NOVEL PSYCHOACTIVE SUBSTANCES: "PYRO"

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The Legislative Analysis and Public Policy Association (LAPPA) is monitoring the emergence of novel psychoactive substances (NPS) appearing on the streets of the United States. This fact sheet, which focuses on ***N*-pyrrolidino etonitazene**, is the first in a series that highlights these dangerous drugs.

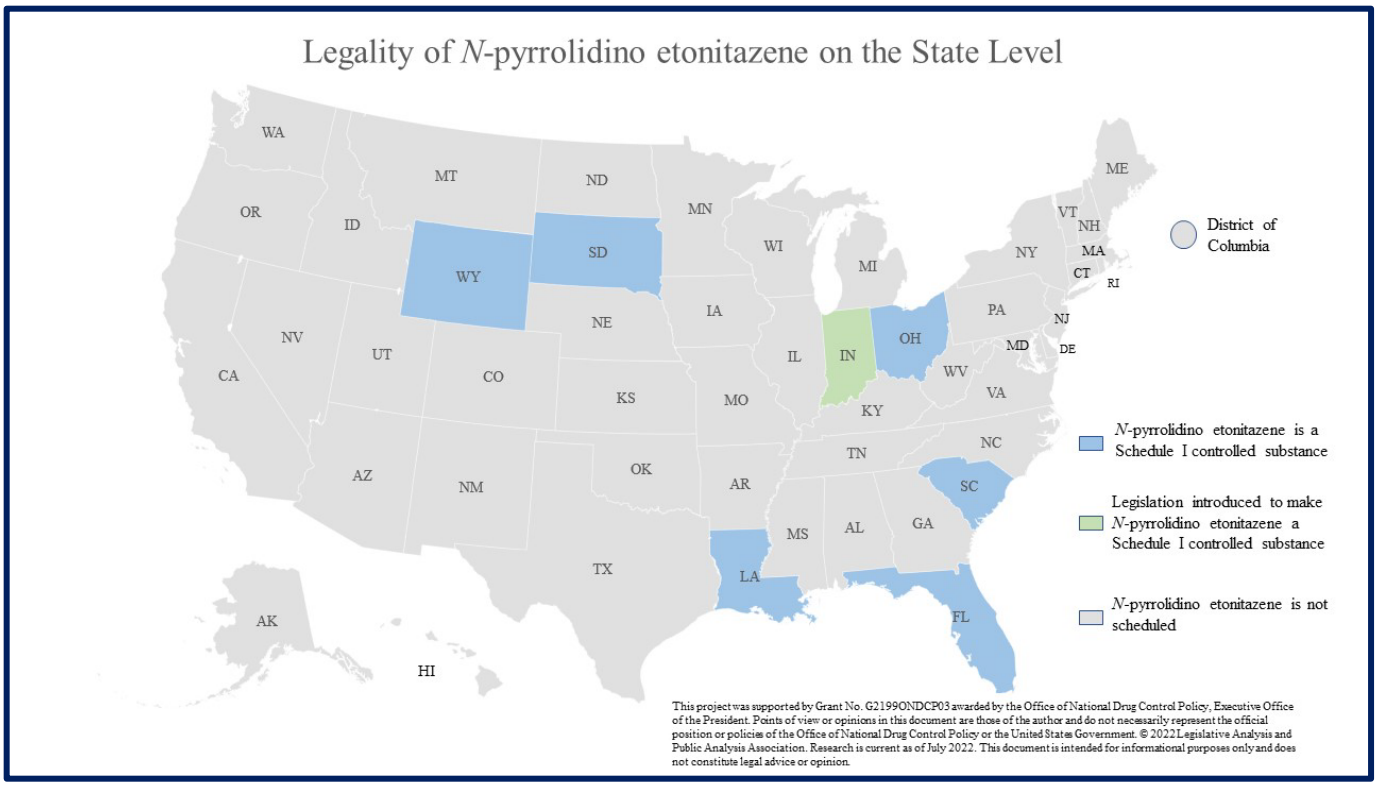
N-pyrrolidino etonitazene, also known as etonitazepyne and by the street name "Pyro," is a relatively new high potency synthetic opioid increasing in prevalence in the U.S. Pyro belongs to an opioid subclass of NPS called 2-benezylbenzimidazoles, or nitazenes, and is structurally similar to etonitazene, a synthetic opioid that is nationally and internationally controlled. The nitazene subclass also includes isotonitazene, also known as "Iso," which the U.S. Drug Enforcement Administration (DEA) temporarily listed as a Schedule I controlled substance on August 20, 2020 and permanently scheduled on December 6, 2021.[1] Unlike other nitazenes identified thus far, *N*-pyrrolidino etonitazene is not described or mentioned in any medical literature or patents, meaning that it is a truly "novel" NPS and likely developed independently from the pharmaceutical industry. Researchers believe that N-pyrrolidino etonitazene is coming to the U.S. via purchases on the dark web and is likely being produced in China. *N*-pyrrolidino etonitazene can be found in powder form or pressed into pills to resemble other substances. Studies estimate that *N*-pyrrolidino etonitazene is over 800 times more potent than morphine and 20-40 times more potent than fentanyl. Like other opioids, *N*-pyrrolidino etonitazene use can potentially cause fatal respiratory depression in the person ingesting the drug. However, because *N*-pyrrolidino etonitazene is an opioid, naloxone can be used to reverse an overdose.

The Center for Forensic Science Research & Education's NPS Discovery program first reported *N*-pyrrolidino etonitazene in the U.S. in May 2021. This first encounter stemmed from a fatal overdose investigation in West Virginia. A subsequent toxicological study confirmed the presence of *N*-pyrrolidino etonitazene in the blood samples of 21 postmortem cases collected between January and October 2021. Of the 21 cases, 17 were from the U.S. (eight cases from West Virginia, two cases from Florida, and single cases from Colorado, Kentucky, Minnesota, New Jersey, New York, Pennsylvania, and Tennessee). The other four cases were from British Columbia, Canada. In all 21 cases, researchers identified other substances along with *N*-pyrrolidino etonitazene in the biological specimen. Researchers identified *N*-pyrrolidino etonitazene in combination with fentanyl in 12 cases, in combination with methamphetamine in 12 cases, and in combination with NPS benzodiazepines in 11 cases. The study found very low concentrations of *N*-pyrrolidino etonitazene in the 21 blood samples (less than 10 ng/mL),[2] which corresponds with the high potency of the substance. The low concentrations also stress the need for highly sensitive instrumentation to detect nitazene opioids.

[1] Schedules of Controlled Substances: Temporary Placement of Isotonitazene in Schedule I, 85 Fed. Reg. 51,342 (Aug. 20, 2020); Schedules of Controlled Substances: Placement of Isotonitazene in Schedule I, 86 Fed. Reg. 60,761 (Nov. 4, 2021).
[2] Nanograms per milliliter. A nanogram is one billionth of a gram.

On April 12, 2022, the DEA temporarily placed *N*-pyrrolidino etonitazene on the list of Schedule I controlled substances along with six other nitazenes.[3] The DEA believes that *N*-pyrrolidino etonitazene, and the other six substances, should be listed in Schedule I due to their similarity to etonitazene and isotonitazene, which are both Schedule I substances. Additionally, the DEA found that the available data and information on *N*-pyrrolidino etonitazene and the other six nitazenes indicates that these substances have a high potential for abuse, no currently accepted medical use, and a lack of accepted safety for use under medical supervision. The temporary scheduling order is effective until April 12, 2024, unless it is extended or made permanent before then.

In addition to the temporary scheduling of *N*-pyrrolidino etonitazene on the federal level, several states recently placed the substance into their respective controlled substance schedules. As of July 2022, *N*-pyrrolidino etonitazene is a Schedule I controlled substance in Florida,[4] Louisiana,[5] Ohio,[6] South Carolina,[7] South Dakota,[8] and Wyoming.[9] Additionally, Indiana introduced a bill in 2022 to place *N*-pyrrolidino etonitazene on the list of Schedule I controlled substances, but the bill did not pass before the legislative session ended.[10]



With its high potency, *N*-pyrrolidino etonitazene will be expected to cause a rise in overdoses as it spreads throughout the U.S. drug supply. As the presence of the drug increases, more states will likely introduce legislation to schedule the substance.

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[3] Schedules of Controlled Substances: Temporary Placement of Butonitazene, Etodesnitazene, Flunitazene, Metodesnitazene, Metonitazene, *N*-pyrrolidino etonitazene, and Protonitazene in Schedule I, 87 Fed. Reg. 21,556 (April 12, 2022).
[4] FLA. ADMIN. CODE ANN. r. 2ER22-1 (West 2022). *N*-pyrrolidino etonitazene scheduled effective April 26, 2022.
[5] LA. STAT. ANN. §40:964 (West 2022). *N*-pyrrolidino etonitazene scheduled effective August 1, 2022.
[6] OHIO ADMIN. CODE 4729:9-1-01.2 (West 2022). *N*-pyrrolidino etonitazene scheduled effective April 6, 2022.
[7] South Carolina Board of Health and Environmental Control, Placement of Butonitazene, Etodesnitazene, Flunitazene, Metodesnitazene, Metonitazene, *N*-pyrrolidino etonitazene, and Protonitazene in Schedule I for Controlled Substances (May 5, 2022), https://scdhec.gov/sites/default/files/media/document/Signed%20Board%20Order.pdf.
[8] S.D. CODIFIED LAWS § 34-20B-12 (West 2022). *N*-pyrrolidino etonitazene scheduled effective February 10, 2022.
[9] 015-0015.1 WYO. CODE R. § 3 (West 2022). *N*-pyrrolidino etonitazene scheduled effective April 19, 2022.
[10] S.B. 209, 2022 Gen. Assemb., Reg. Sess. (Ind. 2022). (Passed in Senate and House, pending in conference committee upon adjournment).

RESOURCES

"New High Potency Synthetic Opioid *N*-Pyrrolidino Etonitazene (Etonitazepyne) Linked to Overdoses Across United States." *NPS Discovery*, June 2021, https://www.npsdiscovery.org/wp-content/uploads/2021/06/Public-Alert_N-Pyrrolidino-Etonitazene_NPS-Discovery_061721.pdf.

Khaled, Fatma. "New Drug about 10 Times Stronger Than Fentanyl Circulating in Colorado." *Newsweek*, July 22, 2022. https://www.newsweek.com/synthetic-opioid-pyro-fentanyl-colorado-1727307.

Vandeputte, Marthe M., et al. "Pharmacological Evaluation and Forensic Case Series of *N*-pyrrolidino etonitazene (etonitazepyne), a Newly Emerging 2-benzylbenzimidazole 'Nitazene' Synthetic Opioid." *Archives of Toxicology* 96, no. 6 (April 2022): 1845-1863. https://doi.org/10.1007/s00204-022-03276-4.

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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 timely model laws and policies that can be used by national, state, and local public health, public safety, and substance use disorder practitioners who want the latest comprehensive information on law and policy as well as up-to-the-minute comparative analyses, publications, educational brochures, and other tools ranging from podcasts to fact sheets. Examples of topics on which LAPPA has assisted stakeholders include law enforcement/community engagement, naloxone laws, alternatives to incarceration for those with substance use disorders, medication for addiction treatment in correctional settings, and the involuntary commitment and guardianship of individuals with alcohol or substance use disorders.

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