Journal of Acute Medicine 8(4): 168-178, 2018
DOI:10.6705/j.jacme.201812_8(4).0004
Original Article

Clinical Predictors for Intensive Care Unit Admission in Patients With Benzodiazepines Poisoning in the Emergency Department

Chai-Yi Lu[1,2], Ching I Chang[3], Hsien-Hao Huang[1,4,5], David Hung-Tsang Yen[1,4,5,*]

[1]Institute of Emergency and Critical Care Medicine, College of Medicine, National Yang-Ming University, Taipei, Taiwan
[2]Department of Pharmacy, Mackay Memorial Hospital, Tamsui Branch, New Taipei City, Taiwan
[3]Department of Nursing, Taipei Veterans General Hospital, Taipei, Taiwan
[4]Department of Emergency Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[5]Emergency Medicine, College of Medicine, National Yang-Ming University, Taipei, Taiwan

Objective: To investigate the clinical predictors for intensive care unit (ICU) admission for patients with benzodiazepine (BZD) overdose and their clinical characteristics in the emergency department (ED).
Methods: A retrospective case-control study of acute BZD overdose patients aged ≥ 18 years presenting to the ED in our hospital from July 1, 2012 through June 30, 2015 were enrolled in this study. We collected demographic information on underlying diseases, initial presentations, causes and the classifications of BZD, complications, dispositions, and outcomes. Analyses were conducted among subgroups and were identified the possible predictive clinical factors determining ICU admission in these patients.
Results: A total of 140 patients were enrolled in the study, with a mean age of 51.3 ± 19.1 years (mean ± standard deviation [SD]) and female predominance with 2.59:1. The most common cause of BZD overdose was suicidal attempt. The most common underlying disease is major depression disease or bipolar disorder occupying 85.7% of all study patients. Suicide attempt accounted for 84.3% (118/140) of all study patients, among whom 41.4% (58/140) has previous history of suicide attempt. Sixty-nine point two percent (83/120) needed hospital admission, including 20 patients (14.3%) with ICU admission and a total three patients mortalities (2.1%, 3/140). Two clinical predictive factors of ICU admission were identified, including pneumonia and flumazenil use in ED.
Conclusion: The incidence of mortality in patients with BZD overdose is low, but all-cause mortality remains high in those admitted to ICU (15%). Emergency physicians are suggested to pay more attentions on BZD overdose patients with suicidal attempt and major depression/bipolar disorder, who have pneumonia or flumazenil use in the ED. The incorporation of hospital healthcare team resource management in dealing with the recording, intervention, and prevention of these patients was mandatory to decrease repeat overdose, enhance care quality, and improve outcomes.

Key words: *benzodiazepines, emergency department, intensive care unit, overdose*

Introduction

Benzodiazepines (BZDs), possessing effect of sedative and hypnotics, were wildly used in the world.[1,2] In additions, they also can be used as the medicine for the treatment of seizure attack, muscle relaxation, anxiety, and insomnia.[3] In recent years, clinical physicians prescribed BZD for alleviating

Received: January 12, 2018; Revised: April 20, 2018 (2nd); Accepted: May 22, 2018.
*Corresponding author: David Hung-Tsang Yen, MD, PhD, Department of Emergency Medicine, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Rd., Beitou Dist., Taipei 112, Taiwan. E-mail: hjyen@vghtpe.gov.tw

anxiety and sleeping disorder patients, and also for certain psychiatric patients.[4-7] Owing to their safety in large proportion of analogues than barbiturates, BZD was considered as the substitute for the barbiturates during the past few years.[5] The side effects and complications of patients with acute BZD overdose would result in morbidity or even to mortality in certain population, especial for those with chronic lung disorders or dysfunctions, and those with chronic renal diseases.[3] Although in previous study reported that patients with drug overdose involving BZD have a low hospital mortality (less than 1%),[8] in our previous study demonstrating about 3.6% of death of geriatric victims with acute poisoning.[9] Also reported is that it happened occasionally that overdose of BZD will lead to death in geriatric patients.[5,10]

It is reported that BZD was the highest percentage of emergency department (ED) admission and second highest percentage of intensive care unit (ICU) admission, respectively, among patient with acute compound overdose.[11] It also was reported that patients with acute BZD overdoses were one of the most common admission to ED (44%), and admission to ICU (31%) among those with acute medication overdose, respectively.[11] Although the incidence of mortality was relative low in patient with BZD overdose, the clinical characteristics and predictors for these patients with ICU admission after ED visit for patient with BZD overdose remains to be elucidated. Due to potential risk for mortality among BZD deliberated patients admission to ICU and little was known about odds of clinical predictor for these patients visiting ED. This study sought to determine the clinical characteristics of patients with acute BZD overdose in the ED and to identify clinical predictors for these patients with ICU admission.

Methods

Study Design and Settings

This study was retrospective study of prospectively registered patients, more than 18 year-old, with BZD overdose, through ED visiting. Taipei Veterans General Hospital, a 3,000-bed, university-affiliated medical center had an annual ED average census of 85,500 ± 4,520 (mean ± standard deviation [SD]) during the past 10 years. The hospital's Institutional Review Board (VGHIRB) approved this study with a waiver of patient's consent (VGHIRB No.: 2016-04-006CC).

Our study recruited patients with BZD overdose visiting ED between July 1, 2012 and June 30, 2015. To verify and avoid missing potential participants, charts were cross-checked for major diagnosis of coding with International Classification of Diseases, 9th Revision, Clinical modification (ICD-9-CM) coding numbers, 969.4 as the major diagnosis of index event, that all study patients presented compatible with majorly clinical manifestations of BZD overdose. We didn't exclude those patients with mixed compound effects, which would cause trivial clinical effect as compared with BZD overdose. Medical charts were comprehensively and extensively reviewed. Exclusion criteria included the followings: less than 18 years of age, charts lacking certain important information (e.g., hospital course or discharge status), dead in ED before hospital admission, and those with do-not-attempt-resuscitation orders. All the recruited patients should fulfill the diagnostic criteria of BZD overdose, including BZD intake by history provided by patients themselves, families, or friends; the positive test results of serum or urine tests, either qualitative or quantitative; signs and symptoms of clinical presentations of acute mental change, dizziness, general malaise, drowsiness, etc. The psychologist was consulted after study patient recovery to consciousness and be able to correctively response to question asked.

Study Protocol

Patient's data entry was started, when all patients were registered in a hospital patient database. These data were then entered into a Microsoft Excel database for analysis later. Variables possibly related to BZD overdose and variables needed for this study were defined before abstracting data from the data bank and medical charts. The abstracted data were abstracted from hospital computer system and entered into the new data bank used for study analyses. The first author was the major collector assisted by second author, and all the corrected data were examined and audited by third and corresponding author. All study patients' characteristics that could be collected shortly after ED arrival were abstracted as variables for determining clinical significances as described in Fig. 1. The clinical variables included age, gender, underlying diseases, Glasgow Coma Scale (GCS), the causes of BZD overdose, BZD-related signs and symptoms, underlying medical diseases, psychiatric diseases, categories and effects of BZD, and complications, that

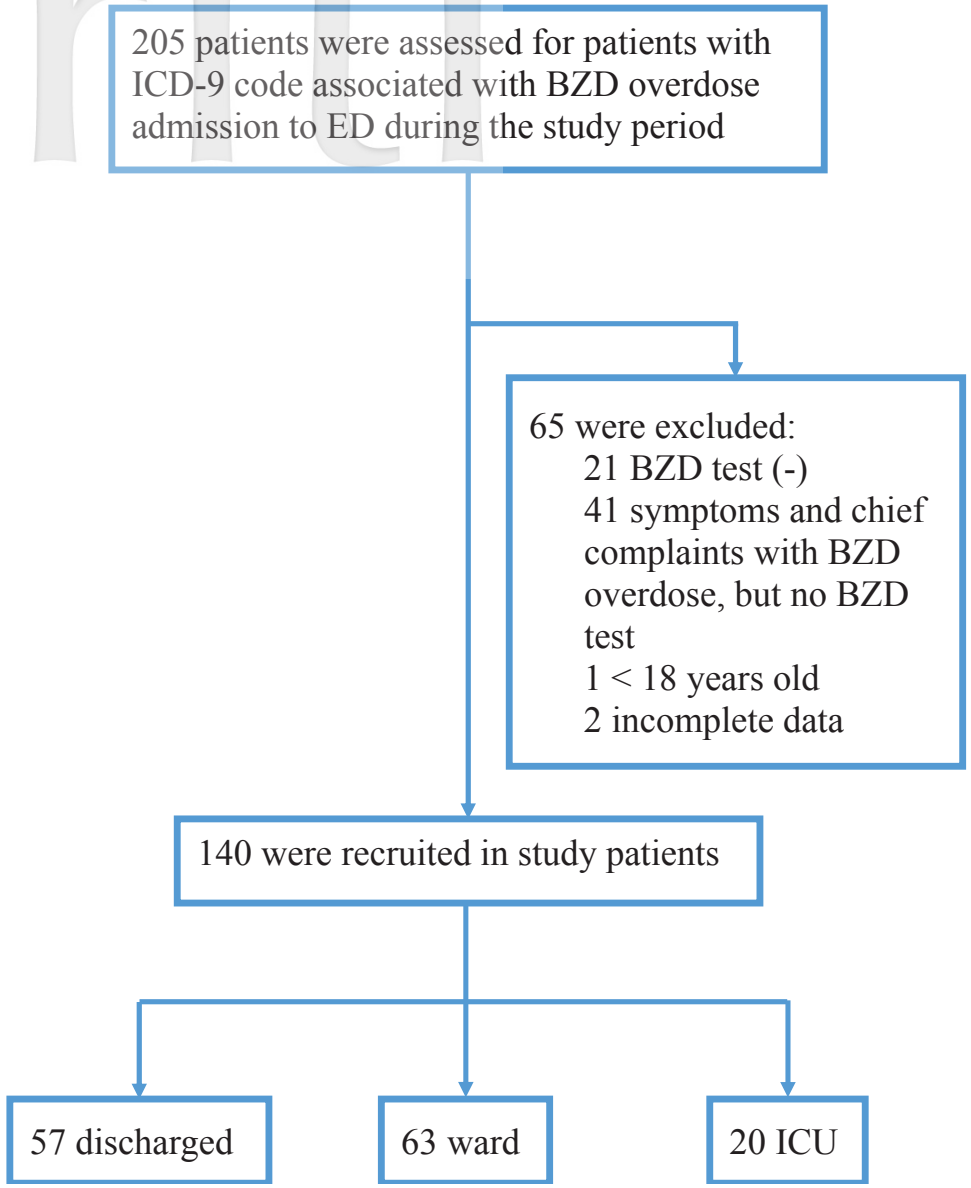

Fig. 1. Flow chart illustrating the selection of patients.
BZD: benzodiazepine; ED: emergency department; ICD: International Classification of Diseases; ICU: intensive care unit.

were referred from our previous study.[9] The definition of acute renal failure, pneumonia, and respiratory failure were also mentioned in our previous study.[9] The outcome assessment was ICU admission, based on which we further compared all documented clinical characteristics, possible predictors for outcomes, within individual group and also between groups. After further analysis of initial ED raw data of vital signs, including mean arterial pressure, heart rate, breathing rate, and body temperature, we found no statistical significance between those who were admitted to ICU compared with those admitted to ward or discharged patients, respectively. Thereafter, we didn't demonstrate these clinical parameters in both text and tables.

Data Analysis

Statistical analysis was performed using SPSS software version 20.0 (IBM Corp., Armonk, NY, USA). Statistical tests were two-sided, and the significance level was set at $p < 0.05$. Data are presented as mean ± SD for continuous variables and as number (%) for categorical variables. The distribution of the data was assessed with the Kolmogorov-Smirnov

test. Comparisons of numerical variables were performed using an unpaired t-test (parametric data) or Mann-Whitney U-test (nonparametric data). Comparisons of categorical variables were done by chi-square or Fisher's exact test. In order not to miss possible statistical clinical predictive factors in multiple logistic regression analysis, we use variable with p value < 0.2 in the univariate analysis.

Results

Clinical Characteristics of Study Patients

A total of 140 patients were recruited in this study. Table 1 presents the demographic and clinical characteristics of all patients with a mean age of 51.3 years old. The ratio of female/male is 2.6. The most common underlying disease is major depression disease or bipolar disorder occupying 85.7% of all study patients. Suicide attempt accounted for 84.3% of all study patients, among whom 41.4% (58/140) has previous history of suicide attempt. The altered mental status (AMS) was the most common clinical presentation, followed by drowsy and general weakness. Of particular note is that one-fourth of all study patients have flumazenil use in ED. Of all the patients, 59.3% (83/120) needed hospital admission, including 20 patients (14.3%) with ICU admission. Three patients (2.5%) were mortalities, of whom two were aspiration pneumonia and 1 was sudden onset of heart attack during hospitalization. All the study patients did not have traumatic brain injury in current index event. Supplement Table 1 demonstrated 112 patients with documented categories of BZD acting effects. Both long acting and intermediating acting BZD accounted for more than 80% of all study patients. Of all 112 patients, among whom 13 combined 2 categories of acting effects and 16 used 2 kinds of BZD.

Table 1. Clinical characteristics of 140 patients with benzodiazepine overdose

Variable	n = 140 (%)
Age (year)[a]	51.3 ± 19.1
Male/female	39/101
Underlying disease	
MDD/bipolar disorder	120 (85.7)
Hypertension	35 (25.0)
OA or DJD of spine	27 (19.3)
Heart disease	19 (13.6)
Stroke/PD	17 (12.1)
DM	13 (9.3)
CKD	11 (7.9)
Seizure disorder	11 (7.9)
Cancer	8 (5.7)
Lung disease	8 (5.7)
Suicidal history	58 (41.4)
Drug allergy history	6 (4.3)
Cause of BZD overdose	
Suicide	118 (84.3)
ADR or accidental event	14 (10.0)
Substance addiction	8 (5.7)
Classification of BZD overdose	
Long acting	34 (24.3)
Intermediate acting	49 (35.0)
Short acting	16 (11.4)
Mix	13 (9.3)
Unknown	28 (20.0)
ED presentation	
Altered mental status	52 (37.1)
Drowsy	41 (29.3)
General weakness	10 (7.1)
Dizziness	7 (5.0)
Agitation	3 (2.2)
Others	27 (19.3)
GCS ≤ 8	49 (35.0)
Acute renal failure	10 (7.1)
Pneumonia	18 (12.9)
Respiratory failure	18 (12.9)
Flumazenil used in ED	35 (25.0)
Disposition after ED	
Discharge	57 (40.7)
Ward admission	63 (45.0)
ICU admission	20 (14.3)

ADR: adverse drug reaction; BZD: benzodiazepine; CKD: chronic kidney disease; DJD: degenerative joint disease; DM: diabetes mellitus; ED: emergency department; GCS: Glasgow Coma Scale; ICU: intensive care unit; MDD: major depressive disorder; OA: osteoarthritis; PD: Parkinson's disease.
[a]Data presented as mean ± standard deviation.

Comparisons of Clinical Characteristics Between Patients Admitted to ICU and Ward, and Patients Discharged

Table 2 presented patients admitted to ICU have higher percentage of AMS, GCS ≤ 8, pneumonia, respiratory failure, and flumazenil use in ED, respectively, than those patients without ICU admission ($p < 0.05$). We categorized all patients into three groups, including ICU admission, ward admission, and discharged, respectively. Further analysis of clinical characteristics by patients with ICU admission, ward admission and ED discharged, respectively. Table 3 presented patients with ICU admission have higher percentage of AMS, GCS ≤ 8, pneumonia, respiratory failure, and flumazenil use in ED, respectively, than those patients with ward admission and those patients discharged, respectively ($p < 0.05$). Discharged patients have lower percentage of underlying diseases as comparison to those patients with ward admission. Of 57 ED discharged patients, 8 (14.0%) patients revisited ED within 72 hours, who were all self-harm. Of all 20 BZD overdose patients with ICU admission, three (15%) were mortalities, among whom 2 were age more than 80 years. The causes of death were aspiration pneumonia with respiratory failure in ICU and sudden cardiac arrest two days after transferred out of ICU, respectively. The third one was a 69 years female with terminal cancer, whose death was not considered directly attributed to BZD overdose at this time of ICU admission.

As our demonstration of clinical characteristics that may be predictive of BZD overdose patients with ICU or ward admission and discharge. The AMS, drowsy, and GCS ≤ 8 were all important clinical symptoms and signs for predictive factors of dispositions and would be suitable for univariate analysis. Due to there was more objective character evaluated by emergency physician as conscious level of GCS ≤ 8 as compared with AMS, we choose GCS ≤ 8 to enter into multi-variate logistic regression. The multiple logistic regression analysis demonstrated that pneumonia and flumazenil use in ED, respectively, were the predictors for ICU admission as comparison with those without ICU admission (Table 4). Further analysis of patients with hospital admission, we found that pneumonia was the only independent predictor for patient admission to ICU as comparison to those patients with ward admission (Table 5).

Discussion

Our study results showed that pneumonia and flumazenil use in the ED would be the significant predictors for ICU admission among patients with BZD overdose compared with those without non-ICU admission (both ward admission and discharged). In additions, among those with hospital admission, including ICU and ward admissions, only pneumonia remains the determinate predictors for ICU admission in comparison for those with ward admission, respectively, in multiple logistic regression analyses ($p < 0.05$). Besides, our study patients with BZD overdose in the ED have a low incidence of mortality with 2.1% (3/140), whereas, it may be up to 15% (3/20) among those patients admitted to ICU. These results suggested patients with BZD overdose admission to ICU should be cautious of comorbidities with high overall mortality and needed further dedicated care and management.

Drugs are the most common reason of overdose.[12,13] Several studies have shown that BZDs were the most commonly used for self-poisoning among the drugs.[7,14-18] Few comprehensive studies had focused on investigating the clinical characteristics and predictors for patients with acute BZD poisoning admitted to ICU, except case report study.[19] Our current study identified that the flumazenil use in ED would be one of the important predictors for hospital admission, including both ICU and ward admission. Flumazenil is a potent antidote of BZD, may accelerate the recovery from the toxicity after BZD overdose.[20] Re-sedation occurs in approximately 30% of total flumazenil-treated cases were reported.[21] This clinical applicable characters indicated that BZD poisoning patients receiving flumazenil use would be those one more sedative than those without use, who need more monitoring system and closely observation of possible risk of aspiration pneumonia. The approved indication of flumazenil use is for the diagnosis and treatment of overdose with only or mainly BZDs,[22] and it was reported not to be used among all of patients suspect BZD poisoning.[23] One review article also suggested that no sufficient evidence to support the routine use of flumazenil in the ED, only depending on clinical benefit and risk evaluation.[24] In our study, up to 60% (12/20) of patients with ICU admission had flumazenil used in ED, with odd ratio of 4.28 than those

Table 2. Comparison of clinical characteristics by intensive care unit and non-intensive care unit admission after emergency department visits in 140 patients with benzodiazepine overdose[a]

Variable	ICU admission (n = 20)	Non-ICU admission (n = 120)	*p* value
Age (year)	53.0 ± 20.6	51.0 ± 18.9	NS
Male/female	6/14	33/87	NS
Underlying disease			
Insomnia	17 (85.0)	111 (92.5)	NS
MDD/bipolar disorder	16 (80.0)	103 (85.8)	NS
Hypertension	6 (30.0)	29 (24.2)	NS
OA or DJD of spine	4 (20.0)	23 (19.2)	NS
Heart disease	3 (15.0)	16 (13.3)	NS
Stroke/PD	3 (15.0)	14 (11.7)	NS
DM	1 (5.0)	12 (10.0)	NS
CKD	2 (10.0)	9 (7.5)	NS
Seizure disorder	1 (5.0)	10 (8.3)	NS
Cancer	3 (15.0)	5 (4.2)	NS
Lung disease	2 (10.0)	6 (5.0)	NS
Suicidal history	9 (45.0)	50 (41.7)	NS
Drug allergy history	1 (5.0)	5 (4.2)	NS
Cause of BZD overdose			
Suicide	16 (80.0)	102 (85.0)	NS
ADR or accidental event	3 (15.0)	11 (9.2)	NS
Substance addiction	1 (5.0)	7 (5.8)	NS
Classification of BZD overdose			
Long acting	3 (15.0)	31 (25.8)	NS
Intermediate acting	3 (15.0)	45 (37.5)	0.049
Short acting	3 (15.0)	13 (10.8)	NS
Mix	2 (10.0)	11 (9.2)	NS
ED presentation			
Altered mental status	15 (75.0)	37 (30.8)	< 0.001
Drowsy	2 (10.0)	39 (32.5)	0.041
General weakness	2 (10.0)	8 (6.7)	NS
Dizziness	0 (0.0)	7 (5.8)	NS
Agitation	0 (0.0)	3 (2.5)	NS
GCS ≤ 8	13 (65.0)	36 (30.0)	0.003
Acute renal failure	3 (15.0)	7 (5.8)	NS
Pneumonia	11 (55.0)	7 (5.8)	< 0.001
Respiratory failure	16 (80.0)	2 (1.7)	< 0.001
Flumazenil use in ED	12 (60.0)	23 (19.1)	< 0.001

ADR: adverse drug reaction; BZD: benzodiazepine; CKD: chronic kidney disease; DJD: degenerative joint disease; DM: diabetes mellitus; ED: emergency department; GCS: Glasgow Coma Scale; ICU: intensive care unit; MDD: major depressive disorder; NS: no significant; OA: osteoarthritis; PD: Parkinson's disease.

[a]Data presented as mean ± standard deviation or number (%).

Table 3. Comparison of clinical characteristics by admission to intensive care unit or ward and discharge after emergency department visits in 140 patients with benzodiazepine overdose[a]

Variable	ICU admission (n = 20)	Ward admission (n = 63)	Discharged (n = 57)	*p* value
Age (year)	53.0 ± 20.6	53.7 ± 19.9	48.0 ± 17.5	NS
Male/female	6/14 (42.9)	21/42 (50.0)	12/45 (26.7)	NS
Underlying disease				
Insomnia	17 (85.0)	57 (90.5)	54 (94.7)	NS
MDD/bipolar disorder	16 (80.0)	57 (90.5)	47 (82.5)	NS
Hypertension	6 (30.0)	21 (33.3)	8 (14.1)**	0.014
OA or DJD of spine	4 (20.0)	13 (20.6)	10 (17.5)	NS
Heart disease	3 (15.0)	13 (20.6)	3 (5.3)**	0.014
Stroke/PD	3 (15.0)	10 (15.9)	4 (7.0)	NS
DM	1 (5.0)	8 (12.7)	4 (7.0)	NS
CKD	2 (10.0)	7 (11.1)	2 (3.5)	NS
Seizure disorder	1 (5.0)	7 (11.1)	3 (5.3)	NS
Cancer	3 (15.0)	3 (4.8)	2 (3.5)	NS
Lung disease	2 (10.0)	6 (9.5)	0 (0.0)*	NS
Suicidal history	9 (45.0)	24 (38.1)	26 (45.6)	NS
Drug allergy history	1 (5.0)	3 (4.8)	2 (3.5)	NS
Cause of BZD overdose				
Suicide	16 (80.0)	51 (81.0)	51 (89.5)	NS
ADR or accidental event	3 (15.0)	8 (12.7)	3 (5.3)	NS
Substance addiction	1 (5.0)	4 (6.3)	3 (5.3)	NS
Classification of BZD overdose				
Long acting	3 (15.0)	20 (31.7)	10 (17.5)	NS
Intermediate acting	3 (15.0)	17 (27.0)	26 (45.6)*	0.034
Short acting	3 (15.0)	9 (14.3)	4 (7.0)	NS
Mix	2 (10.0)	8 (12.7)	6 (10.5)	NS
ED presentation				
Altered mental status	15 (75.0)	24 (38.1)*	13 (22.8)*	< 0.001
Drowsy	2 (10.0)	25 (39.7)*	13 (22.8)*	0.042
General weakness	2 (10.0)	1 (1.6)	7 (12.3)**	0.019
Dizziness	0 (0.0)	3 (4.8)	4 (7.0)	NS
Agitation	0 (0.0)	3 (4.8)	1 (1.8)	NS
GCS ≤ 8	13 (65.0)	24 (38.1)*	12 (21.1)*	0.001
Acute renal failure	3 (15.0)	5 (7.9)	2 (3.5)	NS
Pneumonia	11 (55.0)	7 (11.1)*	0 (0.0)*	< 0.001
Respiratory failure	16 (80.0)	2 (3.2)*	0 (0.0)*	< 0.001
Flumazenil use in ED	12 (60.0)	18 (28.6)*	5 (8.8)*,**	< 0.001

ADR: adverse drug reaction; BZD: benzodiazepine; CKD: chronic kidney disease; DJD: degenerative joint disease; DM: diabetes mellitus; ED: emergency department; GCS: Glasgow Coma Scale; ICU: intensive care unit; MDD: major depressive disorder; NS: no significant; OA: osteoarthritis; PD: Parkinson's disease.

[a]Data presented as mean ± standard deviation or number (%).

*$p < 0.05$ comparison with ICU admission group; **$p < 0.05$ comparison with ward admission group.

Table 4. Independent predictors of intensive care unit admission by using multiple logistic regression model[a]

Variables	BZD overdose (n = 140)		OR	95% CI	*p* value
	ICU (n = 20)	Non-ICU (n = 120)			
Pneumonia	3 (15.0)	7 (5.8)	15.58	4.21–57.74	< 0.001*
Flumazenil use in ED	12 (60.0)	23 (19.1)	3.80	1.05–13.72	0.042*
GCS ≤ 8	13 (65.0)	36 (30.0)	1.82	0.51–6.50	0.356

BZD: benzodiazepine; CI: confidence interval; ED: emergency department; GCS: Glasgow Coma Scale; ICU: intensive care unit; OR: odds ratio.
[a]Results expressed as number (%) for categorical variables and mean (± standard deviation) for numerical variables.
*$p < 0.05$ means statistical significance in multiple regression analysis.

Table 5. Multiple logistic regression analysis of predictors for inpatients in need of intensive care unit admission[a]

Variables	BZD overdose of inpatients (n = 83)		OR	95% CI	*p* value
	ICU admission (n = 20)	Ward admission (n = 63)			
Pneumonia	11 (55.0)	7 (11.1)	9.15	2.51–33.42	< 0.001*
Flumazenil use in ED	12 (60.0)	18 (28.6)	2.71	0.75–9.87	0.130
GCS ≤ 8	13 (65.0)	24 (38.1)	1.76	0.47–6.62	0.405

BZD: benzodiazepine; CI: confidence interval; ED: emergency department; GCS: Glasgow Coma Scale; ICU: intensive care unit; OR: odds ratio.
[a]Results expressed as number (%) for categorical variables and mean (± standard deviation) for numerical variables.
*$p < 0.05$ means statistical significance in multiple regression analysis.

patients without ICU admission (Table 4). This may be related to the patient's medical history, underlying diseases, and clinical manifestations when entering the ED. The most common side effect of flumazenil is seizure, especially for those with underlying seizure history.[25,26] In our study, 7.9% patients has seizure history, who all didn't receive the use of flumazenil. In our clinical practice, before the use of flumazenil, emergency physician also routinely examine the electrocardiography (EKG) morphology to see if there is corrected QT interval (QTC) prolongation to prevent possible medication inducing arrhythmia. Of all those who received use of flumazenil, no one had the complication with seizure attack or heart episode thereafter.

Aspiration pneumonia is a common complication of drug overdose,[26] and even leading to risk of mortality.[21] In our study, one mortality cause by aspiration pneumonia, that is one of the predictors for ICU admission. Continuous flumazenil infusion was suggested to be use for the prevention of aspiration pneumonia.[21] Earlier studies have shown that BZD poisoning patients in the elderly and chronic lung disease will have more serious complications in the population.[8] However, in our study, there is no significant correlation with chronic lung disease. However, we found those mortalities were all elderly patients, that needed further managements in the future.

The hospital mortality rate varies from 0.6% to 6.1%.[6] In this study, the in-hospital mortality rate was 3.6% (3/83) whereas the mortality rate of patients with ICU admission will be up to 15% (3/20). All the three patients with mortality can't be ruled out the complications associated with the excessive use of BZD. This would reflect the fact that even with a wide range of BZD safety and BZD medications that overdose even less likely to cause death.[4] However, the side effects and toxicity associated with BZD medication may cause morbidity and mortality in certain special populations, such as the elderly and those with poor lung function and liver and kidney dysfunction.[3]

In a nested case-control study demonstrated that the use of BZDs in psychiatric outpatients was significantly associated with deliberate self-poisoning, especial in those who have a history of depression or bipolar disorder with higher odds.[22] In our study, 85.7% (120/140) have a history of depression or bipolar disorder. Also shown was 84.3% (118/140) patients having suicidal attempt with BZD poisoning, the most common cause that was an important global public health problem. In ED or after hospitalization, all our study patients received psychologist's consultation and were arranged subsequent follow-up interview in outpatient clinics. Given these results, it is important that these patients receive adequate multidisciplinary support and intervention to try and prevent the long-term consequences associated repeated self-poisoning

and addiction. How to establish a system recording suicide attempt cases in the ED is a crucial step in compiling with suicide information, intervention, and prevention. The cooperation of emergency physicians and nurses, psychiatrists, and social workers, coupled with further patient follow-up systems including hospital admission and outpatient departments, would undoubtedly lead to an increase in positive outcomes.[27]

Our results should be viewed in the light of the study's limitations. First, the study design was a retrospective analysis, and might subject to the limitations of all retrospective studies. Secondly, this study was carried out at a tertiary teaching medical center. The results may not be generalizable to other different hospital settings and levels. Our definition of aspiration pneumonia may include patients with early aspiration pneumonia and the identification of bacteriology would be difficult. We also didn't exclude those patients with mixed compound effects, which would cause trivial clinical effects, under scrutinized inspection by authors, as compared with BZD overdose. To avoid potential clinical bias we use logistic regression models to take into account factors that had some biological plausibility and scientific rationale. For example, in term of study patients with respiratory failure were not entered for regression model because its subjectively role of decision of emergency physician will eliminate most contributing factors prediction. A prospective study of two or more centers might be needed to validate the predictors of ICU and hospital admission for patients with BZD poisoning.

Conclusion

The deliberate self-harm with attempt of BZD ingestion was the most common cause of BZD overdose in this study, especial focusing on those with underlying major depression disease or bipolar disorder. Pneumonia and flumazenil use in ED were identified risk factors associated with ICU admission in comparison with those without ICU admission. Though the incidence of overall mortality among patients with BZD overdose was relative low, there was still high mortality in those with severe overdose victims who were admitted to ICU. Further preventive strategies and educational programs recommending clinicians in the prescribing BZD should be closely focusing on patients' suicide or self-injury tendency and also on elderly patients.

References

1. Kyong YY, Park JT, Choi KH. Serial monitoring of sedation scores in benzodiazepine overdose. *Am J Emerg Med* 2014;32:1438.e5-1438.e6. doi:10.1016/j.ajem.2014.04.004
2. Sessler CN, Grap MJ, Ramsay MA. Evaluating and monitoring analgesia and sedation in the intensive care unit. *Crit Care* 2008;12(Suppl 3):S2. doi:10.1186/cc6148
3. Griffin CE 3rd, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. *Ochsner J* 2013;13:214-223.
4. Prescott K, Stratton R, Freyer A, Hall I, Le Jeune I. Detailed analyses of self-poisoning episodes presenting to a large regional teaching hospital in the UK. *Br J Clin Pharmacol* 2009;68:260-268. doi:10.1111/j.1365-2125.2009.03458.x
5. Longo LP, Johnson B. Addiction: part I. Benzodiazepines—side effects, abuse risk and alternatives. *Am Fam Physician* 2000;61:2121-2128.
6. Berger A, Edelsberg J, Sanders KN, Alvir JM, Mychaskiw MA, Oster G. Medication adherence and utilization in patients with schizophrenia or bipolar disorder receiving aripiprazole, quetiapine, or ziprasidone at hospital discharge: a retrospective cohort study. *BMC Psychiatry* 2012;12:99. doi:10.1186/1471-244X-12-99
7. Novack V, Jotkowitz A, Delgado J, et al. General characteristics of hospitalized patients after deliberate self-poisoning and risk factors for intensive care admission. *Eur J Intern Med* 2006;17:485-489. doi:10.1016/j.ejim.2006.02.029
8. Höjer J, Baehrendtz S, Gustafsson L. Benzodiazepine poisoning: experience of 702 admissions to an intensive care unit during a 14-year period. *J Intern Med* 1989;226:117-122. doi:10.1111/j.1365-2796.1989.tb01365.x
9. Hu YH, Chou HL, Lu WH, et al. Features and prognostic factors for elderly with acute poisoning in the emergency department. *J Chin Med Assoc* 2010;73:78-87. doi:10.1016/S1726-4901(10)70006-X
10. Vukcević NP, Ercegović GV, Šegrt Z, Djordjević S, Stošić JJ. Benzodiazepine poisoning in elderly. *Vojnosanit Pregl* 2016;73:234-238. doi:10.2298/VSP141208025P
11. Henderson A, Wright M, Pond SM. Experience with 732 acute overdose patients admitted to an intensive care unit over six years. *Med J Aust* 1993;158:28-30.
12. Vancayseele N, Portzky G, van Heeringen K. Increase in self-injury as a method of self-harm in Ghent, Belgium: 1987-2013. *PLoS One* 2016;11:e0156711. doi:10.1371/journal.pone.0156711
13. Afshari R, Majdzadeh R, Balai-Mood M. Pattern of acute poisonings in Mashhad, Iran 1993–2000. *J Toxicol Clin Toxicol* 2004;42:965-975. doi:10.1081/CLT-200042550
14. Karbakhsh M, Zandi NS. Pattern of poisoning in the elderly: an experience from Tehran. *Clin Toxicol (Phila)*

2008;46:211-217. doi:10.1080/15563650701638982
15. Jacobsen D, Frederichsen PS, Knutsen KM, Sørum Y, Talseth T, Ødegaard OR. A prospective study of 1212 cases of acute poisoning: general epidemiology. *Hum Toxicol* 1984;3:93-106. doi:10.1177/096032718400300203
16. Rahman A, Martin C, Graudins A, Chapman R. Deliberate self-poisoning presenting to an emergency medicine network in South-East melbourne: a descriptive study. *Emerg Med Int* 2014;2014:461841. doi:10.1155/2014/461841
17. Hendrix L, Verelst S, Desruelles D, Gillet JB. Deliberate self-poisoning: characteristics of patients and impact on the emergency department of a large university hospital. *Emerg Med J* 2013;30:e9. doi:10.1136/emermed-2011-201033
18. Aguilera P, Garrido M, Lessard E, et al. Medication overdoses at a public emergency department in Santiago, Chile. *West J Emerg Med* 2016;17:75-80. doi:10.5811/westjem.2015.11.26068
19. Neale G, Smith AJ. Self-harm and suicide associated with benzodiazepine usage. *Br J Gen Pract* 2007;57:407-408.
20. Krisanda TJ. Flumazenil: an antidote for benzodiazepine toxicity. *Am Fam Physician* 1993;47:891-895.
21. Chern CH, Chern TL, Wang LM, Hu SC, Deng JF, Lee CH. Continuous flumazenil infusion in preventing complications arising from severe benzodiazepine intoxication. *Am J Emerg Med* 1998;16:238-241. doi:10.1016/S0735-6757(98)90091-2
22. Shih HI, Lin MC, Lin CC, et al. Benzodiazepine therapy in psychiatric outpatients is associated with deliberate self-poisoning events at emergency departments—a population-based nested case-control study. *Psychopharmacology (Berl)* 2013;229:665-671. doi:10.1007/s00213-013-3127-4
23. Sivilotti ML. Flumazenil, naloxone and the 'coma cocktail'. *Br J Clin Pharmacol* 2016;81:428-436. doi:10.1111/bcp.12731
24. Ngo ASY, Anthony CR, Samuel M, Wong E, Ponampalam R. Should a benzodiazepine antagonist be used in unconscious patients presenting to the emergency department? *Resuscitation* 2007;74:27-37. doi:10.1016/j.resuscitation.2006.11.010
25. Thomson JS, Donald C, Lewin K. Use of flumazenil in benzodiazepine overdose. *Emerg Med J* 2006;23:162.
26. Seger DL. Flumazenil—treatment or toxin. *J Toxicol Clin Toxicol* 2004;42:209-216. doi:10.1081/CLT-120030946
27. Huang HH, Fan JS, Chen YC, Yen DHT. Coordination between medical care providers and information technology resources in the management of patients with suicide attempts attending the emergency department. *J Chin Med Assoc* 2014;77:275-276. doi:10.1016/j.jcma.2014.05.001

Supplement Table 1. The classification of benzodiazepine overdose[a]

Classification	n = 112
Long acting	
Flunitrazepam	30 (21.4)
Clonazepam	11 (7.9)
Flurazepam	7 (5.0)
Diazepam	2 (1.4)
Intermediate acting	
Alprazolam	26 (18.6)
Estazolam	19 (13.6)
Lorazepam	10 (7.1)
Bromazepam	2 (1.4)
Short acting	
Midazolam	13 (9.3)
Triazolam	5 (3.6)
Brotizolam	2 (1.4)
Clotiazepam	1 (0.7)

[a]Data presented as n (%).