Clinical Update: March 2021

NPS Focus: Designer Benzodiazepines

Aegis launched an extensive and industry-leading testing menu of Novel Psychoactive Substances (NPS) in mid-2020, which includes designer benzodiazepines, designer opioids, synthetic cannabinoids, and synthetic stimulants. In this month's update, we will focus on the evolution of designer benzodiazepines and the challenges associated with detection and monitoring of this class of drugs.

Designer benzodiazepines (DBZD) are a broad class of substances which are either available overseas via prescription, such as etizolam, or created in clandestine labs to mimic the effects of prescription benzodiazepines. These substances are used by individuals to replace or augment prescription benzodiazepines, with the benefit of not being detectable via standard toxicology testing for benzodiazepines. There is increasing evidence that the use of designer benzodiazepines is widespread. One illustration of this trend was highlighted in a study of the National Poison Data System, which reported a 330% increase in DBZD exposures from January 1, 2014 to December 31, 2017.[1] Subsequently, in 2019, a series of six adolescents reported to an emergency room in Oregon after ingesting a substance believed to be alprazolam. Blood and urine samples were collected from three of the six individuals along with a tablet fragment. All were analyzed via via mass spectrometry, and flualprazolam was identified, without any other drugs present. All six patients' symptoms resolved and they were discharged.[2] A study published in January 2021 by Rohrig et. al., described the detection of either flubromazolam or etizolam in 12 impaired drivers.[3]

Use of DBZDs may result in presumptive positive results via immunoassay testing that are unable to be confirmed by traditional mass spectrometry testing methods employed to assess recent use of this class of drugs. In February 2021, a study was published from Vancouver, Canada which describes the rates of designer benzodiazepines in community drug samples from supervised consumption sites or overdose prevention sites. From October 2018 until January 2020, 1,368 samples were voluntarily tested via point of care testing (POCT). Of these, 159 drug samples were also tested mass spectrometry. The study found at least one DBZD present in 15.1% of samples. In drug samples believed to contain opioids by study participants, 15.8% contained a DBZD and 14% contained a DBZD and an opioid when tested via mass spectrometry. In total, they found false positive rates of 17.8% and false negative rates of 29.2% in POCT for DBZD.[4] Another recent study from the Center for Forensic Science Research and Education tested samples which were positive via immunoassay testing but were deemed negative after testing via traditional mass spectrometry methods. In this instance, they found at least one DBZD in 70% of those samples from patients 15-78 years old when they were subjected to targeted testing for DBZD.[5]

The following substances are included in Aegis' DBZD testing:

Bromazolam	Flubromazepam
Clonazolam	Flubromazolam
Diclazepam	Nitrazepam
Etizolam	Phenazepam
Flualprazolam	

Since Aegis began testing for DBZDs, many of these substances have been detected, with the most frequently observed being flualprazolam, etizolam, clonazolam, bromazolam and flubromazolam. However, metabolites of phenazepam and diclazepam have also been detected. In some instances, these samples contained prescription benzodiazepines but, in others, DBZD were the only benzodiazepines detected. This reinforces other studies which suggest that traditional benzodiazepine testing, whether it be immunoassay or mass spectrometry, may not provide a complete picture of an individual's recent substance use. NPS will continue to evolve as recreational chemists develop compounds to avoid regulation and detection. Due to the unknown purity and potency of these compounds, users of DBZD are at risk of adverse events, especially those that combine them with either prescription or illicit benzodiazepines and opioids, or other central nervous system depressants. 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.

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. Carpenter JE, Murray BP, Dunkley C, Kazzi ZN, Gittinger MH. Designer benzodiazepines: a report of exposures recorded in the National Poison Data System, 2014 – 2017. Clin Toxicol. 2018;57(4):282-286.
2. Blumenberg A, Hughes A, Reckers A, Ellison R, Gerona R. Flualprazolam: report of an outbreak of a new psychoactive substance in adolescents. Pediatrics. 2020 Jul 1;146(1).
3. Rohrig TP, Osawa KA, Baird TR, Youso KB. Driving impairment cases involving etizolam and flubromazolam. Journal of analytical toxicology. 2021 Jan;45(1):93-8.
4. Laing MK, Ti L, Marmel A, Tobias S, Shapiro AM, Laing R, Lysyshyn M, Socías ME. An outbreak of novel psychoactive substance benzodiazepines in the unregulated drug supply: Preliminary results from a community drug checking program using point-of-care and confirmatory methods. International Journal of Drug Policy. 2021 Feb 22:103169.
5. Mastrovito RA, Papsun DM, Logan BK. The Development and Validation of a Novel Designer Benzodiazepines Panel by LC–MS-MS. Journal of analytical toxicology. 2021 Jan 21.