil down to is the poor healing of skin wounds in your experience, due to decreased skin oxygenation that might make the person more likely to develop this characteristic skin ulceration and necrosis?

Yeah thanks, it's Lewis Nelson. There is no real understanding at this point of exactly why this happens. I provided a few potential reasons and there are some data, some you know, basic science data that suggests that poor skin oxygenation at a cellular level or even at a vascular level, because these drugs can be vasoconstrictive and reduce blood flow to the wound might be operative. I don't think we have enough understanding of how this works in humans, there are many potential explanations for this, again, given that we've seen it before and some of those prior you know, wound quote-unquote, epidemics like Krokodil or black tar heroin, look qualitatively similar to these wounds and they can be just as dramatic. These just, these are just extremely prevalent in some regions.

Makes you wonder whether it's the xylazine itself or something else that's going on. But if I do tend to believe the xylazine is a component of this, why exactly it happens is truly yet to be determined. And whether, you know, whether it will turn out to be xylazine or not, again, I don't think we really know what the mechanism of xylazine doing it is, I don't think we really know yet.

Thank you for that. Oh, I'm sorry, go ahead.

Hi, it's Rachel Wightman, I was just going to add on to what Dr. Nelson was saying. I agree with everything that he said, there have been a lot of papers proposing kind of single mechanisms too for what's going on with these wounds. And I feel like it may also be multi-factorial, so a lot of those mechanisms that Dr. Nelson mentioned may be adding on each other, so things like compression related injury plus tissue hypoxia, and potential cytotoxicity and vasoconstriction all compounding.

Thank you for that. And we have time for one last question, and the question asks; in your experience, have you seen people develop a tolerance to xylazine over time and is xylazine habit forming?

So, this is a challenging one, because we've been seeing xylazine mixed with fentanyl, and our knowledge of testing and pharmacokinetics is pretty limited, picking out the difference between what is a true xylazine withdrawal syndrome versus what could be a fentanyl withdrawal syndrome, versus a combination, is really hard. Because a lot of the sedative hypnotic withdrawal syndromes have overlapping features and the way that we really diagnose a withdrawal syndrome is by clinical signs and symptoms after a known exposure and removal of that agent. And so, putting all those pieces together with xylazine complicated by fentanyl added and has been pretty challenging.

Thank you very much for that. And at this time, I want to thank everyone for joining us today with a special thanks to our presenters and subject matter experts. We appreciate your time. Next slide please.

This year, CDC is moving from the Training and Continuing Education Online System that provides access to CDC educational activities for continuing education, to CDC TRAIN. If you do not already have a TRAIN account, please create one at https://www.train.org/cdctrain. All new activities that offer continuing education from CE will only be listed in CDC TRAIN. CDC TRAIN is a gateway into the TRAIN learning network, the most comprehensive catalog of shared public health training opportunities.

This transition will allow you to access non-credit and for-credit educational activities and track your learning, including CE, in one place. Many CDC accredited activities are already listed in CDC TRAIN. The move to one system improves efficiency and makes it easier for learners, staff, and partners, to offer and earn CE in one place. You can continue to use TCEO for existing activities that have CE set to expire in 2024 since these courses will not move to CDC TRAIN. You may also use TCEO for existing activities with CE set to expire in 2025, before the courses' transition to CDC TRAIN sometime next year.

If you begin one of these courses in TCEO, we will let you know when the course will move to CDC TRAIN. You can access and download CE transcripts and certificates in TCEO through the end of 2025. Instructions will be available in both platforms and a learners' support team will be available to answer questions. All continuing education for COCA calls is issued online through CDC TRAIN, those who participate in today's live COCA call and wish to receive continuing education, please complete the online evaluation and post-test before April 1, 2024, with the course code; **WC4520R-022924**. The registration code is **COCA022924**.

Those who will participate in the on-demand activity and wish to receive continuing education should complete the online evaluation between April 2, 2024, and April 2, 2026, and use course code, **WD4520-022924**. The registration code is **COCA022924**. Today's COCA call will be available to review on-demand a few hours after the live call at emergency.cdc.gov/coca.

A transcript and close captioned video will be available on-demand on the COCA Calls webpage next week. You can visit emergency.cdc.gov/coca for more details about this COCA call and other upcoming COCA calls. We invite you to subscribe to receive announcements for future COCA calls by visiting emergency.cdc.gov/coca/subscribe.asp. You will also receive other COCA products to help keep you informed about emerging and existing public health topics. Again, thank you for joining us for today's COCA call and have a great day.