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著者	OMICHI Chie, AYANI Nobutaka, OYA Nozomu, MATSUMOTO Yoshihiro, TANAKA Maki, MORIMOTO Takeshi, KADOTANI Hiroshi, NARUMOTO Jin
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## Association between discontinuation of benzodiazepine receptor agonists and post-operative delirium among inpatients with liaison intervention: A retrospective cohort study



Chie Omichi <sup>a</sup>, Nobutaka Ayani <sup>a,b,\*</sup>, Nozomu Oya <sup>a</sup>, Yoshihiro Matsumoto <sup>a</sup>, Maki Tanaka <sup>c</sup>, Takeshi Morimoto <sup>d</sup>, Hiroshi Kadotani <sup>e</sup>, Jin Narumoto <sup>a</sup>

<sup>a</sup> Department of Psychiatry, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan

<sup>b</sup> Department of Psychiatry, National Hospital Organization, Maizuru Medical Center, 2410 Yukinaga, Maizuru, Kyoto 625-8502, Japan

<sup>c</sup> Department of Medical Safety Management, University Hospital, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan

<sup>d</sup> Department of Clinical Epidemiology, Hyogo College of Medicine, 1-1 Mukogawa, Nishinomiya, Hyogo 663-8501, Japan

<sup>e</sup> Department of Sleep and Behavioral Sciences, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu City, Shiga 520-2192, Japan

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### ABSTRACT

**Background:** Several studies have investigated the association between benzodiazepine receptor agonist (BZDRA) use during the perioperative period and an elevated incidence of delirium. However, no study has focused on the time course of BZDRA use, including continuation, discontinuation, initiation, and no use. This study aimed to examine the influence of the time course of BZDRA use on post-operative delirium.

**Methods:** This retrospective cohort study was conducted by reviewing medical records. We included patients who were scheduled for surgery under general anesthesia and had been referred to a liaison psychiatrist for pre-operative psychiatric assessment. The patients were classified into four groups based on the pre- and post-operative time course of oral BZDRA use, as follows: continuation, discontinuation, initiation, and no use (never used). The primary outcome was the prevalence of post-operative delirium in non-intensive care unit settings. We also performed stratified analyses according to age, the presence of cognitive impairment, the presence of delirium history, and antipsychotic drug use on admission.

**Results:** Among 250 patients, 78 (31%) developed post-operative delirium. The Discontinuation group had a higher rate of delirium (49%, 24/49) than the other groups (Continuation [14%, 4/29]; Initiation [38%, 3/8], Never used [29%, 47/164],  $p = 0.008$ ).

**Conclusions:** Abrupt discontinuation of BZDRAs during the perioperative period may be a risk factor for post-operative delirium and should therefore be avoided.

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### 1. Introduction

Delirium is the most prevalent mental disorder among hospitalized patients. In medical wards, the prevalence of delirium among hospitalized patients ranges from 10% to 30% [1]; moreover, 51% of patients develop post-operative delirium [1]. Post-operative delirium is associated with higher rates of cognitive/functional decline, severe acute illness, prolonged length of hospitalization, and economic costs [2–5]. Old age (over 70 years), cognitive impairment, and a history of delirium are the primary risk factors for delirium [6–9]; further, perioperative use

of benzodiazepine receptor agonists (BZDRAs) has also been reported as a risk factor [6,10].

BZDRAs are widely used among patients with insomnia and anxiety [11–13], and are generally considered to be safe and effective during short-term use. However, extended use (for >2 months) may cause increased drug tolerance, dependence, and other adverse effects such as falls and cognitive disturbances [14,15]. Long-term users are advised to discontinue BZDRAs to avoid adverse effects [16–20]; however, abrupt discontinuation frequently leads to benzodiazepine withdrawal syndrome, which can lead to severe symptoms, including agitation, seizures, and delirium. A previous study among hospitalized patients reported that delirium was related to benzodiazepine withdrawal in approximately 20% (4/19) of patients aged 65 years and older [21].

While there have been many reports describing the association between BZDRA use and post-operative delirium [6,10,22–26], no cohort study has compared the risk of post-operative delirium after continued,

\* Corresponding author at: Department of Psychiatry, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan.

E-mail address: [lingren@koto.kpu-m.ac.jp](mailto:lingren@koto.kpu-m.ac.jp) (N. Ayani).

discontinued, or newly initiated BZDRA use in the perioperative period with that in patients not using BZDRAs at all. This study aimed to determine the influence of continuation, discontinuation, and initiation of oral BZDRA administration on post-operative delirium among hospitalized patients in the non-intensive care unit (ICU) setting.

## 2. Material and methods

### 2.1. Study design and patient population

This retrospective cohort study was conducted at the University Hospital of Kyoto Prefectural University of Medicine (KPUM), which is a 1065-bed tertiary care center in Kyoto prefecture, Japan.

Perioperative patients admitted between January 2016 and December 2018 who had received preventive intervention from a liaison psychiatrist before surgery were included in our study. Attending surgeons decided whether the consultation-liaison service (CLS) should be sought for preventive intervention. There were no specific criteria for these requests; however, surgeons often requested the interventions to prevent delirium in patients at risk, such as those with older age, cognitive impairment, and a history of delirium or severe surgical invasion. In cases where surgeons requested the CLS, they made the final decision on whether medications should be adjusted based on advice and guidance from the latter.

We considered that each admission event during the study period involved one individual patient, regardless of readmission, because repeated requests for preventive intervention are rare in cases where the same patient undergoes repeated operations in a short period of time.

We excluded patients undergoing local anesthesia for surgery to ensure a similar degree of surgical invasion among the study group. In addition, we also excluded patients who died within 24 h of surgery, had an ICU stay beyond the study period, and received intervention for assessing organ transplant eligibility. The Institutional Review Board of KPUM approved the study and waived the requirement for informed consent because all data were obtained as part of daily routine practice.

### 2.2. Consultation-liaison interventions

The CLS of the Department of Psychiatry at the KPUM provides interventions in the form of guidance regarding the treatment and prevention of mental disorders for patients in the general medical ward.

For patients with significant risk factors for delirium (e.g., older age, history of delirium, cognitive impairment, and alcohol use disorders), liaison psychiatrists advise reduction or discontinuation of BZDRAs and anticholinergic drugs; they advise the prescription of other hypnotic drugs such as ramelteon, suvorexant, or trazodone, the last of which is frequently prescribed for hospitalized patients with insomnia in Japan owing to its efficacy in managing the symptoms of delirium [27].

### 2.3. BZDRA and the time course of BZDRA use

All benzodiazepines and non-benzodiazepines, including hypnotic, anti-anxiety, and antiepileptic drugs, were considered as BZDRAs. The following BZDRAs were available for use at the study site and selected for our study: alprazolam, bromazepam, brotizolam, clonazepam, clotiazepam, cloxazolam, diazepam, estazolam, eszopiclone, etizolam, ethyl loflazepate, flunitrazepam, lorazepam, lormetazepam, nitrazepam, quazepam, triazolam, zolpidem, and zopiclone. We investigated whether the participants received BZDRAs during the perioperative period.

The participants were classified into the following four groups based on the time course of BZDRA use: "Continued," "Discontinued," "Initiated," and "Never used." The "Continued" group had been taking BZDRAs continuously from admission to the end of the study period. Participants who resumed BZDRAs within 2 days after surgery were considered to be in the "Continued" group if medications were interrupted due to post-operative fasting; this was based on the fact

that withdrawal symptoms usually occur within 48 h of short-acting BZDRA administration [28]. The "Discontinued" group included participants who were taking BZDRAs on admission but discontinued them after surgery; those who resumed treatment at more than 3 days after surgery were also included in this group. Since patients are usually admitted to the hospital a few days before surgery, BZDRAs were discontinued abruptly. Participants who were not taking BZDRAs on admission but received new BZDRA prescriptions (including rescue use) post-operatively were classified in the "Initiated" group. Finally, those who did not take BZDRAs at any time during the study period were classified into the "Never-used" group.

### 2.4. Data collection and outcomes

Data on baseline patient characteristics, including background information, length of hospitalization, operative times, Charlson comorbidity index [29], psychiatric comorbidities such as cognitive impairment and alcohol use disorders, delirium history, and perioperative use of psychiatric medications, including oral BZDRAs and antipsychotics, were obtained from electronic medical records. Psychiatric comorbidities were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria based on the information collected from the medical records [30].

BZDRAs were classified into two categories based on the duration of action, namely, ultrashort-/short-term and intermediate/long-term BZDRAs. Ultrashort- (including eszopiclone, triazolam, zolpidem, and zopiclone), short- (including brotizolam, clotiazepam, etizolam, and lormetazepam), intermediate- (including alprazolam, bromazepam, estazolam, lorazepam, and nitrazepam), and long- (including clonazepam, diazepam, ethyl loflazepate, flunitrazepam, and quazepam) acting BZDRAs have a half-life of <6, 6–12, 12–24, and > 24 h, respectively [31,32].

The primary outcome was the prevalence of post-operative delirium in the non-ICU setting. We reviewed the medical records till post-operative day 14 to determine the occurrence of delirium. Delirium (including hyperactive, hypoactive, and mixed types of delirium) that occurred up to 7 days after surgery was defined as post-operative delirium, based on a previous report [33]. In addition, any delirium that developed within 7 days of ICU discharge (and within 14 days after surgery) was also considered to be post-operative delirium. We also examined delirium occurring in the ICU; however, we did not evaluate this in the current study, as we intended to investigate the association between oral BZDRA use and the development of post-operative delirium in a general ward setting.

Delirium was diagnosed according to DSM-5, based on the available information collected from the medical records. The four reviewers, including three experienced psychiatrists who were familiar with the clinical practice of delirium diagnosis, checked all relevant information and confirmed the diagnosis of delirium through a consensus.

### 2.5. Statistical analysis

Continuous variables, presented as means and standard deviations or medians and interquartile ranges (IQRs), were compared using *t*- or Wilcoxon rank-sum tests. Categorical variables, presented as counts and percentages, were compared using chi-square or Fisher's exact tests. The prevalence of delirium was calculated as the number of patients with delirium divided by the number of patients in each group. We performed stratified analysis to adjust for certain confounding factors associated with the development of delirium (age 70 years or higher, presence of cognitive impairment, history of delirium, and anti-psychotic drug use on admission) as multivariate analysis could not be used to compare the prevalence in the four groups after examination with chi-square tests.

All tests were two-sided, and values of  $p < 0.05$  were considered statistically significant. All statistical analyses were conducted using the JMP 14.0 for Mac software package (SAS Institute Inc).

### 3. Results

#### 3.1. Baseline characteristics

We included 250 patients in the final analysis (Fig. 1); they had a mean age of 67 years and 143 (57.2%) were male (Table 1). Among them, 51 (20.4%) and 32 (12.8%) experienced cognitive impairment and had a history of delirium, respectively. According to the time course of BZDRA use, 29 (11.6%), 49 (19.6%), 8 (3.2%), and 164 (65.6%) patients were classified into “Continued,” “Discontinued,” “Initiated,” and “Never-used” groups, respectively. The cardiovascular surgery department had the highest number of patients referred for liaison preventive intervention ( $n = 70$ , 28.0%) (Table 1).

Inter-group comparison showed that the “Continued” group had the shortest operative duration (198 min, IQR: 79, 269.5) and the highest rate of psychiatric comorbidities (76%, 22/29) and antipsychotic drug usage on admission (24.1%, 7/29). The “Discontinued” group had the highest mean age (73.1 years, SD = 9.6). Only three patients in this group were not under treatment with other sleep medications (ramelteon, suvorexant, or trazodone), and only one patient was not under treatment with any psychotropic medication at all. In contrast, the mean age of the “Initiated” group was the lowest (53.5 years, SD = 23.9), and none of the patients were taking antipsychotics. The “Never-used” group had the highest rate of cognitive impairment (25.0%, 41/164).

#### 3.2. Outcomes

The prevalence of post-operative delirium in all patients was 31.2% (78/250) (Table 2). The “Discontinued” group had the highest rate among the four groups (49.0%, 24/49), and “Continued” group had the lowest (13.8%, 4/29). There was a significant difference in the prevalence of delirium among the four groups ( $p = 0.008$ ) (Table 2).

On stratified analysis, we observed that the prevalence of post-operative delirium was the highest in the “Discontinued” group and in patients who did not have cognitive impairment, a history of delirium, or a history of antipsychotic use on admission, all of which are

considered strong risk factors for the development of post-operative delirium. Even after excluding patients aged 70 years and older, who were at high risk for delirium, the “Discontinued” group continued to show the highest prevalence; however, there was no significant difference in the rates between the groups (Table 3).

The prevalence of delirium among patients in the “Continued” and “Discontinued” groups taking short-acting drugs was 50% and 51%, respectively. The incidence of delirium among patients taking long-acting drugs was 4% and 38%, respectively. In addition, the prevalence of post-operative delirium in the “Discontinued” group according to the type of BZDRA used on admission was 51% and 38% for ultrashort/short and intermediate/long-acting BZDRAs, respectively ( $p = 0.70$ ). Conversely, in the “Continued” group, the prevalence was 50% and 4% respectively, with a significantly higher rate in the group taking ultrashort/short-acting BZDRAs ( $p = 0.02$ ).

### 4. Discussion

In this study, we assessed the relationship between the time course of oral BZDRA use (continuation, discontinuation, initiation, and no use) and the occurrence of post-operative delirium in general ward inpatients; an independent association was observed between the discontinuation of BZDRA use and post-operative delirium. Many previous studies have reported an association between delirium and BZDRA administration; however, a majority of these studies analyzed ICU patients, who received intravenous BZDRA for sedation and anxiety reduction [22–25].

In contrast, there have been few studies on the association between oral psychoactive medications and post-operative delirium in general ward patients. A nested case-control study by Marcantonio et al. on a prospective cohort of post-operative patients with delirium reported an association between oral BZDRA and meperidine use and delirium occurrence (odds ratio, 3.0; 95% confidence interval, 1.3–6.8) [10]. Similarly, a cohort study by Gaudreau et al. among hospitalized patients with cancer reported that the use of oral BZDRAs, corticosteroids, and opioids was an independent risk factor for delirium [26]. These previous findings indicate an association between the use of some drugs during hospitalization, including BZDRAs, and the development of delirium. To our knowledge, the present study is the first to demonstrate an association between the time course of BZDRA use (continuation, discontinuation, new initiation, and no use) and delirium.

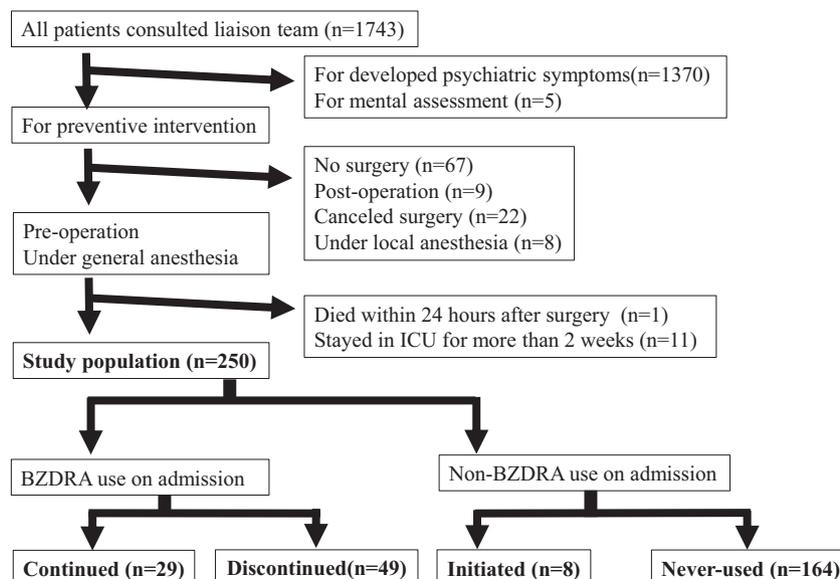


Fig. 1. Flowchart of the patients who met the inclusion criteria for the study. BZDRA: benzodiazepine receptor agonists.

**Table 1**  
Demographics and clinical variables on admission.

Variables	Total N = 250	Continued N = 29	Discontinued N = 49	Initiated N = 8	Never used N = 164	p-value
Age, mean (SD)	66.7 (17.1)	57.9 (16.9)	73.1 (9.6)	53.5 (23.9)	67.0 (17.7)	<0.001
Male sex, n (%)	143 (57.2)	9 (31.0)	29 (59.2)	5 (62.5)	100 (60.9)	0.03
Length of stay, median (IQR)	30 (15, 45)	13 (7, 24)	34 (17, 51)	28 (15, 46)	33 (18, 46)	0.006
Operative time, median (IQR)	291 (141, 443)	162 (79, 270)	326 (185, 527)	232 (91, 303)	314 (159, 477)	0.007
Charlson comorbidity index $\geq 3$ , n (%)	43 (17.2)	3 (10.3)	10 (20.4)	0 (0)	30 (18.3)	0.37
History of delirium	32 (12.8)	3 (10.3)	6 (12.2)	1 (12.5)	22 (13.4)	0.97
<b>Psychiatric comorbidity</b>						
All psychiatric comorbidities, n (%)	101 (40.4)	22 (75.9)	15 (30.6)	4 (50.0)	60 (36.6)	<0.001
Psychotic disorder, n (%)	8 (3.2)	5 (17.2)	1 (2.0)	0 (0)	2 (1.2)	<0.001
Mood disorder, n (%)	16 (6.4)	12 (41.4)	1 (2.0)	1 (12.5)	2 (1.2)	<0.001
Mental retardation, n (%)	14 (5.6)	2 (6.9)	0 (0)	0 (0)	12 (7.3)	0.22
Cognitive impairment, n (%)	51 (20.4)	0 (0)	9 (18.4)	1 (12.5)	41 (25.0)	0.019
Alcohol use disorder, n (%)	11 (4.4)	0 (0)	6 (12.2)	1 (12.5)	4 (2.4)	0.010
<b>Medication on admission</b>						
Antipsychotic drugs, n (%)	21 (8.4)	7 (24.1)	3 (6.1)	0 (0)	11 (6.7)	0.012
Ultrashort/short-acting BZDRAs, n (%)	47 (60.3)	6 (20.7)	41 (83.6)	NA	NA	<0.001
<b>Main treatment department</b>						
Cardiovascular surgery, n (%)	70 (28.0)	5 (17.2)	14 (28.6)	1 (12.5)	50 (30.5)	0.37
Otolaryngology, n (%)	41 (16.4)	4 (13.8)	9 (18.4)	1 (12.5)	27 (16.5)	0.95
Gastroenterology, n (%)	38 (15.2)	1 (3.5)	10 (20.4)	0 (0)	27 (16.5)	0.12

SD, Standard deviation; IQR, Interquartile range; NA, Not applicable

The prevalence of post-operative delirium and the time course of BZDRA use were considered to be related to the patient characteristics in each group. The prevalence in the “Continued” group (13.8%) was lower than that in the “Never-used” group (28.7%). The “Continued” group had a high proportion of patients with psychiatric comorbidities. BZDRAs may have been continued for the stabilization of psychiatric comorbidities rather than to mitigate the risk of developing delirium; therefore, this group had the highest number of prescriptions for antipsychotics on admission, and all patients remained on antipsychotics during the study period. In the “Initiated” group, BZDRAs were initiated post-operatively because of the difficulty in controlling insomnia; however, the prevalence of delirium in the “Initiated” group (37.5%) was higher than that in the “Never-used” group, where the patients had the second highest mean age and the highest proportion of cognitive impairment. Cognitive impairment was considered to be a risk factor for delirium; this may have been related to the lack of BZDRA administration in the “Never-used” group.

The “Discontinued” group had the highest mean age, which was considered a risk factor for delirium, and led psychiatrists to recommend BZDRA reduction or discontinuation. Liaison psychiatrists recommended that BZDRAs should be discontinued for the purpose of reducing the risk of delirium, especially in elderly patients, and those with a history of delirium and cognitive impairment. The attending surgeon, therefore, often discontinued BZDRAs. In this study, all participants in the “Discontinued” group had abruptly discontinued BZDRAs; they were admitted to the hospital a few days before surgery and the CLS was requested even later; hence, discontinuation following the advice of the CLS had to be abrupt.

Unlike gradual tapering, abrupt BZDRA discontinuation is likely to cause withdrawal syndromes, including insomnia and delirium [31]. Abrupt discontinuation of BZDRAs after surgery could induce rebound

insomnia and withdrawal delirium in patients who had been taking BZDRAs for a long time. Because we did not collect data regarding the duration of BZDRA intake before surgery, inferences regarding the impact of duration of BZDRA administration on discontinuation-associated delirium cannot be drawn. However, it is estimated that the number of patients who develop post-operative delirium due to BZDRA discontinuation is not small, as BZDRAs are routinely prescribed to many patients in Japan.

In order to adjust for potential confounding factors, stratified analysis was conducted according to the absence of cognitive impairment, history of delirium, and antipsychotic drug usage. Stratified analysis revealed that the “Discontinued” group had the highest rate of delirium occurrence. This indicates that post-operative abrupt BZDRA discontinuation affects delirium even after adjustment for previously reported risk factors of delirium (cognitive impairment and delirium history) [34]. Similar findings were also obtained in the absence of antipsychotic use, which reportedly reduces the onset of delirium [35,36].

In addition, the prevalence of delirium in patients in the “Continued” group who used ultrashort/short-acting BZDRAs (50%) was significantly higher than that in those who used intermediate/long-acting BZDRAs (4%); however, there was no significant difference in the prevalence of delirium between those using ultrashort/short- and intermediate/long-acting BZDRAs in the “Discontinued” group. As patients generally undergo surgery soon after admission, it may be difficult to change the type of BZDRA after admission. However, these results suggest that it may be advisable to switch from ultrashort/short-acting BZDRAs to intermediate/long-acting types if they are continued after surgery.

This study has some strengths and limitations. First, as this was a four-group analysis of the time course of BZDRA use, it was not possible to perform multivariate analysis, and only simple adjustment for confounding factors was performed through stratification. In order to assess

**Table 2**  
Prevalence of delirium.

	Total N = 250	Continued N = 29	Discontinued N = 49	Initiated N = 8	Never used N = 164	p-value
Post-operative delirium, n (%)	78 (31.2)	4 (13.8)	24 (49.0)	2 (11.8)	47 (28.7)	0.008

**Table 3**  
Stratified analysis.

	Continued	Discontinued	Initiated	Never used	p-value
Patients without cognitive impairment, n	29	40	7	123	
Post-operative delirium, n (%)	4 (13.8)	19 (47.5)	2 (28.6)	32 (26.0)	0.016
Patients without a history of delirium, n	26	43	7	142	
Post-operative delirium, n (%)	3 (11.5)	21 (48.8)	3 (42.9)	36 (25.3)	0.003
Patients with no antipsychotic use on admission, n	22	46	8	153	
Post-operative delirium, n (%)	4 (18.2)	24 (52.2)	3 (37.5)	44 (28.8)	0.011
Patients under 70 years of age, n	20	15	6	68	
Post-operative delirium, n (%)	1 (5.0)	5 (33.3)	1 (16.7)	10 (14.7)	0.15

\*Prescribed at the time of admission

the effect of continuation and discontinuation of BZDRAs on post-operative delirium, it is preferable to focus only on the “Continued” and “Discontinued” groups and perform multivariate analysis. However, this study intended to investigate the clinical use of BZDRAs before and after surgery and compare the prevalence of delirium in the “Continued,” “Discontinued,” “Initiated,” and “Never-used” groups. The notion that BZDRA has a negative effect on post-operative delirium is popular in consultation-liaison psychiatry; we intended to identify patients who discontinued, continued, or initiated the use of BZDRAs and compare the prevalence of post-operative delirium among patients who used and did not use these drugs under similar circumstances.

Second, although the presence or absence of BZDRA medication upon admission was considered, the actual BZDRA administration history was not determined. An individual survey is required during admission to accurately determine administration history. Finally, this study collected data through a retrospective review of medical records; therefore, we may have underestimated the occurrence of delirium due to cases being overlooked. Notably, a previous report has indicated that hypoactive delirium is likely to be missed [37]. However, since this was a retrospective cohort study, daily clinical practice information could be observed and analyzed without involving the medical staff. The design also allowed a comprehensive analysis of continuation, discontinuation, and initiation of BZDRA use as a risk factor for delirium.

## 5. Conclusions

These findings indicate a relatively high occurrence of delirium in patients in the “Discontinued” group, which could be attributed to the withdrawal syndrome or insomnia resulting from BZDRA discontinuation. In BZDRA users, it is important to consider BZDRA use carefully during the perioperative period. Moreover, gradual tapering is important in outpatient settings for patients who continue BZDRA use. Although BZDRA use is a known risk factor, abrupt discontinuation should be avoided to reduce the risk of delirium.

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## Author contributions

CO, NA, TM, and JN designed the study and wrote the protocol. NO, YM, and MT contributed to the acquisition of the data and clinical review. CO wrote the first draft of the manuscript. NA and JN revised the manuscript. TM and HK supervised the data analysis. All authors contributed to and have approved the final manuscript.

## Declaration of Competing Interest

The authors declare that they have no competing interests.

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