December 11, 2023

Speaker Mike Johnson
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House Minority Leader Hakeem Jeffries
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Chair Cathy McMorris Rodgers
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Ranking Member Frank Pallone
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Chair Jim Jordan
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Ranking Member Jerrold Nadler
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CC: Senate Majority Leader Chuck Schumer; Minority Leader Mitch McConnell; Chair Bernie Sanders, U.S. Senate Committee on Health, Education, and Labor, and Ranking Member Bill Cassidy, U.S. Senate Committee on Health, Education, and Labor, U.S. Senate Judiciary Committee

Re: Opposition to Placing Xylazine on Schedule III of the CSA (Sec. 203, Title II of H.R. 4531)

Dear Speaker Johnson, Majority Leader Scalise, Minority Leader Jeffries, Chair McMorris Rodgers, Ranking Member Pallone, Chair Jordan, Ranking Member Nadler, and Honorable Members of Congress:

We, as public health professionals, scientists and researchers, urge you to oppose placing xylazine on Schedule III of the Controlled Substances Act (CSA), as found in Sec. 203, Title II of the Support for Patients and Communities (SUPPORT) Reauthorization Act (H.R. 4531).

As members of the scientific and public health community, we are concerned Congress is placing xylazine on the CSA before thorough scientific studies and research on xylazine can be conducted. Current research on xylazine shows there is a strong need for further research to better understand the pharmacological properties of xylazine, the pathophysiological effects of xylazine, overdose risk, clinical treatments, harm reduction responses, potential racial and gender disparities, and patterns of use, among other needed research.[1]

[1] "Mitigating Risks from Human Xylazine Exposure." *U.S. Food and Drug Administration*, October 4, 2023 (https://www.fda.gov/news-events/mitigating-risks-human-xylazine-exposure-10042023).

From a scientific perspective, we have three major concerns. First, large states that have scheduled xylazine have seen increases in drug overdose deaths. Placing xylazine in Schedule III is not effective in preventing overdose deaths. Second, we are on the precipice of scientific discoveries to medically address skin wounds and overdose related to xylazine. Placing xylazine in Schedule III would have an immediate chilling effect in our ability to find biomedical solutions. Third, placing xylazine in Schedule III would have massive disruptive impacts on medical practice.

1. Xylazine bans do not prevent overdose. We all want our loved ones and communities to be safe, but scheduling xylazine does not prevent overdose deaths. For example, a ban on xylazine in Florida shows that criminalizing the substance has not reduced overdose deaths. Florida placed xylazine on Schedule I of the state CSA in 2018. [2] In 2018, there were 3,727 opioid overdose deaths in Florida; in 2021 that number had grown to 6,442.[3]

2. Scheduling xylazine would halt critical xylazine-related research. Very recent research reveals that scientific understanding of xylazine is outdated: Xylazine is an active and strong agonist at the kappa opioid receptor, as well as the traditionally known activity at alpha-2 adrenergic receptors (α2-ARs).[4] Within the medical community there are urgent questions that need answers, such as how effective naloxone is in reversing xylazine overdoses and treatment of xylazine wounds.[5] Placing xylazine in Schedule III at this time would have an immediate chilling effect on the public health and biomedical drive to find solutions.

Xylazine upends traditional remediation measures in drug policy (e.g., "Backbone Scheduling" for fentanyl analogues) because of the widespread use of closely related medicines. Seven out of 9 FDA-approved drugs most similar to xylazine are not scheduled, and none are Schedule III (Table 1). No other α2 or kappa opioid agonists are in Schedule III. Several other notable kappa opioid agonists include pentazocine (Schedule IV), butorphanol (Schedule IV), and nalbuphine (not scheduled).[6] Considering the variability in scheduling for these comparable drugs, it remains uncertain how the classification of xylazine on Schedule III could be justified without additional research. Further, scheduling xylazine on Schedule III would create precedent to automatically schedule nearly identical molecules (Figure 1) without the necessary research to investigate how these substances are used in many places throughout veterinary and human medical practice. Furthermore, the international drug scheduling standards set by the United Nations do not support the placement of xylazine at Schedule III.[7]

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[2] "CHAPTER 2018-13." Committee Substitute for Committee Substitute for House Bill No. 21, March 19, 2018. https://laws.flrules.org/files/Ch_2018_013.pdf.

[3] 2021 is the year the most recent complete data for mortality. Florida Department of Health, FL Health Charts, Substance Use Dashboard. https://www.flhealthcharts.gov/ChartsDashboards/rdPage.aspx?rdReport=SubstanceUse.Overdose

[4] Zagorski, Claire M. et al. 2023. "Reducing the Harms of Xylazine: Clinical Approaches, Research Deficits, and Public Health Context." *Harm Reduction Journal* 20(1).

[5] Bedard, Madigan L. et al. 2023. "Xylazine Is an Agonist at Kappa Opioid Receptors and Exhibits Sex-Specific Responses to Naloxone Administration." Preprint. *Neuroscience*.

[6] Gupta, Rahul, David R. Holtgrave, and Michael A. Ashburn. 2023. "Xylazine — Medical and Public Health Imperatives." *New England Journal of Medicine* 388(24):2209–12.

[7] "Drug Conventions." *United Nations : Office on Drugs and Crime*. (https://www.unodc.org/unodc/en/commissions/CND/Mandate_Functions/Scheduling.html).

Figure 1. Several FDA-Approved Medications Are Nearly Identical to Xylazine

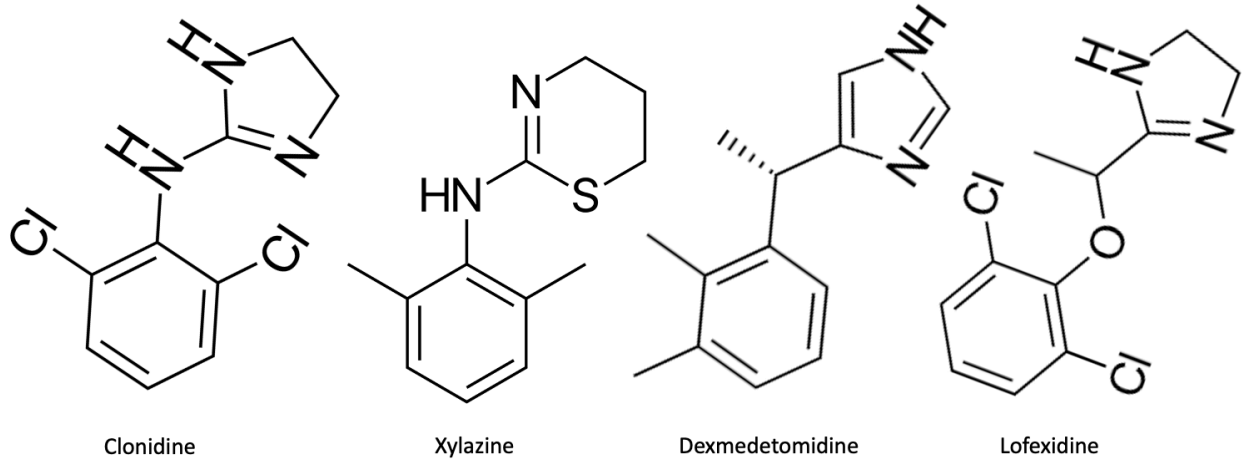

Table 1. FDA-Approved Medications Similar to Xylazine are Either Unscheduled or in a Lower Schedule.

Drug	Federal Schedule	Population	Medical Use
Alpha 2 agonists			
Clonidine	None	Human	Hypertension, opioid withdrawal
Lofexidine	None	Human	Opioid withdrawal
Apraclonidine	None	Human	Post-surgery eye drops
Medetomidine	None	Animals	Analgesia and sedation
Dexmedetomidine	None	Human	**1. Ubiquitous** in hospital ICUs for surgical procedure 2. Schizophrenia
Dexmedetomidine	None	Animal	1. Dog behavior training 2. **Widely and frequently** used for sedation in biomedical research
Romifidine	None	Animal	Analgesia and sedation
Kappa opioid agonists			
Pentazocine	IV		Severe pain
Butorphanol	IV	Human and animal	Migraine and severe pain
Nalbuphine	None	Human	Severe pain

3. Scheduling xylazine would disrupt medical practices. For instance, dexmedetomidine (Precedex) is a very similar and widely used medicine to xylazine, and is unscheduled. Dexmedetomidine is the go-to medication in hospital intensive care units (ICUs) and emergency departments (EDs) for initial sedation during surgical and intubation procedures. It is widely used specifically because it is unscheduled and can therefore be administered rapidly by a wide range of nurses and doctors at critical times. Given the structural similarities, putting xylazine in the CSA paves the way to also place dexmedetomidine in the CSA: In March 2023, DEA NFLIS[8] reported that dexmedetomidine (also known as medetomidine) has emerged in the United States as a street drug mixed with fentanyl. The disruption to medical practice would be severe.

Including xylazine in the CSA would hinder research into the pharmacological characteristics and toxicology of xylazine, as well as disrupt studies focused on harm reduction strategies related to xylazine.[9] Moreover, scheduling xylazine could impede essential biomedical research aimed at comprehending sex-specific responses to xylazine, exploring the use of other α2 antagonists, and examining the potential impact of xylazine on other receptors. Beyond substance use, xylazine is routinely used in pharmaceutical development because it is unscheduled to study new medications, from diabetes to Alzheimer's to cancer. Placing xylazine in Schedule III would be massively disruptive to essential American industry.

Typically for a substance to be classified on the CSA, the U.S. Department of Health and Human Services conducts a scientific evaluation of medical use and abuse, and makes a recommendation to the Department of Justice.[10] However, if Congress schedules xylazine by force without accounting for science, it would create a dangerous precedent halting scientific researchers and pharmaceutical companies from conducting research regarding the pathophysiology of xylazine, overdose risk, use patterns and behaviors, and both clinical and harm reduction responses to xylazine use. Additionally, the scheduling of xylazine would affect the ability for researchers to further explore the potential for other reversal agents and treatment for withdrawal symptoms.[11]

Policy Solutions

As dedicated scientists and public health officials who are working on the frontlines to address and prevent further harm from the overdose crisis, we focus our commitment to aiding people in advancing overall public health and wellbeing. We prioritize science-driven approaches to the prevention of overdoses and drug user safety. A critical aspect of these endeavors is to continue to guarantee that federal agencies, researchers, pharmaceutical companies, and other public health agencies can evaluate emerging substances for their potential therapeutic value, including xylazine and similar kappa opioids.

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[8] National Forensic Laboratory Information System. March 2023. *NFLIS Drug Snapshot March 2023.* https://www.nflis.deadiversion.usdoj.gov/nflisdata/docs/12557NFLISSnapshot2023March.pdf

[9] Kolla, Gillian and Carol Strike. 2020. "Practices of Care among People Who Buy, Use, and Sell Drugs in Community Settings." *Harm Reduction Journal* 17(1).

[10] "Drug Scheduling." *United States Drug Enforcement Administration*. (https://www.dea.gov/drug-information/drug-scheduling).

[11] Harvey, Leah H., Traci C. Green, Ju Nyeong Park, and Josiah D. Rich. 2023. "Xylazine in the Drug Supply: A Research Agenda." *International Journal of Drug Policy* 120:104190.

Rather than rushing to place xylazine on the CSA, lawmakers should prioritize expanding federal funding available for research on xylazine and other kappa opioids so that we can better understand the pharmacological effects of xylazine, evaluate the effectiveness of other medications to aid xylazine withdrawal symptoms, and know how to treat xylazine use in clinical settings.[12] Additionally, lawmakers should strengthen harm reduction efforts to aide in addressing the overdose epidemic; including expanding access to naloxone, buprenorphine, and naloxone, funding xylazine test strips, and overdose prevention services.

As further scientific research regarding xylazine is critical, **we strongly urge Congress to oppose temporarily or permanently placing xylazine on Schedule III of the CSA.** Thank you for reading this letter.

Sincerely,

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[12] "Senate Bill S. 1280." 2023-2024 Legislative Session, April 25, 2023. https://www.congress.gov/bill/118th-congress/senate-bill/1280/text?s=1&r=90.

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