November 2020

Updated Trend Reporting for the NPS Benzodiazepine Clonazolam Based on Data-Mining for 8-Aminoclonazolam

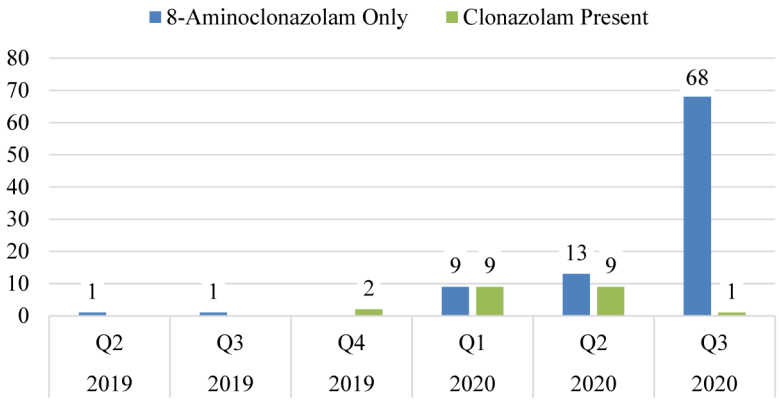
Purpose: The objective of this public announcement is to provide updated information on drug testing trends to laboratory personnel, medical examiners and coroners, clinicians, public health and public safety, law enforcement, and other related communities regarding the NPS benzodiazepine **clonazolam**.

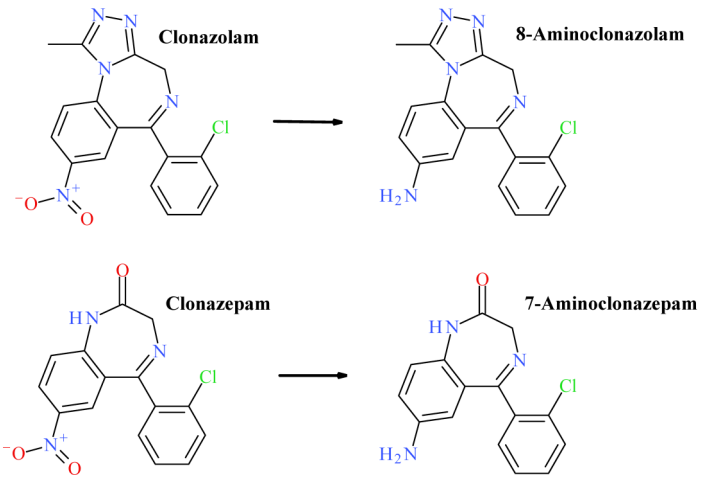
Background: NPS benzodiazepines, sometimes referred to as designer benzodiazepines, are synthetically manufactured drugs with unknown biological effects and health risks. NPS benzodiazepines are of public health and safety concern due to high potency at low doses, producing strong sedation and amnesia. Additional adverse effects include loss of coordination, drowsiness, dizziness, blurred vision, slurred speech, muscle relaxation, respiratory depression, and, in some cases, death. These factors make the presence of NPS benzodiazepines in forensic casework of high importance.

Clonazolam (also called clonitazolam) first emerged in the recreational drug supply in 2014 (Europe) and 2016 (United States). Like many NPS, clonazolam was first synthesized during drug development in 1971 but was never approved for therapeutic use. Clonazolam is the triazolo– counterpart to clonazepam (Klonopin, Rivotril). Clonazolam appears in various drug preparations, including powders, tablets (i.e. counterfeit pharmaceuticals), liquids, and blotters. Clonazolam has been linked to adverse events resulting in hospitalization or death and is commonly reported in combination with other drugs and/or NPS, including benzodiazepines and opioids. Trend reports developed by NPS Discovery previously indicated a decline in clonazolam positivity in Q3 2020. However, recent developments show that the positivity of clonazolam is currently increasing based on new data collected after testing for its metabolite.

Summary: Assessments of drug prevalence and positivity are contingent on accurate characterization of drug targets within specific samples. These assessments include consideration of the analytical methods used for drug testing and the drug species (e.g. parent drug, metabolite) targeted during method development and/or data processing. Nitro–group–containing benzodiazepines (e.g. clonazolam, clonazepam) are metabolized in the body to amino–counterparts (e.g. 8-aminoclonazolam, 7-aminoclonazepam). Additionally, instability of these drugs can lead to the production of these same amino–species. Therefore, data-mining for 8-aminoclonazolam was conducted on all samples analyzed in 2019 and 2020 to re-evaluate the positivity of clonazolam in our sample populations. The results indicate that the positivity of clonazolam was previously underreported when targeting only the parent drug and 8-aminoclonazolam appears to be a more appropriate biomarker for accurate determination of clonazolam use.

Identifications by Analyte in Toxicology Cases





Recommendations for Public Health

- Implement surveillance for rapid identification of drug overdose outbreaks.
- Track and monitor geographical distribution and trends for emerging drugs, including substances identified in suspected counterfeit pill or tablet preparations.
- Raise awareness about the risks and dangers associated with benzodiazepine use, especially in combination with opioids and other depressants.

Recommendations for Clinicians

- Become familiar with the signs and symptoms associated with benzodiazepine use (e.g. sedation, drowsiness, slurred speech, motor incoordination).
- Be mindful that counterfeit drug products often contain unknown synthetic substances that may differ in expected clinical effects of traditional pharmaceutical preparations.
- Counsel about the dangers of NPS benzodiazepine products and other drugs.

Recommendations for ME's & Coroners

- Test for NPS benzodiazepines and their biomarkers in suspected drug overdose cases.
- Consider testing for NPS benzodiazepines and their metabolites if circumstances result in an unspecified drug fatality.
- Be aware that screening procedures (e.g. immunoassays) for benzodiazepines may not be sufficiently cross reactive or targeted to the newest NPS and/or their metabolites; consider comprehensive mass spectrometry-based screening.

Recommendations for Laboratories

- Review analytical data for Clonazolam and 8-Aminoclonazolam.
- Prioritize the addition of NPS biomarkers for drugs that exhibit rapid metabolism or instability.
- Develop sensitive drug testing methods.
- Share data on NPS benzodiazepine drug seizures and toxicology testing with local health departments, medical examiners, coroners, and other forensic practitioners.

Acknowledgements: This report was prepared by Alex J. Krotulski, PhD, Donna M. Papsun, MS, D-ABFT-FT, and Barry K. Logan, PhD, F-ABFT. Funding for this study was provided internally by the Fredric Rieders Family Foundation; no external funding was received. The opinions, findings, conclusions, and/or recommendations expressed in this publication are those of the authors and do not necessarily reflect those of federal, state, local, and/or private agencies.

References and Related Articles:

• Murphy, L; Melamed, J; Gerona, R; Hendrickson, RG. Clonazolam: a novel liquid benzodiazepine. *Toxicology Communications*. 2019, 3, 75-78.
• WHO: Critical Review Report: Clonazolam
• NPS Discovery: Trend Report: Q3 2020 NPS Benzodiazepines in the United States

Rapid NPS Testing Now Available:

If your agency suspects NPS benzodiazepine toxicity with no identifiable cause of death or your jurisdiction is noticing an increase in overdose patients requiring analytical testing, contact NPS Discovery at the Center for Forensic Science Research and Education; a non-profit organization in collaboration with DOJ and CDC which has received funding to provide rapid testing of novel drug outbreaks in the United States.

Website: www.npsdiscovery.org **Email:** npsdiscovery@cfsre.org