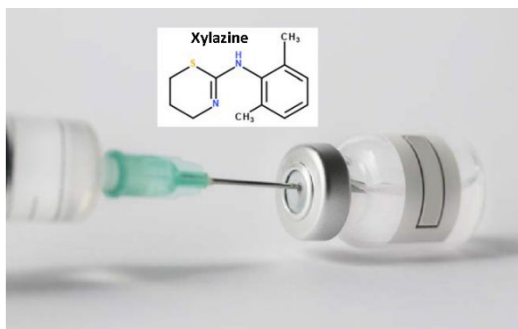


NOVEL PSYCHOACTIVE SUBSTANCES: XYLAZINE – UPDATE

MARCH 2024

The Legislative Analysis and Public Policy Association (LAPPA) is monitoring the emergence of novel psychoactive substances (NPS) appearing on the illicit drug market in the United States. The term “novel” does not denote a brand new, never-before-seen substance, but rather a substance that is newly available in the drug market. This fact sheet, the second in a series highlighting these dangerous drugs, is an examination of xylazine, also known by the street names “tranq,” “tranq dope,” or “sleep cut,” a powerful veterinary sedative increasingly appearing as an adulterant in heroin and fentanyl mixtures in the U.S., particularly since 2020.



The Bayer Company first developed xylazine in 1962. Xylazine has a chemical structure similar to compounds called phenothiazines and operates by decreasing the release of norepinephrine and dopamine in the central nervous system, resulting in analgesia, sedation, and muscle relaxation. Researchers at the company initially studied xylazine’s effect on humans but ultimately terminated the clinical trials due to the drug’s severe depressant effects on blood pressure and the central nervous system. Studies on the use of xylazine in animals, however, proved to be successful, and in 1972, the U.S. Food and Drug Administration approved its use in veterinary medicine as a sedative, analgesic, and

muscle relaxant. For veterinary use, xylazine is available in liquid form and is typically sold in vials or pre-loaded syringes under the brand names Rompun, Sedazine and AnaSed. Veterinarians purchase xylazine through pharmaceutical distributors and internet supply sites. However, individuals without ties to the veterinary profession can also purchase xylazine from websites that do not require buyers to prove a legitimate need for the product. According to the Drug Enforcement Administration, an individual can purchase a kilogram of xylazine powder from Chinese suppliers for \$6-\$20 per kilogram.¹

Xylazine has been detected intermittently in the U.S. illicit drug supply since the 1970s, but in the early 2000s, drug researchers began describing the substance as a frequent additive in Puerto Rico’s drug supply. In the late 2000s, the drug became more prevalent in the U.S. mainland’s illicit opioid supply with especially high concentrations of the substance in the mid-Atlantic region. Philadelphia, Pennsylvania was, and still remains, the epicenter of xylazine use. Between 2010 and 2015, only two percent of unintentional heroin or fentanyl overdose deaths in Philadelphia also involved xylazine.² Since then, xylazine’s involvement in heroin and fentanyl overdoses in Philadelphia increased greatly: 11 percent in 2016, 18 percent in 2018, and 31 percent in 2019.³ In 2021, 90 percent of the illicit drug samples tested in Philadelphia contained xylazine.⁴ A study of 10 U.S. cities showed that xylazine was included in less than one percent of overdose deaths in 2015 and in nearly seven percent in 2020.⁵ Data from the Centers for Disease Control and Prevention estimate that the number of overdose deaths in the U.S. involving xylazine grew from 260 in 2018 to 3,480 in 2021, an increase of 1,238 percent.⁶ As of March 2023, fentanyl mixed

¹ “The Growing Threat of Xylazine and its Mixture with Illicit Drugs,” Drug Enforcement Administration, Dec. 21, 2022, <https://www.dea.gov/documents/2022/2022-12/2022-12-21/growing-threat-xylazine-and-its-mixture-illicit-drugs>.

² David T. Zhu, “Public Health Impact and Harm Reduction Implications of Xylazine-Involved Overdoses: A Narrative Review,” *Harm Reduction Journal* 20 (Sept. 2023):4, <https://doi.org/10.1186/s12954-023-00867-x>.

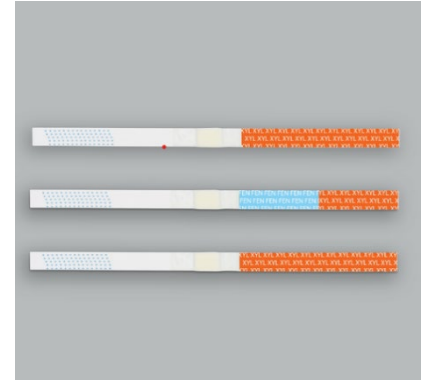
³ *Id.*

⁴ Rahul Gupta, David R. Holtgrave, and Michal A. Ashburn, “Xylazine — Medical and Public Health Imperatives,” *New England Journal of Medicine* 388, no. 24 (June 2023): 2210, <https://www.nejm.org/doi/10.1056/NEJMp2303120>.

⁵ “What You Should Know About Xylazine,” Centers for Disease Control and Prevention, last updated Feb. 22, 2024, <https://www.cdc.gov/drugoverdose/deaths/other-drugs/xylazine/faq.html#:~:text=References-,What%20is%20xylazine%3F,8>.

⁶ Gupta, et al., *supra* note 4.

with xylazine has been found in drug seizures in 48 states.⁷ A September 2023 report from the drug testing laboratories of Millennium Health found that nationally, over 99 percent of xylazine-positive specimens also contained fentanyl, while 16 percent of fentanyl-positive specimens contained xylazine.⁸ Drug researchers are not sure why xylazine has been introduced into the illicit drug market. It is possible that xylazine may be used as a bulking agent by drug traffickers to allow them to increase profits by reducing the amount of fentanyl or heroin used in a mixture. Alternatively, drug traffickers may add xylazine to their products to attract customers looking for a longer high and delayed withdrawal symptoms. Xylazine is pharmacologically similar to clonidine and lofexidine, two drugs used to treat the physical symptoms of opioid withdrawal, so it is possible that drug traffickers add xylazine to their products in an effort to mitigate a consumer's withdrawal symptoms between doses. Anecdotal reports from people who use drugs (PWUD) describe xylazine as having similar effects as fentanyl but with a longer-lasting effect than the use of fentanyl alone. While some PWUD may intentionally seek out heroin or fentanyl mixed with xylazine, there are some PWUD who are unaware that xylazine may be included in their drugs as an adulterant or who actively try to avoid opioids mixed with xylazine. Xylazine test strips are commercially available for PWUD who wish to test their drugs for xylazine prior to using.



Xylazine intoxication can result in central nervous system depression, low blood pressure, and slow heart rate. Respiratory depression can also occur, which increases the risk of overdose when combined with opioid-induced respiratory depression. PWUD also report extended periods of sedation and immobility when using xylazine. The drug's effects generally last from six to eight hours and can leave the user unconscious and helpless during that time. As a result, PWUD who experience xylazine sedation may end up exposed in the sun or snow or left vulnerable to compression injuries from lying in one position for hours on end. Once unconscious, PWUD face additional dangers such as an attack or sexual assault. Overdoses involving xylazine present public health challenges: because xylazine is not an opioid, opioid antagonists, such as naloxone, are ineffective against it. Public health officials, nevertheless, recommend administering naloxone, as xylazine typically appears alongside fentanyl or other opioids, but it does little to reverse the deep sedative effects of xylazine itself. Currently, there is no xylazine-reversal agent approved for use in humans. Additionally, there is limited data available to clinicians on how to treat xylazine withdrawals in inpatient settings.

In addition to its acute effects, xylazine use has become associated with severe necrotic skin ulcers. While it is common for people who inject drugs to develop wounds around an injection site, xylazine wounds differ in that they can occur in areas of the body not used for injection and can develop on individuals consuming xylazine through inhalation or ingestion. The scientific community is uncertain as to why xylazine causes such severe wounds in humans, but it is hypothesized that it is related to the drug's ability to vasoconstrict (*i.e.*, narrow) blood vessels, which can lead to less blood passing through the skin. Wound care is vital for people with wounds induced by xylazine so as to prevent limb amputations and life-threatening infections.

FEDERAL ACTIONS REGARDING XYLAZINE

On April 12, 2023, Rahul Gupta, MD, Director of the White House Office of National Drug Control Policy (ONDCP), designated fentanyl adulterated or associated with xylazine as an emerging threat to the U.S.⁹ The Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and

⁷ *Id.*

⁸ Millennium Health, "Zeroing in on Xylazine: The First 100 Days After U.S. Emerging Threat Designation," *Millennium Health Signals Report* 5.1 (Sept. 2023), <https://resource.millenniumhealth.com/signalsreportxylazine>.

⁹ "Biden-Harris Administration Designates Fentanyl Combined with Xylazine as an Emerging Threat to the United States," The White House, April 12, 2023, <https://www.whitehouse.gov/ondcp/briefing-room/2023/04/12/biden-harris-administration-designates-fentanyl-combined-with-xylazine-as-an-emerging-threat-to-the-united-states/>.

Communities Act of 2018¹⁰ requires ONDCP to “monitor novel and evolving patterns of substance use, establish criteria for determining when a substance or combination of substances should be designated an emerging threat, and declare emerging threats when the Director deems appropriate based on the criteria.”¹¹ In January 2023, ONDCP published the criteria for designating evolving and emerging drug threats.¹² The criteria are as follows: (1) an increase in morbidity or mortality due to drug overdose occurring in at least three census regions among the general population; (2) an increase in polysubstance use and substance use disorders involving multiple substances occurring in at least three census regions among the general population; (3) an increase in individuals or cohorts (e.g., a particular age group, ethnicity, gender, sexual orientation, and the like) diagnosed with substance use disorder, or an increase in drug-related overdose rates in a specific cohort occurring in at least three census regions; (4) an increase in emergency department visits, hospitalizations, or treatment admissions related to the use of a new or evolving drug, class of drugs, or other substance occurring in at least three census regions; and (5) increased reporting by health care providers or laboratories of new or novel clinical illnesses by patients with suspected or known exposure to a drug, class of drugs, or other substance occurring in at least three census regions.¹³ Per an ONDCP directive, a decrease of at least 15 percent with respect to the criteria in at least three of the four census regions would trigger a review of whether a previously issued emerging or evolving drug threat designation should be terminated.¹⁴

On July 11, 2023, ONDCP released a National Response Plan (Plan) to coordinate a government-wide response against fentanyl combined with xylazine.¹⁵ The Plan outlines action steps and responsibilities for federal departments and agencies and directs them to develop and submit an implementation report to the White House. ONDCP’s Plan focuses on six pillars of action: (1) testing; (2) data collection; (3) evidence-based prevention, harm reduction, and treatment; (4) supply reduction; (5) scheduling and monitoring; and (6) research.¹⁶ The ultimate goal of ONDCP’s plan is a 15 percent reduction (using 2022 as the baseline year) of xylazine positive drug poisoning deaths in at least three of four U.S. census regions by 2025.¹⁷ Short term goals include: (1) developing laboratory tests for xylazine to be used in clinical care settings; (2) developing and implementing best practices for initiating and maintaining treatment of fentanyl adulterated or associated with xylazine in healthcare settings; (3) developing and implementing best practices for treating wounds associated with fentanyl adulterated or associated with xylazine; and (4) identification and commencement of implementation strategies to identify the sources and to reduce the diversion and/or illicit supply of xylazine.¹⁸

As of this writing, xylazine is not scheduled as a controlled substance on the federal level. ONDCP’s Plan, however, includes exploring possible regulatory actions under the Controlled Substances Act,¹⁹ including scheduling xylazine. Scheduling xylazine will present its own challenges because of the drug’s use in veterinary medicine. Any scheduling actions regarding xylazine will need to consider how the action will affect the legitimate supply of xylazine in veterinary medicine. If the federal government chooses not to schedule xylazine, it would still be able to implement criminal penalties against the illicit distribution of xylazine. In March 2023, Senator Catherine

¹⁰ 21 U.S.C. § 1708.

¹¹ Emerging threat designation, *supra* note 9.

¹² OFFICE OF NATIONAL DRUG CONTROL POLICY, EXEC. OFFICE OF THE PRESIDENT, DIR. NO. 2022-002, CRITERIA FOR DESIGNATING EVOLVING AND EMERGING DRUG THREATS (2023). <https://www.whitehouse.gov/wp-content/uploads/2023/01/Emerging-Threats-Criteria-Directive.pdf>.

¹³ *Id.*

¹⁴ *Id.*

¹⁵ “FACT SHEET: In Continued Fight Against Overdose Epidemic, the White House Releases National Response Plan to Address the Emerging Threat of Fentanyl Combined with Xylazine,” The White House, July 11, 2023, <https://www.whitehouse.gov/briefing-room/statements-releases/2023/07/11/fact-sheet-in-continued-fight-against-overdose-epidemic-the-white-house-releases-national-response-plan-to-address-the-emerging-threat-of-fentanyl-combined-with-xylazine/>.

¹⁶ “Fentanyl Adulterated or Associated with Xylazine Response Plan,” Office of National Drug Control Policy, Executive Office of the President, July 2023, <https://www.whitehouse.gov/wp-content/uploads/2023/07/FENTANYL-ADULTERATED-OR-ASSOCIATED-WITH-XYLAZINE-EMERGING-THREAT-RESPONSE-PLAN-Report-July-2023.pdf>.

¹⁷ *Id.* at 10.

¹⁸ *Id.* at 11.

¹⁹ 21 U.S.C. § 801, *et seq.*

Cortez Masto (D-NV) and Representative Jimmy Pancetta (D-CA) introduced the Combating Illicit Xylazine Act.²⁰ This bill, which has bipartisan support, would establish criminal penalties for manufacturing, distributing, dispensing, or possessing with intent to manufacture, distribute, or dispense, xylazine for illicit use in accordance with the penalties for Schedule III substances. The American Veterinary Medical Association endorsed the bill, stating in a press release that “[i]t strikes the right balance of protecting our communities while preserving veterinary access to this critically important animal drug.”²¹ Under the bill, the legitimate importation, manufacture, dispensing, and administration of xylazine for animals would not be subject to the restrictions and requirements of scheduling.

STATE ACTIONS REGARDING XYLAZINE



A number of states have taken action to schedule xylazine. As of March 2024, seven states have scheduled xylazine: one state (Florida²²) as Schedule I, four states (Delaware,²³ Ohio,²⁴ Pennsylvania,²⁵ and South Dakota²⁶) as Schedule III, one state (West Virginia²⁷) as Schedule IV, and one state (Rhode Island²⁸) as Schedule V. Florida was the first state to schedule xylazine and the only state to do so prior to ONDCP’s designation of fentanyl adulterated or associated with xylazine as an emerging threat. Florida’s law does not mention the use of xylazine in veterinary medicine, leaving the use of the drug in animals technically a legal gray zone. According to a past

president of the Florida Veterinary Medical Association, at a time after the state made it a controlled substance, legal counsel at the Florida Department of Agriculture said that veterinarians may use xylazine in their practices.²⁹ Florida lawmakers have introduced legislation that would address this issue by specifically exempting xylazine for veterinary use from Schedule I status.³⁰ In addition to the states that have scheduled xylazine, there are two states (Louisiana³¹ and Tennessee³²) that have chosen to criminalize the illicit production, manufacturing, distribution, and possession of xylazine without scheduling the substance.

There are several states that have recently introduced legislation to schedule xylazine. Three states (Arizona,³³ Illinois,³⁴ and New York³⁵) have introduced legislation to make xylazine a Schedule I substance. The Arizona and New York bills include exemptions for licensed veterinarians who lawfully acquire, use, prescribe, dispense, or administer the drug within their professional practice; however, the Illinois bill does not mention the use of xylazine in veterinary medicine. Two states (Illinois³⁶ and Michigan³⁷) introduced legislation to make xylazine a Schedule II

²⁰ S. 993, 118th Cong. (1st Sess. 2023) and H.R. 1839, 118th Cong. (1st Sess. 2023).

²¹ “AVMA Endorses Federal Legislation to Address Illicit Xylazine,” American Veterinary Medical Association, last updated March 28, 2023, <https://www.avma.org/blog/avma-endorses-federal-legislation-address-illicit-xylazine>.

²² FLA. STAT. ANN. § 893.03 (West 2024) (xylazine scheduled July 1, 2016).

²³ DEL. CODE ANN. tit. 16, § 4718 (West 2024) (xylazine scheduled June 2, 2023).

²⁴ OHIO ADMIN. CODE 4729:9-1-03 (2024) (xylazine scheduled September 28, 2023).

²⁵ Pennsylvania Department of Health, Notice Letter on Temporary Scheduling of Substance Xylazine as a Schedule III Controlled Substance (June 3, 2023).

<https://www.dos.pa.gov/ProfessionalLicensing/BoardsCommissions/VeterinaryMedicine/Documents/Special%20Notices/NOTICE%20-%20Xylazine%20-%20Temporary%20Scheduling%20as%20Schedule%20III%20Controlled%20Substance.pdf>.

²⁶ S.D. CODIFIED LAWS § 34-20B-20.2 (West 2024) (effective February 12, 2024).

²⁷ W. VA. CODE ANN. § 60A-2-210 (West 2024) (xylazine scheduled June 8, 2023).

²⁸ 21 R.I. GEN. LAWS ANN. § 21-28-2.08 (West 2024) (xylazine scheduled June 26, 2023).

²⁹ Lisa Wogan, “Patchwork Effort to Curb Illicit Use of Xylazine Raises Concerns,” *Vin News Service*, April 13, 2023, <https://news.vin.com/default.aspx?pid=210&Id=11464312&f5=1>.

³⁰ H.B. 743, 2024 Leg., Reg. Sess. (Fla. 2024) and S.B. 700, 2024 Leg., Reg. Sess. (Fla. 2024).

³¹ LA. STAT. ANN. § 40:989.4 (West 2024) (effective August 1, 2023).

³² TENN. CODE ANN. § 39-17-456 (West 2024) (effective July 1, 2023).

³³ H.B. 2045, 56th Leg., 2nd Reg. Sess. (Ariz. 2024).

³⁴ S.B. 2089, 103rd Gen. Assemb., Reg. Sess. (Ill. 2024).

³⁵ A. 8395, 2023-2024 Gen. Assemb., Reg. Sess. (N.Y. 2024) and S. 7763, 2023-2024 Gen. Assemb., Reg. Sess. (N.Y. 2024).

³⁶ H.B. 4352, 103rd Gen. Assemb., Reg. Sess. (Ill. 2024) and H.B. 3873, 103rd Gen. Assemb., Reg. Sess. (Ill. 2024).

³⁷ H.B. 4913, 2023-2024 Leg., Reg. Sess. (Mich. 2023).

substance, and eight states (California,³⁸ Hawaii,³⁹ Illinois,⁴⁰ Missouri,⁴¹ Nebraska,⁴² New Jersey,⁴³ New York,⁴⁴ and South Carolina⁴⁵) introduced legislation to make xylazine a Schedule III substance. Vermont has introduced legislation to make xylazine a regulated drug.⁴⁶ There are also a few states that have introduced legislation to criminalize xylazine without scheduling it. Indiana introduced a bill that would make the possession of illicit xylazine a Class A misdemeanor and the dealing of illicit xylazine a Level 5 felony.⁴⁷ New York has proposed prohibiting the sale of xylazine to individuals under the age of 21 and without proof of the intended use for institutional, veterinary, or scientific purposes.⁴⁸ Finally, Virginia introduced a bill that would make the manufacture, sale, or distribution of xylazine for human consumption a Class 5 felony and the possession of xylazine for human consumption a Class I misdemeanor.⁴⁹

CONCLUSION

Xylazine’s spread across the U.S. has been devastating to communities and presents a public health crisis. With fentanyl adulterated or associated with xylazine now designated as an emerging drug threat, there will be a government-wide response to curb the distribution and use of illicit xylazine. Creative solutions are necessary to stop the flow of illicit xylazine while still ensuring that the drug is accessible to veterinarians. LAPP will continue to monitor the spread of xylazine and any new regulatory response at the state and federal levels.

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³⁸ A.B. 3029, 2023-2024 Leg., Reg. Sess. (Cal. 2024).

³⁹ H.B. 2086, 2023-2024 Leg., Reg. Sess. (Haw. 2024) and S.B. 2749, 2023-2024 Leg., Reg. Sess. (Haw. 2024).

⁴⁰ H.B. 4450, 103rd Gen. Assemb., Reg. Sess. (Ill. 2024) and S.B. 3640, 103rd Gen. Assemb., Reg. Sess. (Ill. 2024).

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⁴⁵ H.B. 4617, 2023-2024 Leg., Reg. Sess. (S.C 2024) and S.B. 849, 2023-2024 Leg., Reg. Sess. (S.C 2024).

⁴⁶ H.B. 866, 2023-2024 Gen. Assemb., Reg. Sess. (Vt. 2024). In Vermont, regulated drugs are generally illegal except as specifically allowed.

⁴⁷ H.B. 1203, 123rd Gen. Assemb., 2nd Reg. Sess. (Ind. 2024) (enrolled).

⁴⁸ S. 6084, 2023-2024 Gen. Assemb., Reg. Sess. (N.Y. 2024) and A. 6506, 2023-2024 Gen. Assemb., Reg. Sess. (N.Y. 2024).

⁴⁹ H.B. 1187, 2024 Leg., Reg. Sess. (Va. 2024) and S.B. 614, 2024 Leg., Reg. Sess. (Va. 2024).

ABOUT THE LEGISLATIVE ANALYSIS AND PUBLIC POLICY ASSOCIATION

The Legislative Analysis and Public Policy Association (LAPPA) is a 501(c)(3) nonprofit organization whose mission is to conduct legal and legislative research and analysis and draft legislation on effective law and policy in the areas of public safety and health, substance use disorders, and the criminal justice system.

LAPPA produces up-to-the-minute comparative analyses, publications, educational brochures, and other tools ranging from podcasts to model laws and policies that can be used by national, state, and local criminal justice and substance use disorder practitioners who want the latest comprehensive information on law and policy. Examples of topics on which LAPPA has assisted stakeholders include naloxone laws, treatment in emergency settings, alternatives to incarceration for those with substance use disorders, medication for addiction treatment in correctional settings, and syringe services programs.

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