Clinical Update: September 2023

DESIGNER BENZODIAZEPINES

Designer benzodiazepines (DZBDs) represent a major public health issue and their prevalence has increased substantially over the last decade.[1] Slight alterations of chemical substituents at various positions of a benzodiazepine molecule can yield a large number of different DBZDs compounds.[2] These designer drugs may possess less, or greater effects when compared to prescription benzodiazepines[3,4,5] and evidence suggests these substances are being used non-medically for their sedative and hypnotic effects.[6] Adverse reactions, which are similar to known benzodiazepines, include CNS depressant-like effects, such as ataxia, altered mental state, respiratory depression, and death.[7] From April-June 2019 to April-June 2020, prescription and illicit benzodiazepine-involved overdose deaths increased 22% and 520%, respectively. Other risks involve the concurrent use of DZBDs along with other prescribed or illicit drugs. During January-June 2020, 93% of benzodiazepine-involved deaths also involved opioids, and 67% involved illicitly manufactured fentanyls.[8]

The increasing illicit availability and prevalence of DZBDs is of concern and has been gaining regulatory attention.[7] Between 2010 and 2015 the first true DZBDs were identified that had never been licensed for medical use anywhere in the world,[2] and by November 2018, at least 24 different DZBDs had been identified.[9,10] A trend highlighted in a study of the National Poison Data System reported a 330% increase in DBZD exposures from January 1, 2014 to December 31, 2017.[11] According to the Center for Forensic Science Research and Education (CFSRE), a non-profit organization in collaboration with the Department of Justice and Centers for Disease Control, between 2020 and 2021, etizolam was the most identified DZBD, identified in 1,012 toxicology cases, many of which were co-identified with fentanyl.[12] In October 2022, the DEA announced they would place five DZBDs, including etizolam, flualprazolam, clonazolam, flubromazolam, and diclazepam on Temporary Schedule I, all meeting the specific criteria outlined for Schedule I and ultimately posing significant risk to public health. In QTR 2, 2022, etizolam and flualprazolam started to decrease in positivity and by QTR 4, 2022, bromazolam started to become strikingly more prevalent. The dramatic increase in bromazolam circulation could be a result of this escalating pressure from the DEA. Temporary Schedule I for the five mentioned DZBDs officially went into effect on July 23, 2023.[7]

Bromazolam, the brominated counterpart to the chlorinated drug alprazolam, was first synthesized during medicinal drug development in the 1970s but it was never approved for therapeutic use in the United States. Bromazolam first emerged in the recreational drug supply in 2016 (Europe) and 2019 (United States) and has been linked to adverse events resulting in hospitalizations and death. It is commonly reported in combination with other drugs, including fentanyl.[13,14] The quarter three drug checking report from CFSRE showed two samples that contained bromazolam between May and September 2022. The first sample contained bromazolam in combination with fentanyl, xylazine, 4-ANPP, and flubromazepam.[15] The second sample was bromazolam in combination with fentanyl, xylazine, 4-ANPP, caffeine, and procaine. A case report from the University of Nebraska medical center describes a patient requiring hospitalization for withdrawal from a combination of phenibut and bromazolam. This patient had obtained bromazolam as a means of self-treating his insomnia caused by long term phenibut use.[16]

Out of 212,295 samples collected at Aegis from June-Aug 2023 which were tested for both benzodiazepines and DZBDs, 196,969 (93%) were without a benzodiazepine indicated as prescribed. For individuals with a benzodiazepine prescribed, the detection of DZBDs is significantly less frequent than for individuals who are not prescribed a benzodiazepine (1.37% vs. 10.6%). This may indicate that those without prescription access to benzodiazepines may be more likely to seek out non-prescribed benzodiazepines, possibly seeking to self-medicate with substances when anxiety is present. While these figures may seem daunting, it is still an underrepresentation of actual positivity, as many samples received at Aegis do not include medical orders for NPS testing.

It is of vital importance to understand and utilize this data as we continue to care for individuals in this current environment. Some publications have demonstrated DBZDs as unexpected positive results in immunoassay testing.[17,18] When these samples are sent for confirmatory testing to a lab that only performs routine testing, the DBZDs may not be detected. These clinically confusing results could easily be dismissed as immunoassay false positives and the individuals may not get the attention needed from having ingested novel psychoactive substances.[19]

Aegis launched an extensive and industry-leading testing menu of Novel Psychoactive Substances (NPS) in mid-2020, which includes DBZDs, designer opioids, synthetic cannabinoids, synthetic stimulants, hallucinogens/dissociatives, xylazine, tianeptine, and phenibut. Aegis's expansive NPS offerings are developed to allow providers the ability to more completely identify substance use and afford them the opportunity to provide more informed care and minimize the potential for these unregulated substances to contribute to adverse events, including overdose deaths.

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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