

FENTANYL ADULTERATED OR ASSOCIATED WITH XYLAZINE RESPONSE PLAN

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Background

On April 12, 2023, Dr. Rahul Gupta, Director of the Office of National Drug Control Policy (ONDCP), formally designated fentanyl adulterated or associated with xylazine as an emerging drug threat, pursuant to 21 U.S.C. § 1708. According to authorities provided to ONDCP by Congress in 2018, such a designation triggers a number of follow-on federal actions, outlined below.

The non-opioid drug xylazine is being distributed illicitly for human use in combination with fentanyl and is associated with significant and rapidly worsening negative health consequences, including fatal overdoses and severe morbidity (including deep flesh wounds). Xylazine is the active ingredient in an approved animal drug (xylazine hydrochloride), which the Food and Drug Administration (FDA) originally approved in 1972 for use in animals as a sedative and analgesic. Xylazine is not approved for use in humans. The Drug Enforcement Administration (DEA) reports that between 2020 and 2021, forensic laboratory identifications of xylazine rose in all four U.S. census regions, most notably in the South (193%) and the West (112%). The DEA also reports that xylazine-positive overdose deaths increased by 1,127% in the South and over 100% in all other regions.¹ For both laboratory identifications and xylazine-positive overdose deaths, the highest overall numbers (not percentage increases) were in the Northeast and Southern United States. These levels of geographic distribution and rapid increase in negative health outcomes meet the Emerging Threats Criteria used by ONDCP to judge when the novel use of a substance should be considered an emerging threat to the nation.

In addition, data from the Centers for Disease Control and Prevention's State Unintentional Drug Overdose Reporting System (SUDORS) shows that in 2021, 23 states and the District of Columbia² reported 41,224 overdose deaths to SUDORS. Xylazine was detected in 2,171 (5.3%) postmortem toxicology analyses and was listed as a cause of death in 1,717 (79.0%) deaths in which it was detected. This represents an increase from 2019, when the same jurisdictions reported 29,125 overdose deaths to SUDORS, and 667 (2.3%) overdose deaths with xylazine detected in postmortem toxicology analyses, and xylazine was listed as a cause of death in 427 (64.0%) of deaths in which it was detected. In 2021, 99.5% of xylazine-involved deaths also involved illicitly manufactured fentanyl or fentanyl analogues.

In deliberating this decision, Dr. Gupta consulted with the ONDCP-led Evolving and Emerging Threats Committee, representatives from the National Drug Control Program Agencies, the U.S. Emerging Threats Coordinator, and other governmental and non-governmental experts (including leaders in law enforcement and other first responders and frontline service providers, state and local officials, subject matter experts on the ground, and public health officials). During the Evolving and Emerging Threats Committee's January 17, 2023 meeting, the group expressed acute concern for the safety of those consuming both xylazine and fentanyl. Because xylazine is not an opioid and is therefore not impacted by the opioid reversal agent naloxone, persons using fentanyl adulterated with xylazine may be less responsive to naloxone—which should still be

¹ [The Growing Threat of Xylazine and its Mixture with Illicit Drugs \(dea.gov\)](#)

² Jurisdictions with sufficient toxicology report coverage and deaths with a toxicology report.



administered due to its lifesaving actions on fentanyl effects should an overdose occur. Those who develop dependence on these drugs also experience severe withdrawal symptoms requiring skilled, simultaneous treatment for both fentanyl and xylazine. Dr. Gupta noted in a statement:

The United States today faces the most dangerous illicit drug supply in the history of the country. The deadly drug fentanyl is sold on its own and in combination with street drugs trafficked as heroin, cocaine, and methamphetamine, and it is contained in fraudulent prescription medications sold as opioid pain killers, sedatives, and stimulants. To make matters worse, the country now faces a severe challenge from xylazine, especially when combined with fentanyl. There is an urgent need to determine the source of xylazine and how to reduce the illicit supply; to develop evidence-based testing and overdose response protocols; and to determine how to treat those who have become dependent on the dangerous fentanyl and xylazine combination.

The emerging threat designation, made under the authority provided by *The Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act of 2018* (P.L. 115-271), requires the Executive Branch to take several steps:

- First, ONDCP, in collaboration with relevant federal agencies, must draft and publicly issue a fentanyl adulterated or associated with xylazine Response Plan (within 90 days of designation).
- Second, ONDCP must issue Implementation Guidance to agencies (120 days after designation).
- Third, agencies must provide a specific Agency Implementation Report to ONDCP (180 days after designation).
- Fourth, ONDCP must publish a National Implementation Report on the Response Plan (in February 2024, with other ONDCP annual reports).

The response plan presented here fulfills the first of these requirements and addresses urgent public health and safety needs. The SUPPORT Act also requires that the ONDCP Director decide whether a stand-alone national media campaign would be effective in addressing the emerging threat. In the case of xylazine-adulterated fentanyl, Director Gupta has determined that it will be productive to include such public messaging on fentanyl adulterants in existing campaigns and other federal messaging on fentanyl, in lieu of establishing a new stand-alone campaign focused solely on xylazine.

The SUPPORT Act requires that an emerging threat response plan include evidence-based prevention, treatment, and supply reduction action steps, in addition to establishing goals and performance measures informed by comprehensive data. In the plan outlined below, we apply those requirements to the case of fentanyl adulterated or associated with xylazine and describe critically important and urgent next action steps.



Actions

Testing

Xylazine testing is being conducted in community and law enforcement settings for the purpose of detecting xylazine in drug products and postmortem toxicology settings, and the results of such tests can provide important information about this emerging threat. However, the use of such testing for xylazine is uneven across the United States, impeding the development of a full national threat picture. With respect to clinical testing, FDA has not authorized any in vitro diagnostic products (IVDs) intended to detect xylazine in human specimens.

The federal government will pursue the following xylazine-related testing action steps outlined below. Some of these efforts will more broadly focus on the class of α_2 -adrenergic agonists, potentially on other drug classes, and on detecting other compounds of concern in the drug supply.

Standardize Forensic Testing Practices

There is a need to standardize practices across drug analysis laboratories, medical examiners and coroners, and public health laboratories, and to scale up forensic testing and postmortem toxicology testing to better estimate population level usage of or exposure to xylazine, alone or in combination with other drugs (especially fentanyl).

Develop New Tests for Clinical Settings

Develop, validate, authorize marketing of, and deploy, as appropriate, rapid tests for xylazine and fentanyl intended for real time clinical care (point of care testing).

Deploy Testing in Community Settings

Further develop, validate, and deploy, as appropriate, a test to detect xylazine in drug samples at all levels in the supply chain, from wholesale seizure quantities to retail levels within communities (including harm reduction services).

Target Testing to Those In-Need

During the development of the above-referenced tests, devise a statistical and clinical algorithm for predicting whether a patient has used xylazine based on epidemiological information, such as background community prevalence and clinical indicators, including flesh wounds. Validate the clinical algorithm and obtain any applicable FDA marketing authorization, as appropriate.



Epidemiology and Comprehensive Data System

The SUPPORT Act and public health and public safety best practices require comprehensive, accurate, and timely data systems to address an emerging threat. The increases in samples from drug seizures testing positive for xylazine and drug poisoning deaths involving xylazine demonstrate that xylazine exposure is increasing rapidly. Accordingly, fentanyl adulterated with xylazine meets ONDCP’s central criteria to determine whether a substance is an “emerging threat.” Additional information is needed to inform, implement, and evaluate a comprehensive and coordinated public health and public safety response. Examples of such additional information might include xylazine sourcing and determining to what degree persons are encountering xylazine alone or xylazine-adulterated products. To advance this work, the federal government will pursue the following steps:

Epidemiological System Enhancement, Coordination, and Development

Enhance and coordinate data systems to develop a comprehensive epidemiologic data system, including utilization of new testing strategies noted above; standardize medical examiner and coroner reports regarding the presence and role of xylazine in fatalities; create a central repository of key data; develop and publish a timely “dashboard” of the spread and impact of xylazine-adulterated fentanyl on counties across the country; and, as needed, develop and utilize novel data collection strategies such as wastewater testing.

Standardize Use of Diagnostic Codes

Develop recommendations for ICD-10-CM and ICD-10 coding of xylazine to optimize precision in data systems.

Develop an Impact Assessment

Develop an assessment of the differential impact of xylazine-adulterated fentanyl on communities (where disparities are defined broadly and as described in recent federal reports on best-practices in equitable data collection and analysis), as well as an assessment of key social determinants of health that may be related to xylazine use.

Evidence-Based Prevention, Harm Reduction, and Treatment Implementation and Capacity Building

Xylazine-adulterated fentanyl poses a number of unique health challenges, including but not limited to: (a) insufficient responses to the naloxone required to address fentanyl overdoses but that doesn’t impact xylazine effects; (b) severe breathing difficulty given xylazine’s analgesic and central nervous system depressant effects, requiring intensive breathing assistance; (c) the development of “dual” dependence on both fentanyl and xylazine associated with extremely severe withdrawal symptoms; (d) difficulty initiating addiction treatment, including medication for opioid use disorder, for people using both fentanyl and xylazine given lack of consensus on the best treatment protocols, and because severe withdrawal symptoms may cause a patient to leave treatment against medical advice; and (e) development of serious wounds, the severity of



some requiring limb amputation. To address these and other concerning health challenges, the federal government will:

Develop and Deploy a Treatment Framework

Develop and disseminate best practices based on emerging clinical efforts with patients exposed to xylazine to identify the most promising clinical stabilization, withdrawal management (detoxification), and treatment protocols. Relatedly, utilize or establish efficient mechanisms for sharing and regularly updating current best practices information, using both federal and non-federal channels of communication such as health departments. Information about withdrawal management, treatment initiation, treatment retention, and re-engagement strategies will be particularly important.

Develop and Deploy Overdose Treatment and Other Harm Reduction Strategies

Rapidly evaluate potential xylazine overdose reversal strategies (including reversal agents) and inform educational and capacity-building efforts for persons who use drugs, community bystanders witnessing drug poisonings, persons leaving carceral settings, healthcare providers, harm reduction staff, and first responders on best practices to address overdoses due to xylazine, including overdoses involving xylazine and fentanyl (focused on the use of assisted breathing, hands-only CPR, and naloxone). These constituencies should be involved in message development to maximize credibility.

Capacity Building Among First Responders and Other Service Providers

Prioritize efforts to educate and equip healthcare providers, harm reduction staff, health-sector payers, and first responders on best practices to treat flesh wounds associated with xylazine. This should include explicitly encouraging federal grantees to utilize grant monies to address xylazine-related challenges, e.g., the purchasing of wound care kits and other resources needed for wound healing, or other validated intervention tools and strategies to coordinate care across a number of types of necessary services. These efforts may involve a variety of channels of communication.

Educate the Public

Collaborate with private and nonprofit sector partners to integrate adulterant information into existing national media campaign efforts related to fentanyl or toxicity of the drug supply more broadly, and continually gauge the need for xylazine-specific messaging.

Source and Supply Information and Intelligence; and Supply Reduction Actions

Xylazine is the active ingredient in an animal drug approved for veterinary use, but not human use. It is not a controlled substance, and public health and public safety officials need to know more about the sources of xylazine in the illicit drug supply chain and markets in the United States. This information will be critical when considering effective actions to take to disrupt the supply of xylazine destined for human use. The federal government will:



Identify the Illicit Supply Chain

Identify sources of xylazine and determine whether it is diverted from legitimate supplies and/or synthesized for illicit use, including who may be synthesizing it (including the development of analytic protocols to identify such sources), and identify points and methods of illicit drug supply adulteration to disrupt and reduce the supply and trafficking of the illicit supply.

Enhance Regulation Capabilities

Enhance ability and jurisdiction to regulate the supply chain (e.g., from active pharmaceutical ingredient (API) producer, finished dosage form manufacturer, to the veterinarian) while maintaining availability for its legitimate uses in animals and research, and, separately, to restrict the unlawful entry of xylazine active pharmaceutical ingredients and finished dosage form drug products into the country.

Develop Interdiction Tactics

Identify and develop additional targeted and coordinated law enforcement actions and efforts to reduce the illicit supply of xylazine and the precursor chemicals associated with the production of illicit xylazine, and disrupt trafficking of fentanyl adulterated or associated with xylazine. Identify whether other substances may supplant xylazine as a fentanyl additive in the future.

Regulatory Control and Monitoring Options

As part of this action plan, the U.S. government should assess regulatory options to disrupt the production, distribution, illegal sale and trafficking (even if not scheduled), and exposure to illicit xylazine. The particular chemical nature of this non-opioid tranquilizer may pose challenges for traditional methods of testing drugs in scheduling decisions. The federal government will:

Explore Scheduling and Other Regulatory Options

Progress toward decisions on possible regulatory actions under the Controlled Substances Act, including scheduling of xylazine while simultaneously maintaining the legitimate supply of xylazine in veterinary medicine, and prioritizing facilitation of access to xylazine for research purposes. The government will also consider other potential avenues for prosecuting those who manufacture, import, export, sell, or distribute xylazine in order to support fentanyl trafficking.

Investigate Scope of Scheduling

Discuss whether any potential regulatory actions should be xylazine-specific or for a broader class of drugs or pharmacologically similar substances that could replace xylazine as a fentanyl adulterant.

Support Interdiction Efforts

Identify opportunities to enhance importation oversight, prevent diversion throughout the legitimate supply chain, and to further enable both civil and criminal actions by authorities to effectively interdict and reduce illicit supply.



Basic and Applied Research

As noted above, there are multiple areas that require further knowledge for the comprehensive, optimal prevention and treatment of fentanyl-adulterated xylazine use and poisoning (i.e., identification of the most impactful treatment protocol for overdoses caused by fentanyl adulterated or associated with xylazine). Below are further areas of needed basic and applied research (though the topics may shift as this fast-moving area unfolds):

Treatment Development

Conduct research to evaluate as quickly as possible potential xylazine antidotes in humans, and identify the most promising clinical stabilization, detoxification, and treatment protocols.

Investigate How Xylazine Impacts Humans Physiology and Behavior

Conduct basic research on drug-drug interactions to understand the pharmacology, chemistry, biology and toxicology of how xylazine and fentanyl interact in humans and the behavioral consequences. Examine whether any of these effects vary across modes of xylazine administration (e.g., injecting, smoking, or inhalation). Include research on the effects of fentanyl adulterated with xylazine used during pregnancy.

Research Social Outcomes of Xylazine Use in Humans

Conduct applied research on population-level health, social, equity, and economic drivers and consequences of exposure to fentanyl adulterated with xylazine.

Research on Use Motivations

Conduct research on awareness of and motivations for use of xylazine-containing products, strategies people use to reduce harm, how motivations related to use are changing over time, as well as the recovery process for those who have been able to stop use after a sustained period of consumption of xylazine-adulterated fentanyl.

Goals

Pursuant to the SUPPORT Act and the Criteria for Designating Evolving and Emerging Drug Threats (Dir. No. 2022-002), the Director of National Drug Control Policy is establishing a national goal that, if met, would lead to the termination of fentanyl adulterated or associated with xylazine as an emerging threat. The goal is:

A 15% reduction (compared to 2022 as the baseline year) of xylazine positive drug poisoning deaths in at least three of four U.S. census regions by 2025.

Key shorter-term actions include the following by the end of fiscal year (FY) 2024 (*additional FY24 action objectives may be provided by National Drug Control Program agencies in their emerging threat implementation report due to ONDCP 180 days after fentanyl adulterated with xylazine is designated an emerging threat, and other important action steps are listed in the plan above*):



- Development, validation, marketing authorization, and deployment, as appropriate, of tests for xylazine and/or fentanyl intended for real-time clinical care (point of care testing). [Measured dichotomously on each of the four stages listed here.]
- Development and rapid evolution of best practices for initiating and maintaining treatment of fentanyl adulterated or associated with xylazine in healthcare settings. [Measured dichotomously and evidenced by publicly-available best practices document.]
- Development and rapid evolution of wound care best practices for successfully treating flesh wounds associated with fentanyl adulterated or associated with xylazine in community-based and other situations. [Measured dichotomously and evidenced by publicly-available best practices document.]
- Implementation of capacity-building programs focused on fentanyl adulterated or associated with xylazine treatment and wound care to be available (virtually) to all healthcare providers (including harm reduction service providers) in the United States. [Measured dichotomously and evidenced by publicly available capacity building materials online.]
- Identification and commencement of implementation strategies to identify the sources and to reduce the diversion and/or illicit supply of xylazine, especially focused on xylazine being used as an adulterant with fentanyl. [Measured dichotomously by actions described in briefing materials to ONDCP Director and which may or may not be publicly-available depending on sensitivity of information.]



Conclusions and Key Federal Leadership Responsibilities

Xylazine is a substance not meant for human consumption and is particularly harmful in combination with fentanyl. All those who may use fentanyl adulterated with xylazine are encouraged to seek medical care as well as behavioral health services. Although more information is necessary to develop the most effective testing and treatment protocols, medical professionals possess enough information to improve the health and safety of those exposed to xylazine and facing serious negative health consequences. Partnering with the community, especially community-based programs with experience working with individuals actively using fentanyl adulterated with xylazine, will be critical for maximum impact.

While this plan outlines action steps the federal government will pursue to address this threat, we need a whole-of-society effort to save lives. Healthcare providers are encouraged to be on the alert for signs and symptoms of patients' exposure to fentanyl adulterated with xylazine and to provide effective care for overdose and wounds, and initiate or transfer care to opioid use disorder treatment services wherever these patients are encountered. State, county, and city health authorities are encouraged to proactively seek out those believed to be consuming fentanyl adulterated with xylazine to offer mobile, low-threshold care before their conditions worsen. Addiction treatment and emergency responders should consult with experts on xylazine detoxification methods to understand emerging practices. Law enforcement and elected officials must coordinate with their public health colleagues in order to enhance the efficacy of their efforts to reduce and disrupt the illicit supply chain and go after traffickers. Community-based programs will be amongst the first to interface with individuals vulnerable to fentanyl adulterated with xylazine and will be key partners in these efforts. These are urgently needed, practical steps that can help mitigate the harmful impacts of xylazine as the elements of the response plan described above come to fruition.

As further actions are taken on this response plan, multiple federal agencies and many partners will have important roles to play. In the table below, some initial key areas of federal department-level leadership are noted; as each agency develops an implementation strategy to enact this response plan, this list of departmental-level leadership and partnership may evolve.



Key Department-level Leadership and Partnership Roles, by Activity Area

Testing	Department of Health and Human Services, Department of Justice, Department of Veterans Affairs
Standardize Forensic Testing Practices	Centers for Disease Control and Prevention
Develop New Tests for Clinical Settings	Food and Drug Administration, Centers for Disease Control and Prevention
Deploy Testing in Community Settings	Substance Abuse and Mental Health Services Administration, Health Resources Services Administration, Centers for Disease Control and Prevention
Target Testing to Those In-Need	Centers for Disease Control and Prevention, Food and Drug Administration
Epidemiology and Comprehensive Data	Department of Health and Human Services, Department of Justice, Department of Transportation
Epidemiological System Enhancement, Coordination, and Development	Centers for Disease Control and Prevention, Substance Abuse and Mental Health Services Administration, Drug Enforcement Administration
Standardize Use of Diagnostic Codes	Centers for Disease Control and Prevention
Develop an Impact Assessment	Substance Abuse and Mental Health Services Administration, Health Resources Services Administration
Evidence-based Prevention, Harm Reduction, and Treatment Implementation and Capacity Building	Department of Health and Human Services, Department of Veterans Affairs, Department of Transportation
Develop and Deploy a Treatment Framework	Substance Abuse and Mental Health Services Administration, National Institute on Drug Abuse, Veterans Health Administration, Health Resources and Services Administration, Centers for Medicare and Medicaid Services



Develop and Deploy Overdose Treatment and Other Harm Reduction Strategies	Substance Abuse and Mental Health Services Administration, Veterans Health Administration, National Institute on Drug Abuse, Centers for Disease Control and Prevention
Capacity Building Among First Responders and Other Service Providers	Substance Abuse and Mental Health Services Administration, Centers for Disease Control and Prevention, National Highway Traffic Safety Administration
Educate the Public	Centers for Disease Control and Prevention
Source and Supply Information and Intelligence; and Supply Reduction Actions	Department of Justice, Department of Homeland Security, Department of State, Department of Health and Human Services
Identify the Illicit Supply Chain	Food and Drug Administration, Drug Enforcement Administration
Enhance Regulation Capabilities	Food and Drug Administration, Drug Enforcement Administration
Develop Interdiction Tactics	Bureau of International Narcotics and Law Enforcement, Drug Enforcement Administration, Food and Drug Administration
Regulatory Control and Other Regulatory Options	Department of Health and Human Services, Department of Justice
Explore Scheduling and Other Regulatory Options	Food and Drug Administration, Drug Enforcement Administration
Investigate Scope of Scheduling	Food and Drug Administration, Drug Enforcement Administration, National Institute on Drug Abuse
Support Interdiction Efforts	Drug Enforcement Administration, Food and Drug Administration
Basic and Applied Research	Department of Health and Human Services, Department of Justice, Department of Veterans Affairs
Treatment Development	National Institute on Drug Abuse, Food and Drug Administration



Investigate How Xylazine Impacts Humans Physiology and Behavior	National Institute on Drug Abuse
Research Social Outcomes of Xylazine Use in Humans	Centers for Disease Control and Prevention, National Institute on Drug Abuse
Research on Use Motivations	Substance Abuse and Mental Health Services Administration, National Institute on Drug Abuse
Oversight and Coordination	White House Office of National Drug Control Policy