

Beyond Sound Sleep: The Wake-up Call on Benzodiazepine Overdose

Carol S D'Silva¹, Bhuvana Krishna²

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In India, majority of the cases of deliberate self-harm (DSH) occur following pesticide poisoning, and this is attributed to low socioeconomic status and a largely agrarian population. The common precipitants for DSH are family conflicts, dowry, and interpersonal issues.¹ Poisoning due to drugs was traditionally thought to be a problem in Western countries. However, with rapid urbanization and changing social and economic milieu in India, this is no longer the case. In a vast and diverse country as ours, regional variations in geography, culture, economy, and society significantly shape the toxico-epidemiological landscape. Poisoning with over-the-counter prescription drugs and drugs of abuse, such as benzodiazepines (BZDs), have been steadily increasing in urban areas.² A cross-sectional exploratory study done in Thiruvananthapuram, Kerala, showed 48% cases of poisoning occurred due to pharmaceutical drugs, while only 11% occurred due to pesticides.³

In the 16th century, the Swiss physician and alchemist Paracelsus gave a doctrine stating, "all things are poison, and nothing is without poison; the dose alone makes a thing not a poison." This foundational principle of toxicology remains as relevant today as it was then, particularly in the context of BZD poisoning. These drugs, widely prescribed for their anxiolytic, hypnotic properties, exemplify the delicate balance between therapeutic benefit and toxic potential. Ever since BZDs have been introduced in the 1960s, they have been widely used for treatment of anxiety, insomnia, seizures, agitation, and alcohol withdrawal. They remain a popular choice among physicians and psychiatrists owing to its superior safety profile. In the United States, it is one of the most common prescribed psychiatric drug and third most common misused drugs for illicit use.⁴ Between the late 1990s and 2013, BZD prescriptions rose by 2.5% annually, establishing them as one of the most widely prescribed medications globally.⁵ With increasing prescribing, the incidence of misuse/overuse has also escalated concomitantly. Of increasing concern is the availability of illicit combination of BZDs with opioids such as fentanyl and "designer BZDs," such as etizolam, bromazepam, bromazolam, etc.⁶ Newer research has shown an association of use of BZDs, particularly alprazolam, with increased risk for suicide. An exposure-only within-subject time-to-event pharmacoepidemiologic study by Gibbons et al. showed a doubling in the risk for suicide attempts in patients on alprazolam (hazard ratio = 2.21, 95% confidence interval = 2.06–2.38).⁷

Certain groups are more prone for BZD overdose, such as elderly and patients with psychiatric disorders or a history of substance abuse. Overdose in elderly is often accidental and can

^{1,2}Department of Critical Care Medicine, St Johns Medical College Hospital, Bengaluru, Karnataka, India

Corresponding Author: Carol S D'Silva, Department of Critical Care Medicine, St Johns Medical College Hospital, Bengaluru, Karnataka, India, Phone: +91 9766397569, e-mail: calps80@gmail.com

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cause significant morbidity due to delayed drug clearance and polypharmacy.

The sedative hypnotic toxidrome is characterized by hypothermia, drowsiness, bradycardia and bradypnea, which may rarely progress to respiratory depression. Most often patients are deeply sedated at admission, and a small percentage require invasive ventilation for airway protection. Isolated BZD overdose is rarely fatal. Life-threatening respiratory depression can occur with coingestants such as alcohol or opioids.⁵

The mainstay of treatment remains to be supportive care. Flumazenil has long been known as an antidote for BZD overdose. However, flumazenil is not indicated in cases of concomitant ingestions, chronic use of BZD or BZD tolerance for risk of withdrawal seizures, and in patients with prolonged QT intervals. The half-life is about 40–50 minutes, which is shorter than the half-life of most BZDs.⁸

This month's issue features a study by Giftson et al. on the epidemiological profile of patients presenting with BZD overdose to the emergency department. This was a retrospective observational cohort study conducted over 2 years, which extracted data on BZD overdose from a larger subset of DSH. They identified middle-aged females forming the predominant demographic and interpersonal issues as the leading trigger for overdose.⁹

Interestingly, the common presenting features were that of drowsiness and abdominal symptoms. While central nervous system manifestations are common, abdominal symptoms are uncommon following BZD overdose as per existing literature. No cases of mortality were reported in this study. Flumazenil was used in about 20% of patients in this study, with no reported side effects. The study's findings echo a global concern: while BZDs alone rarely cause fatal overdoses, they often feature in polysubstance ingestions, exacerbating their toxic effects. A regression analysis

did not reveal association with BZD type/other drugs and mortality or other outcomes. This study throws light on the changing demographic of DSH due to BZDs. In the existing literature, cases of DSH following BZD use have seen a higher prevalence in younger adults and adolescents.^{10,11}

Due to the low risk of mortality, BZD misuse seems to have taken a backseat among policymakers and law enforcement agencies. Currently, BZDs fall in the H1 category of drugs as per the Drugs and Cosmetics Rules 1945. This schedule imposes certain conditions in their dispensing, which are somewhat midway between Schedule H (that stipulates retail dispensing only against a valid prescription) and Schedule X drugs (drugs with high potential for abuse such as narcotics and amphetamines). Safe and diligent prescribing practices can help to curb the menace of BZD overdose/toxicity. Prescription drug monitoring programs, as successfully implemented in several Western nations, could serve as an effective tool in preventing overuse. Stricter dispensing policies, such as limiting BZD prescriptions to short durations with periodic reassessment, could also mitigate risks associated with chronic use and dependency. Other strategies to mitigate overdose deaths could include reducing the coprescribing of BZDs and opioids and addressing alcohol consumption among individuals prescribed BZDs. Additionally, suicide risk assessments and safety planning may help in reducing the number of overdose deaths.

A deeper understanding on epidemiology of BZD overdose/DSH due to drugs would help identify subgroups who could benefit from prevention and treatment efforts, critical points for intervention, and type of interventions needed.

ORCID

Carol S D'Silva  <https://orcid.org/0000-0002-3920-1366>

Bhuvana Krishna  <https://orcid.org/0000-0002-0003-6797>

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