Clinical Update: October 2023

# NITAZENE ANALOGS

Nitazene analogs are a subclass of designer opioids that are structurally different from opioids but attach to the same mu-opioid receptor.[1] This Novel Psychoactive Substance (NPS) subclass, also known as the 2-benzylbenzimidazoles,[2] is not approved for use in the United States,[3] but rather has been found in the illicit drug supply and has contributed to overdose deaths.[4] Originally, they were developed in the 1950s by a Swiss company with the hopes of being utilized as an opioid analgesic but were never approved for therapeutic use due to their addictive properties[5] and exceptionally high potency.[2]

The course in which the nitazene analogs appeared over time is a story that is perpetually repeated in the illicit drug market. As soon as an analyte is scheduled by the DEA, new NPS analytes appear and take their place. Between 2008 and 2018, the NPS opioid market was saturated with fentanyl and many variations of fentanyl analogs, also known as fentalogs.[5] But in 2019, class-wide bans in both the United States and China slowed the production and circulation of many fentanyl-related drugs.[2] Following the bans, chemists and manufacturers once again searched for new drug options to dodge legislation and found some of the original publications from the 1950s when nitazene analogs were first developed. In 2019, isotonitazene appeared in the recreational drug market and quickly became popular, contributing to hundreds of fatalities.[5] The DEA temporarily placed isotonitazene in Schedule 1 in June 2020 and this went into effect December 6, 2021.[6] However, just like before, new NPS agents took the place of isotonitazene, and it was again the nitazene class that continued to emerge. Four out of ten new synthetic opioids in 2020 were nitazene analogs while there was only one new fentanyl analog reported that year. In the following year 2021, there were seven new nitazene analogs discovered and there were no new fentanyl analogs. While nitazene use is still not as common as fentanyl use, like fentanyl or fluoro fentanyl, suppliers are replacing many tougher-regulated fentanyl analogs with nitazenes.[2] Seven nitazenes, including butonitazene, etodesnitazene, flunitazene, metodesnitazene, metonitazene, N-pyrrolidino etonitazene, and protonitazene, were issued a temporary placement in DEA Schedule 1 from April 12, 2022, to April 12, 2024. If this order is extended or made permanent, the DEA will publish a document in the Federal Register.[7]

Because nitazene analogs have both a high potency and a high affinity for the mu-opioid receptor, they can be much more lethal than opioids. Low blood concentrations of N-pyrrolidino etonitazene were found in accidental overdose victims because it is so potent. Lower doses of some of these analytes may be sufficient to yield significant and deadly opioid effects. A study published in 2021 examined nitazene analogs in vitro and found N-pyrrolidino etonitazene and etonitazenes to be the most potent at 20 times higher than that of fentanyl. Isonitazene, metonitazene, and protonitazene appeared to have a potency 1.5-10 times higher than that of fentanyl, and butonitazene demonstrated a potency 2-10 times lower than that of fentanyl.[5] Additional nitazene analogs since this study seem to have greater and less potencies than fentanyl.[1] Nitazene analogs have been found as yellow, brown, gray, or off-white powders, and are most often sold as “heroin” or “fentanyl” in illicit settings, but are also sold online as powders, ready-to-use nasal sprays, or counterfeit pills. Like fentanyl and heroin, nitazene analogs are most commonly used intravenously and intranasally using spray or insufflation, but can also be smoked, vaporized, or taken sublingually.[8]

In theory, opioid receptor antagonists like naloxone, may inhibit or reverse the action of these drugs. However, conditions that could limit the effectiveness of reversal agents may include the high potency of the drug, amount ingested, route of ingestion, body weight, opioid tolerance, and underlying health conditions. Higher doses and/or redosing of naloxone may be needed based on clinical signs and symptoms. The combination of drugs ingested must also be considered as many of the nitazene analogs have been found to be used with other NPS, illicit, and/or prescribed drugs[1], causing drug-drug interactions and/or compounding intoxication. Users may not always be aware of what is included in the substance they purchase in illicit drug markets, and often, dealers may not be informed either. As with most illicit drugs, nitazenes and other NPS analytes are developed to be cheap, easy to manufacture, highly intoxicating, and outside of DEA regulation. There are no manufacturing standards to maintain purity, quality, or consistency.[4] Since the onset of the opioid epidemic, new synthetic opioids

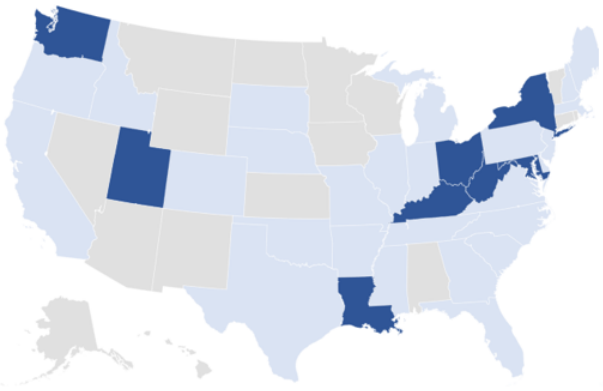
have been reported as the largest contributors to drug overdose deaths in the United States.[1] And for every fatal overdose, there are six to eight non-fatal overdoses which can lead to long-term morbidity.[4]

Aegis testing has included nitazene analogs since 2021 and the menu continues to adapt as the NPS landscape changes. Our latest offering updated in September 2023, includes the following nitazene analogs. These analytes are included in testing when the Designer Opioids are ordered.

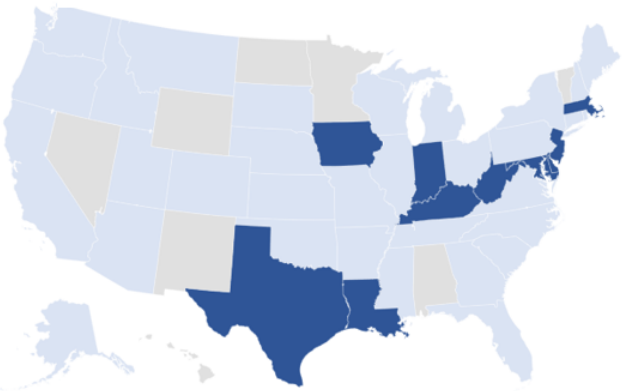
- Butonitazene
- Flunitazene
- Isotonitazene
- Metonitazene
- N-piperidinyl Etonitazene
- N-pyrrolidino Etonitazene
- N-pyrrolidino Metonitazene
- N-pyrrolidino Protonitazene
- Protonitazene

Aegis's positive results for two weeks in 2022 (9/19-10/1) compared to two weeks in 2023 (9/18-9/30), showed the number of different nitazene analogs reported increased from three to eight; however, there was only a small increase in overall positivity year over year. Nitazene analog results between states in the same period are shown in the figures below and direct our attention to how localized the positive results appear over time.

States with Nitazenes Detected
Samples Reported 9/19-10/01/22



States with Nitazenes Detected
Samples Reported 9/18-9/30/23



Dark blue: Nitazene identified
Light blue: Nitazene not identified
Gray: Not tested or <10 total tests (+/-fentanyl, +/- designer opioids, +/-NPS other)

The detection of nitazenes is still not a significant portion of NPS detected at Aegis as the use of fentanyl is found more and more in combination with other drugs. The data show a steep decrease in fentanyl-only positives from 62% to 43% year-over-year in the same two-week periods. The most detected NPS combinations with fentanyl included fentalogs, xylazine, and/or nitazene analogs. Even though NPS use is still under-detected, understanding the use of these lethal drugs improves as continued monitoring improves. Of those samples tested for any NPS and fentanyl, there was a 6% to 7% increase for samples that reported positive for any NPS or fentanyl.

Nitazene analogs are a very potent subclass of designer opioids that are continuing to materialize in the illicit drug market. Every new NPS analyte brings challenges of identification, toxicity risk, and prevalence,[1] and Aegis is prepared to accurately detect these compounds as we continually update our testing. Raising awareness about nitazene analogs and NPS is crucial to reducing harm through increased testing and linkage to treatment for substance use disorders.[9]

**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.

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