PUBLIC ALERT

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Adverse Effects Linked to Next Generation Opioids Reported in Patients Presenting to Emergency Departments After Suspected Opioid Overdose

Purpose: The objective of this announcement is to notify public health and safety, clinicians, law enforcement, first responders, medical examiners and coroners, forensic and clinical laboratory personnel, and all other related communities about new information surrounding new generation synthetic opioids in clinical settings after suspected opioid overdoses and presentation to emergency departments, including: **metonitazene**, ***N*-piperidinyl etonitazene**, **isotonitazene**, and **brorphine**.

Overview: Drug use can lead to adverse events and overdose scenarios where individuals present to emergency departments for clinical evaluation and/or treatment. The culprit can be traditional drugs (e.g., heroin, fentanyl, cocaine, methamphetamine) or novel psychoactive substances (NPS); however, proper drug testing methodologies must be employed for accurate identification and characterization. Street-level drug preparations can contain undeclared or unwanted substances, such as toxic adulterants or NPS, which can potentiate effects or lead to adverse reactions. Understanding emerging drugs can help direct new or revised approaches to clinical treatment and harm reduction efforts.

Objective: A partnership between the American College of Medical Toxicology (ACMT) and the Center for Forensic Science Research and Education (CFSRE) was established to comprehensively assess the role and prevalence of synthetic opioids and other drugs among suspected overdose events in the United States. Patients with a suspected opioid overdose presented to an emergency department at a participating site within ACMT's Toxicology Investigators Consortium (ToxIC). Residual, discarded biological samples were obtained for testing against an expansive library of drugs and other substances. Our findings provide a near real-time assessment of the drug market and allude to resulting implications on clinical institutions. Analysis was performed via liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS). The scope of testing targeted more than 950 drugs. Drug classes included opioids, stimulants, cannabinoids, and benzodiazepines, among others.

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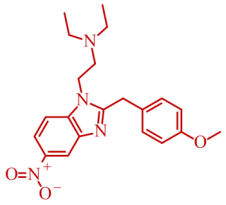
Metonitazene

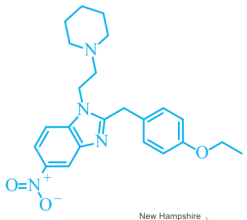


Metonitazene was identified in toxicology samples collected from two patients exhibiting signs and symptoms of suspected opioid overdose. These patients presented to emergency departments in two different states. Both patients were female with approximate ages between 20 and 50 years. The **two patients presented in cardiac arrest** — a significant clinical finding not noted with other next generation opioids presented herein. One patient received 6 mg of naloxone while the second received 10 mg. Positive response to naloxone administration was noted. One patient died.

Comprehensive toxicology testing on serum showed the co-presence of fentanyl (n=2), clonazolam (n=2), flubromazolam (n=1), methamphetamine (n=1), and cocaine (n=1), in addition to other therapeutic drugs, adulterants, and metabolites.

Additional Resource: Krotulski et al. (2021) Metonitazene in the United States—Forensic toxicology assessment of a potent new synthetic opioid using liquid chromatography mass spectrometry. *Drug Testing and Analysis*. 13, 1697-1711.

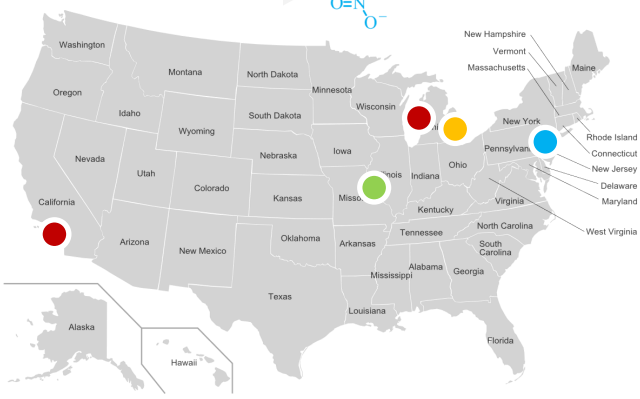
N-Piperidinyl Etonitazene



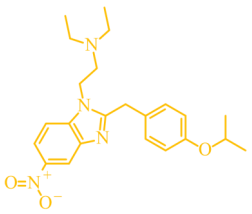
***N*-Piperidinyl Etonitazene** was identified in toxicology samples collected from three patients exhibiting signs and symptoms of suspected opioid overdose. All three patients presented to one location. Two patients were male and one was female with approx. ages between 30 and 60 years. Two patients reported the use of cocaine and denied opioid use; one patient reported the use of "heroin" and alprazolam. Patients received 1-2 doses of naloxone with noted positive response. Opioid toxicity recurrence was also noted.

Comprehensive toxicology testing showed the co-presence of fentanyl (n=2) and cocaine (n=2), in addition to therapeutic drugs, adulterants, and metabolites. In one patient denying opioid use, ***N*-piperidinyl etonitazene was the only opioid detected** (cocaine metabolite positive).

Additional Resource: *N*-Piperidinyl Etonitazene New Drug Monograph (2021)



Isotonitazene



Isotonitazene was identified in toxicology samples collected from two patients who presented to one emergency department experiencing depressed levels of consciousness. Patients were male and female with approximate ages between 40 and 50 years. Both reported use of "heroin" prior to overdose. The two patients received two doses of naloxone each, the first coming from a bystander. Positive responses to naloxone were noted for both patients.

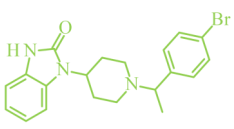
Comprehensive toxicology testing on serum samples showed the co-presence of fentanyl (n=2), heroin (n=2), methamphetamine (n=2), cocaine (n=1), and para-fluorofentanyl (n=1), in addition to various other therapeutic drugs, adulterants, and metabolites.

Additional Resource: Krotulski et al. (2020) Isotonitazene Quantitation and Metabolite Discovery in Authentic Forensic Casework. *Journal of Analytical Toxicology*. 44, 6, 521–530.

Brorphine

Brorphine was identified in toxicology samples collected from two patients who presented to an emergency department in one state. The patients presented with respiratory depression and one patient had decreased oxygen saturation. Patients were male and female with approximate ages between 30 and 60 years. The two patients received approximately 2 mg of naloxone each with noted increased respiratory rate and oxygenation.

Comprehensive toxicology testing on serum samples showed the co-presence of fentanyl (n=2), methamphetamine (n=2), cocaine (n=2), clonazolam (n=1), eutylone (n=1), and heroin (n=1), in addition to various other therapeutic drugs, adulterants, and their metabolites.



Additional Resource: Krotulski et al. (2020) Brorphine—Investigation and quantitation of a new potent synthetic opioid in forensic toxicology casework using liquid chromatography-mass spectrometry. *Journal of Forensic Science*. 66, 2, 664-676.

Drug	EC_{50} (nM)*
Morphine	338
Brorphine	30.9
Fentanyl	14.2
Metonitazene	8.14
Isotonitazene	1.63

*Vandeputte et al. (2021) Synthesis, Chemical Characterization, and μ-Opioid Receptor Activity Assessment of the Emerging Group of "Nitazene" 2-Benzylbenzimidazole Synthetic Opioids. *ACS Chemical Neuroscience*. 12, 7, 1241–1251.