PROVIDER HEALTH ADVISORY

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Xylazine Alert for Health Professionals

The U.S. Food and Drug Administration (FDA), California Department of Public Health (CDPH) and local officials are communicating with health care professionals about serious risks associated with xylazine exposure in humans and considerations for management.

While xylazine has been linked to an increasing number of overdose deaths nationwide, it is an emerging issue in California. Locally, the SLO County Sheriff-Coroner's Office has reported that xylazine detection has begun to increase locally, with approximately seven to 10 samples per month detected by the sheriff's drug lab.

Background

There are no approved uses of xylazine for humans. FDA is aware that xylazine is increasingly detected in the illicit drug supply and in drug overdoses; however, individuals who use illicit drugs may not be aware of xylazine's presence in their supply. Xylazine has primarily been identified in combination with heroin and fentanyl. Stimulants (e.g., methamphetamine and cocaine) have also been combined with xylazine. Reports suggest that xylazine-containing products may be sold under the street names "tranq," "tranq dope," "sleep-cut," "Philly dope," and "zombie drug." There have been reports of individuals combining xylazine with speedball (i.e., an opioid used with a stimulant) to offset unintended effects of the individual components of the mixture.

According to FDA's review of case reports from the FDA Adverse Event Reporting System, National Poison Data System, Toxicology Investigators Consortium, and published medical literature, acute and repeated xylazine exposure may be associated with clinically significant harms such as delaying the diagnosis and management of polysubstance overdose; developing severe, necrotic skin ulcerations; and interfering with the successful treatment of opioid use disorder (OUD).

What is xylazine?

Xylazine is a non-opioid agent that FDA originally approved in 1972 as a sedative and analgesic for use in veterinary medicine. Structurally, xylazine is similar to levamisole, clonidine, and tizanidine and may share some clinical effects. Like clonidine, xylazine acts as a central alpha-2-adrenergic receptor agonist in the brainstem, causing a rapid decrease in the release of norepinephrine and dopamine in the central nervous system (CNS). Xylazine may also bind to other CNS receptors, although further research is needed. Xylazine is not approved for use in humans.

What are the harms associated with xylazine use in humans?

Signs and symptoms of acute xylazine toxicity may include CNS and respiratory depression, hypotension, bradycardia, hypothermia, miosis, or high blood glucose levels. This toxidrome may appear similar to that of opioids, making it difficult to distinguish between toxicity from opioids versus xylazine. Of note, naloxone is not known to be effective in reversing overdoses involving xylazine, as xylazine is not an opioid.

Repeated exposure may also result in dependence and withdrawal. Withdrawal symptoms such as agitation or severe anxiety may occur when usual doses of the drug are decreased or discontinued, and such symptoms may undermine patients' efforts to obtain appropriate treatment for concurrent OUD and perpetuate an individual's dependence upon illicit drugs.

Repeated exposure to xylazine, by injection, has been associated with severe, necrotic skin ulcerations that are distinctly different from other soft-tissue infections (e.g., cellulitis, abscesses) often associated with injection drug use. These ulcerations may develop in areas of the body away from the site of injection.

Why is FDA communicating about xylazine?

FDA is communicating about xylazine because of xylazine's role in complicating management for patients affected by the overdose crisis. Health care professionals treating patients with a known or possible history of illicit drug use should be aware of the following information in situations of possible drug overdose, given trends in the prevalence of xylazine in combination with illicit drugs:

1. **Xylazine is not currently known to be reversed by naloxone.**

   Because xylazine is not an opioid, associated toxicities may not be reversed by naloxone. Healthcare professionals who manage opioid overdoses should consider xylazine exposure if patients are not responding as expected when naloxone is administered or when signs or symptoms of xylazine exposure (e.g., unusual skin necrosis) are present. Other reversal agents regularly used in veterinary medicine (e.g., yohimbine hydrochloride, tolazoline hydrochloride) are not known to be safe and effective treatment options for xylazine-involved overdose in humans and should not be used. Appropriate supportive measures should be provided to patients who do not respond to naloxone.

2. **Xylazine is not detected by routine toxicology screens. Consequently, xylazine should be considered as a potential adulterant in opioid overdoses, particularly when other signs or symptoms of xylazine exposure are present.**

   Xylazine is not readily identified by routine immunoassay toxicology screens and therefore may be under-detected. Additional analytical techniques are required to detect xylazine in biological specimens such as blood and urine. Even with appropriate testing, overdoses involving xylazine may be underdiagnosed due to xylazine's rapid elimination from the body, with a half-life of 23-50 minutes.

   Because individuals may not realize they have been exposed to xylazine, and xylazine is not readily identified in routine toxicology screening, its presence and contribution to life-threatening CNS and respiratory depression may not be identified. Although polysubstance exposures may complicate the clinical picture of overdose, xylazine exposure should be considered when individuals present with concomitant hypotension and bradycardia or cardiac conduction disturbances.

3. **Repeated exposure to xylazine may lead to severe, necrotic skin ulcerations.**

   Health care professionals caring for patients with severe, necrotic skin ulcerations should consider the possibility of repeated xylazine exposures. Additionally, clinicians should assist patients with implementing appropriate treatment plans for complicated wound management involving appropriate selection of antibiotics. If admitted for inpatient care, clinicians must be prepared to manage xylazine withdrawal symptoms simultaneously as the patient undergoes wound treatment.

4. **Individuals with repeated exposures to xylazine may become dependent and experience severe withdrawal symptoms.**

   When xylazine is stopped abruptly, severe withdrawal symptoms may develop. However, withdrawal from xylazine is not managed by standard pharmacological OUD treatment (i.e., methadone, buprenorphine, or naltrexone). Clinicians may need to diagnose and manage xylazine withdrawal when treating patients with OUD, either in the acute setting or as part of an outpatient rehabilitation program. Currently, no medications have an FDA-approved indication to manage xylazine withdrawal in symptomatic individuals.

What can health care professionals do?

Health care professionals should consider potential xylazine exposure when patients presenting with an overdose do not respond to naloxone. In these situations, health care professionals should provide supportive measures and consider screening for xylazine using appropriate tests. Additionally, health care professionals who see patients with severe, necrotic skin ulcerations should consider repeated xylazine exposure as part of the differential diagnosis. Finally, health care professionals caring for patients with OUD should monitor patients for withdrawal symptoms not managed by traditional OUD treatments, as this may indicate xylazine withdrawal.

FDA will continue to monitor for adverse events related to xylazine exposure. FDA encourages health care professionals and patients to report adverse events resulting from possible xylazine exposure to their local health department, poison center, and FDA's MedWatch Adverse Event Reporting program. Complete and submit MedWatch reports online at www.fda.gov/medwatch/report.htm; or download and complete the form, then submit it via fax at 1-800-FDA-0178.

FDA is particularly interested in obtaining information that health care professionals feel is relevant to better understand the patterns and impact of xylazine use, including, but not limited to: geographic location of xylazine exposure; additional substances involved in suspected xylazine-involved overdose; responses to naloxone or other agents in the context of overdose (including information on dose, route, duration, and outcome); and clinician experience treating skin ulcerations and withdrawal symptoms.

More information

The California Department of Public Health's xylazine webpage provides more information.

The Philadelphia Department of Public Health provides a clinical update on xylazine withdrawal management, wound care, harm reduction and more