

A Two-year Retrospective Observational Cohort Study of Benzodiazepine Overdose Cases in the Emergency Department

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ABSTRACT

Background: Deliberate self-harm (DSH) is a significant health concern in developing countries, associated with high morbidity and mortality. Several factors influence patient outcomes. This study aimed to better understand the profile and outcomes of patients with benzodiazepine (BZD) overdose.

Materials and methods: This two-year analysis conducted in the Emergency Department (ED) focused on patients with DSH and BZD toxicity. Key factors and outcomes were recorded and analyzed.

Results: The study included 95 patients with BZD overdoses, some of whom had also taken other drugs. The mean age was 36.52 (SD: 14.2) years, with a female predominance (59.9%). The most common reasons for DSH were interpersonal issues, such as relationship failure ($n = 48$; 50.5%) and domestic fights or abuse ($n = 37$; 38.9%). Single-drug BZD overdose was more frequent among individuals aged 46–60 years. The predominant symptoms were drowsiness ($n = 45$; 47.4%) and nausea or vomiting ($n = 32$; 33.7%). Six patients (6.3%) required definitive airway stabilization in the ED, while two patients (2.1%) required inotropic support. Flumazenil was administered to 19 (20%) patients with no reported side effects. A majority ($n = 49$; 51.6%) of patients were admitted to the hospital, of whom 30 (61.2%) were discharged in stable condition, while 19 (38.8%) left against medical advice. No deaths were reported.

Conclusion: Middle-aged females were most frequently involved in DSH cases. Single-drug BZD overdose was more common in this age-group. The predominant symptoms included drowsiness and gastrointestinal complaints. Most patients required hospital admission.

Keywords: Benzodiazepine overdose, Deliberate self-harm, Drug overdose, Emergency Department, Intentional harm, Suicide.

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HIGHLIGHTS

This 2-year retrospective study analyzed 95 benzodiazepine overdose cases in the Emergency Department (ED). Middle-aged females predominated, with interpersonal issues as key triggers. Single-drug overdoses were common in older age-groups. Symptoms included drowsiness and nausea. Flumazenil was safe and effective. Most patients required hospitalization; no deaths occurred.

INTRODUCTION

Drug overdose is a common form of deliberate self-harm (DSH) in both developed and developing countries, frequently presenting in ED. The clinical presentation varies based on the quantity and type of drugs consumed, as well as the presence of coingestants.^{1,2} The pattern of DSH in developing countries is influenced by socio-economic status, availability of toxic substances, and cultural or religious factors. Regions with lower socioeconomic status often report higher DSH rates.³ Monitoring local poisoning trends are crucial for identifying emerging toxidromes early. Benzodiazepine (BZD) overdose is associated with significant risks of morbidity and mortality.^{1,2} Establishing immediate treatment protocols at primary healthcare centers and developing effective prevention strategies may help reduce morbidity and mortality.

Benzodiazepine Overdose

Leo Sternbach, an Austrian scientist, is credited with discovering BZDs in 1963.⁴ Due to their improved safety profile compared to

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earlier sedative-hypnotics like barbiturates, BZDs quickly gained popularity for treating anxiety and insomnia. However, their widespread use, combined with their addictive potential, has led to significant misuse and toxicity.^{5–7} In India, drug overdose is a leading form of DSH, largely due to the availability of over-the-counter medications and the presence of multiple drugs in households.^{5–7} The Government of India, through policies by the Central Drugs Standard Control Organization (CDSCO) under the Narcotic Drugs and Psychotropic Substances Act, 1985, has made significant progress in reducing the misuse of psychotropic substances like BZDs. By limiting over-the-counter availability, the Government has

helped curb casual access, and most overdoses are now linked to legally prescribed drugs, suggesting improvements in prescription practices. Despite this progress, challenges remain in fully enforcing these regulations, as misuse still occurs. The continued incidence of drug misuse highlights the need for stronger enforcement and awareness campaigns to better prevent abuse and DSH.

In toxic doses, BZDs alone rarely produce severe toxidromes.⁷⁻⁹ Alprazolam, clonazepam, and lorazepam are among the most commonly abused BZDs by adults and teenagers.^{8,9} Patients with isolated BZD overdose typically present with central nervous system (CNS) depression and relatively stable vital signs, which are characteristic of BZD toxicity.⁸⁻¹⁰ Common symptoms include slurred speech, ataxia, and altered mental status. The low density of BZD binding sites in the brainstem's respiratory center accounts for the low incidence of respiratory depression when taken orally.¹⁰⁻¹³ However, when BZDs are combined with substances such as alcohol or other medications, respiratory depression may occur.¹¹⁻¹⁴ The risk of respiratory compromise depends on factors such as dosage, tolerance, body weight, age, co-ingestants, and genetic variability.^{10,13-15} While BZD toxicity rarely leads to cardiac complications or fatalities, large oral doses—especially in combination with other substances—can result in life-threatening respiratory depression.

Treatment and Management

The mainstay treatment for acute BZD toxicity is supportive care. Patients presenting with severe toxicity may be stuporous or comatose, requiring immediate intervention. Recent systematic reviews on BZD toxicity management emphasize supportive care and monitoring but place less focus on flumazenil use, primarily due to concerns about potential harm.¹⁶⁻¹⁸ Flumazenil, a non-specific competitive antagonist at the BZD receptor, may be administered as an antidote to reverse sedation in cases of isolated BZD overdose. However, routine use is not recommended due to its potential risks, including the induction of seizures and cardiac dysrhythmias, such as paroxysmal supraventricular tachycardia (PSVT), with several documented fatalities.¹⁶⁻¹⁸ Current guidelines advocate for a cautious, case-by-case approach in the ED, weighing the benefits of faster recovery against the risks, particularly in patients with mixed overdoses or a history of seizures. While some evidence supports flumazenil's use in shortening hospital stays and improving recovery times, other studies caution against its routine use due to adverse events that may outweigh the benefits in cases of acute toxicity.

This retrospective study, conducted in southern India, aims to describe the clinical profile of patients with BZD toxicity and analyze the incidence across different age-groups. Our objectives were to determine the motives for DSH and assess the impact of early flumazenil administration on the management of BZD overdose in the ED. The findings from this study will contribute to the broader, globally available literature on BZD toxicity and its management.

MATERIALS AND METHODS

Study Design and Setting

This subanalysis was conducted as part of a large retrospective observational cohort study focusing on patients presenting with DSH in the ED of a large tertiary care center in Southern India.⁵

Study Period and Participants

The study was conducted over 2 years, from January 1, 2017 to December 31, 2018, to assess seasonal variations in incidence.

We included all patients aged 18 and older who presented to the ED within 48 hours of BZD ingestion. Patients with incomplete medical records or those deceased upon arrival following an overdose were excluded.

Variables

Patient data were extracted from electronic hospital records and compiled into a comprehensive data collection sheet. The recorded variables included age, gender, vital signs at presentation, triage priority level, prior psychiatric history, presenting symptoms, reasons for DSH, number of ingested medications, co-ingestants (drugs, alcohol, or other substances), details of ED intervention, and both ED and hospital outcomes. Patients were triaged based on their physiological parameters according to the institution's protocol. Priority I was assigned to those with compromised airways, breathing, or circulation, while priority II was for patients with stable airways, breathing, and minor circulatory or sensorium illness.

Data Source and Statistical Analysis

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS), version 23.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as means and standard deviations, while categorical variables were summarized as frequencies and percentages. Univariate logistic regression was used to determine relationships between BZD/other drugs and outcome, with statistical significance set at $p < 0.05$. However, as none of the results were statistically significant, they were not reported. As this was a retrospective study, we could not control exposure or outcome measures and relied on third-party record-keeping, which may have introduced bias.

Ethical Considerations

The Institutional Review Board (IRB) approved the study (IRB Min No: 12269, dated September 25, 2019). Patient confidentiality was ensured through the use of unique identifiers and password-protected data entry software with restricted access. Because of the retrospective nature of the study, the IRB granted a waiver of consent.

RESULTS

During the 2-year study period, a total of 1,43,621 patients presented to our ED, of which 1.3% ($n = 1,821$) had a history of DSH. As shown in Figure 1, 95 (0.06%) patients had overdosed on BZD alone or in combination with other drugs. The mean age of this cohort was 36.52 (SD: 14.2) years, with a predominance of females ($n = 56, 58.9%$).

Baseline Characteristics and Presenting Symptoms

Table 1 summarizes the demographic characteristics. Common comorbidities included diabetes mellitus, essential hypertension, ischemic heart disease, and reactive airway diseases (asthma or COPD). Most patients ($n = 57; 60%$) had received initial first aid at another medical facility before presenting to our ED, and 44 patients (46.3%) were referred after receiving gastric lavage or similar interventions (Table 1). No seasonal trends were observed in this cohort. The majority ($n = 76; 80%$) were triaged as priority II. Table 2 outlines vital signs at the presentation based on triage priorities. Age distribution for drug consumption is detailed in Table 3. BZD overdoses were most prevalent among the middle-aged group (46–60 years), followed by the 31–35 and 36–45 years

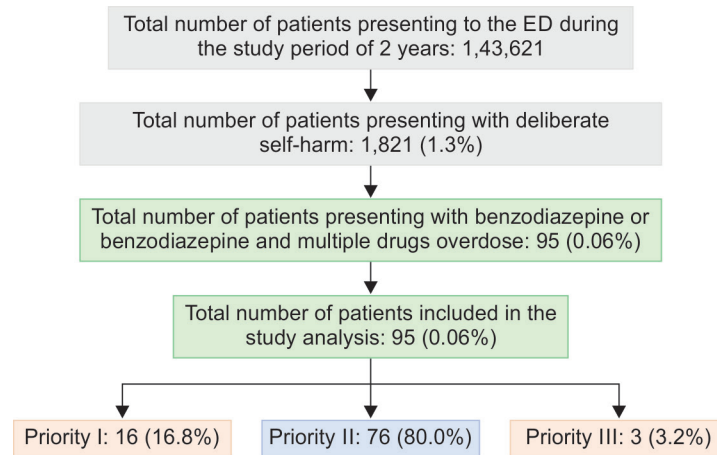


Fig. 1: Reporting of observational studies in epidemiology (STROBE) statement

Table 1: Baseline demographic characteristics of patients presenting with benzodiazepine poisoning to the ED

Variables	Frequency (%)
Age (SD) years	36.52 (SD: 14.2) years
Sex ratio	
Females	56 (58.9)
Males	39 (41.1)
Age category—females	
18–39 years	40 (42.1)
40–59 years	10 (10.5)
More than 60 years	6 (6.3)
Age category—males	
18–39 years	19 (20.0)
40–59 years	15 (15.8)
More than 60 years	5 (5.3)
Comorbidities	
Hypertension	3 (3.2)
Diabetes mellitus	5 (5.3)
Others ^a	5 (5.3)
Personal history	
Marital status: married	71 (74.7)
Past history of deliberate self-harm	14 (14.7)
Past psychiatric history ^b	17 (17.9)
History of alcohol or other illicit drug consumption prior to the incident	8 (8.4)
Prehospital and medical management elsewhere	
Yes	57 (60.0)
No	38 (40.0)
Gastric lavage done	44 (46.3)
Activated charcoal	3 (3.2)
Use of injection flumazenil	0 (0.0)
Initiated on oxygen therapy or intubated with mechanical ventilation	8 (8.4)

SD, standard deviation. ^aOthers: reactive airway disease, ischemic heart diseases, cerebrovascular accident, malignancies, pregnancy; ^bPast psychiatric history: Schizophrenia, bipolar disorder, depressive disorder, acute psychosis

groups. Common symptoms included drowsiness ($n = 45$; 47.4%), nausea and vomiting ($n = 32$; 33.7%), and abdominal pain ($n = 14$; 14.7%) (Fig. 2).

A small subset of patients ($n = 9$; 9.5%) were conscious but drowsy, while others ($n = 12$; 12.6%) were arousable to painful stimuli with intact plantar reflexes, and some ($n = 8$; 8.4%) were non-arousable even with painful stimuli. A history of psychiatric disorders was present in 17 patients (17.9%), including bipolar disorder, depression, schizophrenia, behavioral disorders, and acute psychosis. Figure 3 illustrates the motives behind DSH, with interpersonal issues, domestic conflicts, or abuse, academic or workplace-related stress, and health concerns being the predominant factors.

ED Treatment and Outcome

Each patient underwent a comprehensive evaluation and was managed based on their symptoms and physiological status. Six patients (6.3%) required definitive airway stabilization in the ED, while eight patients (8.4%) were managed conservatively with supplemental oxygen. Two patients (2.1%) required inotropic support following fluid resuscitation due to compromised circulatory systems. Flumazenil was administered to 19 (20%) patients, 11 of whom were triaged as priority I and the remaining as priority II. All these patients were confirmed to have isolated BZD toxicity with no prior history of neurological or cardiac conditions, or chronic BZD use. They all presented within 8 hours of BZD consumption. Before administration, an ECG was performed to ensure that there were no QRS abnormalities. Among them, eight patients presented with respiratory distress, while the others had severe drowsiness. There were no seizures or adverse effects reported post-administration.

ED Disposition and Hospital Outcome

The majority of patients were offered admission, with 49 (51.6%) patients being admitted, including six (6.3%) to the Intensive Care Unit (ICU). Thirty-seven (38.9%) patients left against medical advice, and nine patients (9.5%) were discharged in stable condition with follow-up instructions for the Medicine and Psychiatry outpatient departments. Of those admitted, 30 (61.2%) patients were discharged in stable condition, while 19 (38.8%) left against medical advice. No fatalities were reported in this cohort.

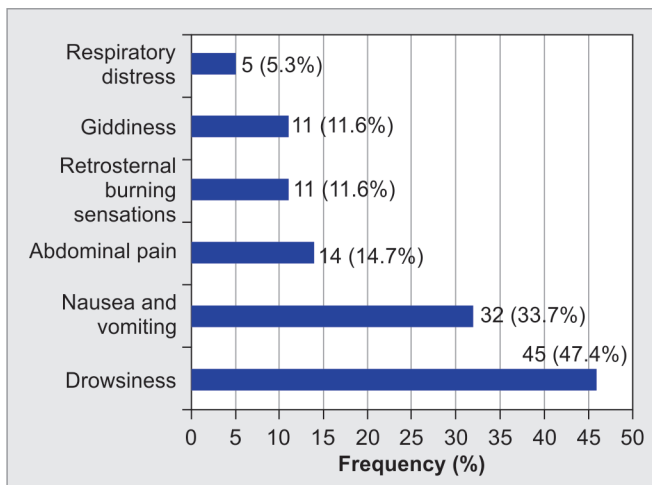
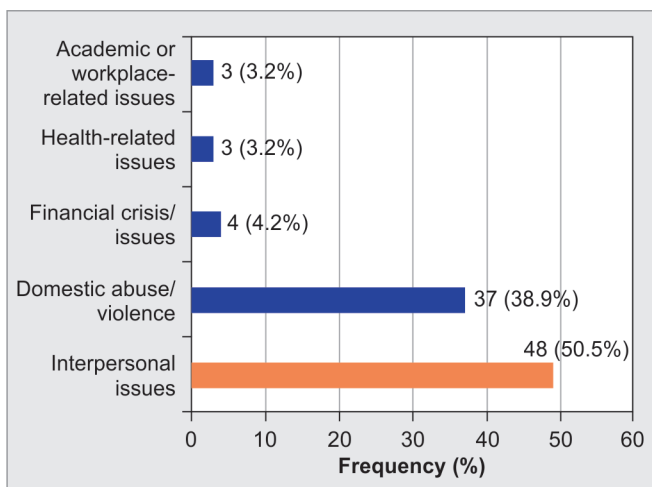
Table 2: Vital signs at presentation to the emergency department according to triage priority levels

Variables	Pulse rate (mean: SD)	Respiratory rate (mean: SD)	Systolic BP \leq 90 mm Hg; n (%)	SpO ₂ (mean: SD)
Priority I (n = 16; 16.8%)	87.87 (19.07)	27.2 (6.7)	8 (50.0)	92.2 (4.77)
Priority II (n = 76; 80.0%)	93.07 (19.1)	22.5 (3.1)	0 (0.0)	97.3 (2.4)
Priority III (n = 3; 3.2%)	90.2 (6.6)	22.2 (1.2)	0 (0.0)	98.6 (0.4)

BP, blood pressure; SD, standard deviation

Table 3: Age-wise distribution of deliberate self-harm associated with the consumption of benzodiazepines and other drugs

Age-groups (years)	Drug(s): n (%)				
	Benzodiazepine	Benzodiazepine + antipsychotics	Benzodiazepine + NSAIDs	Benzodiazepine + antihypertensives	Benzodiazepine + multiple other drugs
18–25 (n = 24)	17 (70.8)	4 (16.7)	2 (8.3)	–	1 (4.2)
26–30 (n = 18)	12 (66.6)	4 (22.2)	1 (5.6)	–	1 (5.6)
31–35 (n = 11)	9 (81.8)	2 (18.2)	–	–	–
36–45 (n = 21)	16 (76.2)	2 (9.5)	–	1 (4.8)	2 (9.5)
46–60 (n = 12)	11 (91.7)	–	1 (8.3)	–	–
>60 (n = 9)	7 (77.8)	–	–	1 (11.1)	1 (11.1)

**Fig. 2:** Presenting complaints in the ED following drug overdose**Fig. 3:** Motives for deliberate self-harm in the study group

DISCUSSION

This sub-analysis is part of a larger study conducted at our ED involving patients with DSH over 2 years.⁵ We specifically focused on patients who overdosed on BZD alone or in combination with other substances.

Since the introduction of BZDs in the 1960s, overdose prevalence has increased, peaking in the 1990s as a reflection of its widespread clinical use. The rise in intentional BZD poisoning, particularly starting in the late 1980s and peaking in the mid-1990s, then stabilized, driven partly by higher prescription rates and the availability of over-the-counter medications without valid prescriptions.^{8,10} In our cohort, the clinical effects of BZD overdose were generally mild, influenced by factors such as the quantity ingested, prior medical care, and the time to ED presentation. Due to the retrospective nature of the study, we were unable to categorize BZDs by their chemical or market forms. The majority of cases involved a history of BZD overdose, with middle-aged females being the most affected, which raises concerns for our society. Common risk factors included interpersonal issues (e.g., relationship failure, domestic conflicts), academic pressures, and financial difficulties. Many patients had a history of psychiatric disorders and were already taking BZDs or other antipsychotics. Such individuals are at higher risk for suicidal ideation, warranting stricter regulation of BZD prescriptions in this population. The packaging and quantity of prescriptions can impact the risk and severity of intentional self-poisoning. In a developing country like ours, regulating the availability of over-the-counter drugs without prescriptions is essential.¹⁹ Alcohol and opioids, often associated with severe toxicity, were frequently reported. While some patients disclosed alcohol use during the overdose, blood alcohol concentrations were not routinely tested, so reliance on available medical records was necessary.

Effective management of these patients requires thorough history-taking and clinical assessment. For those with moderate to severe sedation, current guidelines recommend establishing intravenous (IV) access, continuous cardiac monitoring, and administering oxygen as needed.^{11,15,20} Naloxone may be administered to patients with altered mental status and suspected

BZD toxicity, with or without opioid exposure.^{20–22} However, it was not used in our cohort due to minimal opioid availability in the region. The use of flumazenil in BZD toxicity remains controversial. While it can reverse sedation and central nervous system (CNS) depression, potentially avoiding endotracheal intubation, it should be administered with caution. The American Academy of Clinical Toxicology recommends its use only in isolated, non-chronic BZD overdoses, with intensive monitoring capabilities.^{16–18,23} Potential risks include seizures in cases of poly-drug overdoses or patients with pre-existing seizure disorders, as well as withdrawal symptoms in those with chronic BZD use.^{16–18} In our study, flumazenil was administered to approximately 20% of patients following consultation with a senior ED physician and the poison control board. A meta-analysis-based NNT (Number Needed to Treat) for harm generally advises against the use of flumazenil.¹⁶ However, the same report suggests it may reverse respiratory depression in rare cases of severe, isolated BZD or “Z” drug toxicity, provided there are no contraindications.¹⁶ We ensured all contraindications were ruled out before its administration. None of the patients in our study group experienced seizures or adverse side effects after flumazenil administration, though specific outcomes, such as time to reversal, were not consistently documented in the charts. Routine gastrointestinal decontamination with activated charcoal (AC) is not recommended for isolated BZD overdoses, as supportive care and BZD metabolism are usually sufficient. Activated charcoal can complicate airway management and increase the risk of aspiration if the patient becomes more sedated.^{24,25} However, AC may be beneficial in cases with protected airways and suspected co-ingestion of potentially fatal substances (e.g., colchicine, aspirin), especially with a cuffed endotracheal tube.^{24,25} Most patients in our cohort were admitted to the ICU, or general wards and responded well to supportive care. No fatalities occurred, highlighting the positive outcomes achievable with timely and appropriate treatment.

Limitations

Due to the retrospective nature of the study, several variables, including drug concentration results, urine toxicity screening, and blood alcohol concentration, were not consistently measured and thus could not be included in the analysis. The data were collected from a single large tertiary care center, which may have introduced selection and referral pattern biases. Additionally, the course of treatment could not be uniformly assessed due to incomplete documentation.

CONCLUSION

Middle-aged females were the most commonly affected group in cases of intentional self-harm involving BZDs and other substances. This represents a significant public health concern, as they often serve as both breadwinners and/or homemakers. The primary underlying causes included interpersonal conflicts, domestic disputes, or abuse. Clinically, patients mainly presented with drowsiness and abdominal discomfort. Single-drug BZD overdose was more common in this age-group. Approximately one-fifth of the patients received flumazenil, and notably, no adverse effects, such as seizures or withdrawal symptoms, were reported following its administration. This study adds valuable data to the global literature on BZD toxicity and management, highlighting the need for tailored approaches in the care of BZD toxicity cases.

AUTHORS' CONTRIBUTIONS

JG: Data acquisition, concept design, definition of intellectual content, literature search, initial data analysis, manuscript preparation DH, GC: Critical revision and design of the work, analysis and interpretation of data, manuscript preparation and editing, and manuscript review. GC: Concept, design, definition of intellectual content, substantial revision of the manuscript, and guarantor.

Ethical Approval

The authors of this manuscript declare that it adheres to the EQUATOR Network's reporting quality, formatting, and reproducibility guidelines. The authors also attest that this clinical study was done after obtaining clearance from the Institutional Review Board/Ethics Committee review, and the corresponding protocol/approval number is IRB Min no: 12269 dated September 25th, 2019. We also certify that we have not plagiarized the contents of this submission and that we have performed a Plagiarism Check.

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