



Clinical Update: July 2021

## NPS FOCUS: "NITAZENE" SYNTHETIC OPIOIDS

Aegis launched an extensive and industry-leading testing menu of Novel Psychoactive Substances (NPS) in mid-2020, which includes phenibut, tianeptine, xylazine, designer benzodiazepines, designer opioids, hallucinogens/dissociatives, synthetic cannabinoids, and synthetic stimulants, and continues to expand. In this month's update, we will focus on the evolution of the non-fentanyl opioid analogue drug class commonly referred to as "nitazenes" and the challenges associated with detection and monitoring of these illicit substances.

Origins of the "nitazenes" have been traced back to decades old pharmaceutical industry attempts to develop a novel opiate alternative to morphine.<sup>1-2</sup> However, due to a high risk for abuse potential and reports of an overdose in early human studies, the "nitazenes" were deemed "not suitable for human consumption" and never gained approval for clinical use. With the increased regulation of older substances such as fentanyl and Schedule 1 illegal drugs, more varied chemical classes of opioids are in high demand. In response, the "nitazenes" have recently been "re-discovered" as an equally effective substitute and are illicitly marketed as a drug less detected in drug monitoring programs.

Isotonitazene (also referred to as "iso"), is the prototypical, most frequently encountered member of the "nitazenes". Iso is an extremely potent mu opioid receptor agonist and is structurally unrelated to fentanyl or traditional opioids.<sup>1</sup> It first appeared in Canada and Europe in March 2019. By July 2019, isotonitazene was found in biological samples in the United States and has since been identified in over 250 drug overdose deaths. The DEA placed a temporary Schedule I ban on isotonitazene the following year in August 2020. Consequently, isotonitazene also debuted on the DEA's 2020 Annual Emerging Threat Report opioid/analgesics list, identifying isotonitazene as a significant threat to public health in the United States.<sup>3</sup>

The increased regulation of isotonitazene has led to unscheduled "nitazenes" such as butonitazene and metonitazene currently experiencing a trend in increased distribution and use. As recently as January to February 2021, butonitazene, was identified in Belgium and the U.S.<sup>1</sup> Metonitazene, a closely related analogue, was also recently found in confiscated material in the U.S. where it appears to be steadily gaining in popularity.<sup>1-2</sup> In fact, the Center for Forensic Science Research & Education (CFSRE) recently released their 2021 Q1 Trend Report revealing metonitazene commonly being used in combination with fentanyl and flunitazene, as well as with NPS benzodiazepines.<sup>4</sup>

The risks associated with the use of these substances are largely unknown but have the potential to be significant. *In vitro* studies have shown the "nitazenes" to not only be potent full mu opioid receptor agonists, but also more efficacious than morphine, and some more potent than fentanyl.<sup>1,5</sup> Due to the unethical nature of conducting human studies to further investigate the effects of this emerging synthetic opioid class, no published pharmaceutical *in vivo* data is available.<sup>1-2,5</sup> However, low blood concentrations reported in isotonitazene-related fatalities suggest that the high mu opioid receptor action potential observed *in vitro* is mirrored by high *in vivo* activity as well. The pharmacological characteristics of the "nitazenes" indicate that the risks associated with their use would be comparable to opioids, including dependence, respiratory depression, and possibly life-threatening overdose.<sup>1,5-6</sup> Further, as these compounds are not routinely screened in most drug monitoring programs or may be present at very low concentrations, their presence can easily be overlooked in intoxication cases.<sup>1</sup> Each of the previously mentioned factors, combined with the documented increased availability of the "nitazenes" in uncontrolled environments only augments the complexity to the ongoing opioid epidemic.

Unfortunately, NPS will continue to evolve and emerge as recreational chemists develop and manipulate compounds to evade regulation and detection. Improvements in screening for the accurate detection of these



varying compounds requires highly sensitive analytical instruments. As a result, Aegis continues to track drug use trends and offer state-of-the-art NPS testing to help better inform providers and facilitate optimal care for individuals struggling with substance use.

The following substances are included in Aegis' "nitazenes" testing\*:

Desnitroisotonitazen	Metodesnitazene (metazene)
Etonitazene	Metonitazene
Etazene	Protonitazene
Isotonitazene	

\*Accurate as of July 1, 2021. Substances included in testing are continuously updated to reflect current trends in drug use.

**NOTICE:** The information above is intended as a resource for health care providers. Providers should use their independent medical judgment based on the clinical needs of the patient when making determinations of who to test, what medications to test, testing frequency, and the type of testing to conduct.

### References:

1. Vandeputte MM, Uytfanghe KV, Layle NK, St Germaine DM, Iula DM, Stove CP. Synthesis, chemical characterization, and  $\mu$ -opioid receptor activity assessment of the emerging group of "nitazene" 2-benzylbenzimidazole synthetic opioids. *ACS Chem Neurosci*. 2021;12(7):1241–1251.
2. United Nations Office on Drugs and Crime. Global SMART update 2020: the growing complexity of the opioid crisis. Accessed June 21, 2021. [https://www.unodc.org/documents/scientific/Global\\_SMART\\_Update\\_2020-Vol.24-Eng-Final.pdf](https://www.unodc.org/documents/scientific/Global_SMART_Update_2020-Vol.24-Eng-Final.pdf)
3. Center for Substance Abuse Research. DEA emerging threat report: annual 2020. Accessed June 22, 2021. <https://cesar.umd.edu/sites/cesar.umd.edu/files/pubs/DEA-Emerging-Threat-Report-2020-Annual.pdf>
4. Center for Forensic Science Research & Education. 2021 Q1 NPS Opioids Trend Report. Accessed June 21, 2021. [https://www.npsdiscovery.org/wp-content/uploads/2021/04/2021-Q1\\_NPS-Opioids\\_Trend-Report.pdf](https://www.npsdiscovery.org/wp-content/uploads/2021/04/2021-Q1_NPS-Opioids_Trend-Report.pdf)
5. Ujváry I, Christie R, Evans-Brown M, et al. DARK classics in chemical neuroscience: etonitazene and related benzimidazoles. *ACS Chem Neurosci*. 2021;12(7):1072-1092.
6. European Monitoring Centre for Drugs and Drug Addiction. EMCDDA technical report on the new psychoactive substance N,N-diethyl-2-[[4-(1-methylethoxy) phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine (isotonitazene). Published online June 2020.