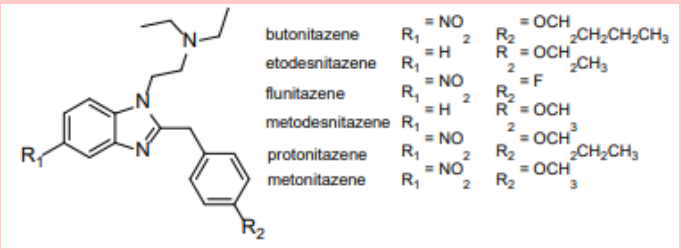
Alert!

Emerging Illicit Synthetic Opioids

Benzimidazole Class - Nitazenes

Background

The benzimidazole structural class of opioids were developed through pharmaceutical research in the late 1950s. These products were never approved for medical use in the United States given their extreme potency. Compared to morphine, metonitazene is about 100-fold more potent and protonitazene is about 200-fold more potent as analgesics. In comparison, according to the National Institute on Drug Abuse, fentanyl is 50 to 100 times more potent than morphine.



Synthetic Opioids and the Opioid Epidemic

Fentanyl, another potent synthetic opioid which is structurally different than nitazenes, has been the primary driver behind the 3rd wave of the opioid epidemic. Synthetics, like fentanyl and nitazenes are less expensive to produce than other opium-derived molecules. Fentanyl and its analogs can be synthesized in high yield with a three-step process. Likewise, benzimidazoles are synthesized in 3 to 4 steps with simple starting materials. The vast number of synthetic analogs circulating in the illicit drug market creates several challenges, which includes ensuring current laboratory technology has the capability to screen for these emerging synthetics in healthcare facilities.

A Reason for Concern

In 2019, isotonitazene emerged on the illicit drug market and has been involved in numerous fatal overdose events since. Because of this, the Drug Enforcement Administration designated all of the nitazene opioids within the benzimidazole structural class a Schedule I substance to avoid imminent hazard to public safety.

Will Naloxone Still Be Effective?

For over 50 years, naloxone has been the "gold standard" for reversing opioid overdoses. The effective dose is symptom driven and with potent synthetics like fentanyl, higher naloxone doses are often required for full reversal. Case reports involving isotonitazene related overdose suggest that naloxone is effective but may require even higher doses. In 2021, the Food and Drug Administration approved an 8mg naloxone nasal spray product, brand name Kloxxado, which delivers twice the dose of standard Narcan Nasal Spray (4mg). The half-life is similar, however, higher naloxone doses may result in more severe withdrawal symptoms experienced by the patient. With the landscape of emerging potent synthetics, more research is needed on the effectiveness of overdose reversal agents, as well as considerations for naloxone alternatives.

DEPARTMENT OF HEALTH & HUMAN SERVICES, USA

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