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ORIGINAL RESEARCH

Benzodiazepines Prescribed to Hospitalized Patients with Major Depressive Disorder: A 3-year Retrospective Observational Study

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Objective: Major Depressive Disorder (MDD) has a relatively high prevalence in China, and its treatment often involves benzodiazepines. This study investigated the proportion and types of benzodiazepines prescribed to hospitalized patients with MDD, and assessed changes in prescribing patterns over a 3-year follow-up period.

Methods: This retrospective study analyzed electronic health records of inpatients diagnosed with MDD at the Affiliated Kangning Hospital of Ningbo University from January 1 to December 30, 2020. Comprehensive data were collected, encompassing sociodemographic details and baseline clinical characteristics. A follow-up assessment was conducted three years later.

Results: The present study ultimately included 278 inpatients with MDD. At baseline, 236 (84.9%) were prescribed benzodiazepines. At 3 years, 102 (36.7%) patients were prescribed benzodiazepines. Benzodiazepine use varied significantly over time ($P < 0.001$), with the most substantial decrease in the proportion of benzodiazepine prescriptions occurring within the first 12 months. For non-selective benzodiazepines at baseline, the most commonly prescribed were lorazepam (39.6%, n=110), oxazepam (23.7%, n=66), and clonazepam (16.2%, n=45). The use of lorazepam and oxazepam over time was significantly different ($P < 0.001$). However, the use of clonazepam, estazolam, and alprazolam remained comparable ($P > 0.05$). For selective benzodiazepines at baseline, zopiclone was the most prescribed (n=81, 29.1%). While its use varied significantly over time ($P < 0.001$), changes in zolpidem, zaleplon, and eszopiclone use were not statistically significant ($P > 0.05$). At the 3-year follow-up, benzodiazepine prescriptions were significantly associated with the number of siblings, patient age, disease duration, and hospital stay length.

Conclusion: Overall, our findings suggest that benzodiazepine prescriptions are highly prevalent among inpatients diagnosed with MDD. It is advisable to limit benzodiazepine prescriptions for MDD patients to within 12 months. Discontinuing benzodiazepines becomes more challenging after prolonged use beyond this period.

Keywords: benzodiazepines, major depressive disorder, retrospective, inpatients, prescriptions

Introduction

Major depressive disorder (MDD) is widespread in China. According to a 2019 epidemiological survey on mental disorders by Professor Huang et al, the prevalence of MDD was 3.6% in China.[1] MDD is now understood to significantly contribute to disability, diminished quality of life, decreased work productivity, and substantial economic burden.[2–4] The current clinical management for MDD still primarily relies on pharmacological intervention. While most patients with MDD are prescribed antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs), a considerable number do not adequately respond to initial antidepressant monotherapy, leading to the implementation of add-on treatment strategies with other psychotropic medications.[5,6]

Sleep disturbance is one of the nine diagnostic criteria for MDD as outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[7] Insomnia reportedly affects up to 80% of MDD patients, manifesting as

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difficulty falling asleep, staying asleep, or early awakening.[8] Since the 1960s, benzodiazepines have primarily been used as hypnotics, gradually replacing more toxic drugs such as barbiturates, meprobamate, and chloral hydrate.[9] However, the potential for tolerance and dependence has emerged, leading to prescription restrictions in many countries in recent decades.[10] The prescription rate of benzodiazepines has significantly increased over the last twenty years, despite existing concerns. Alprazolam, clonazepam, and lorazepam rank among the top ten psychiatric medications, with over 5% of the US population filling prescriptions for them.[11] Benzodiazepines are commonly prescribed for patients with MDD due to their effectiveness in treating acute anxiety and severe sleep disturbances.[12–14]

A preliminary double-blind, placebo-controlled study demonstrated that incorporating a benzodiazepine to tricyclic antidepressant therapy decreased the elevated total rapid eye movement sleep typically observed in MDD patients and enhanced depressive symptoms.[15] However, even with benzodiazepine treatment, patients with MDD may continue to suffer from residual insomnia, with rare instances of treatment-resistant insomnia reported.[16–18] Chronic benzodiazepine use has been linked to increased depression symptoms and the risk of dependence or tolerance.[19–21] From the mid-1990s to 2013, benzodiazepine prescriptions rose by 67%, with the quantity prescribed tripling.[22] A study[23] identified a comparable upward trend in benzodiazepine prescriptions within ambulatory care. Notably, benzodiazepines rank as the third most frequently misused illicit or prescription drugs among both adults and teenagers in the US, a trend concurrent with rising overdose death rates. Despite a slight decline in benzodiazepine prescriptions from January 2018 to March 2021, the high frequency of these prescriptions remains a significant concern.[24]

Prolonged benzodiazepine use has been associated with adverse health effects, including dependence, tolerance, cognitive impairments, and increased risk of falls and fractures, especially in older adults. Consequently, most guidelines recommend limiting benzodiazepine use to a maximum of 4 weeks. Guidelines specific to MDD advise monotherapy and limit benzodiazepine use to short-term treatment.[25] In clinical practice, benzodiazepines are frequently used long-term for patients with chronic insomnia and those with MDD accompanied by insomnia, despite existing cautions and concerns.

Notwithstanding the mounting apprehension surrounding the prolonged utilisation of benzodiazepines, a paucity of research has been conducted into the long-term progression of benzodiazepine prescriptions among specific patient demographics, notably those admitted to hospital with a primary diagnosis of major depressive disorder (MDD). This lacuna in the extant literature is especially evident in the context of longitudinal, real-world data, as there is a paucity of studies that have examined the temporal evolution of benzodiazepine prescriptions within the population of hospitalized MDD patients.

This retrospective observational study sought to examine real-world benzodiazepine prescribing patterns in inpatients with MDD. This longitudinal study, with a 3-year follow-up period, is designed to characterize trends in benzodiazepine prescribing for MDD patients and to elucidate the factors predictive of long-term use. The insights gained will serve as a critical reference for shaping rational and safe benzodiazepine prescribing practices in the management of MDD.

Methods

Data Collection

This retrospective study reviewed the electronic patient records of individuals prescribed medication between January 1 to December 30, 2020, using the Clinical Data Analysis and Reporting System at the Affiliated Kangning Hospital of Ningbo University. The study was approved by the hospital's Institutional Review Board. Considering the reliability of diagnosis and the homogeneity of the patients, all patients in this study were hospitalized. All patients included in the study were required to meet the International Classification of Diseases, Tenth Edition (ICD-10) criteria for MDD. The diagnosis of MDD was made by a psychiatrist during hospitalization, and all patients received psychotropic drug treatment.

Patients were excluded for a history of schizophrenia, bipolar disorder, epilepsy, alcohol or psychoactive substance dependence, organic brain disease, or other severe physical or endocrine diseases. Besides, patients who were pregnant, lactating, or for whom a change in diagnosis or death was recorded after the initial prescription were excluded. Broad inclusion criteria were used to ensure a diverse patient population was represented in the study.

Demographic and clinical data were collected, encompassing age, gender, marital and educational status, occupation, MDD duration, somatic comorbidities, hospital stay length, and the 17-item Hamilton Rating Scale for Depression (HAMD-17).[12] This study collected the quantity and types of benzodiazepines used in patients with MDD. The quantity and types of benzodiazepines prescribed within three years of admission were documented. Assessment data were collected at 3, 6, 12, 18, 24, 30, and 36 months after baseline.

Benzodiazepine Prescriptions

Drugs were classified according to the Anatomical Therapeutic Chemical (ATC) system. In addition to any hypnotics and sedative drugs, we separately analyzed benzodiazepines, including non-selective benzodiazepines (ATC: N05CC) and selective benzodiazepines (ATC: N05CD). Benzodiazepine prescriptions were collected by electronic patient records.

Statistical Analysis

Descriptive statistics were used to summarize patient demographics, clinical characteristics, and study variables, with percentages for discrete variables and means ± standard deviation (SD) for continuous variables. The chi-square test was used to evaluate differences in benzodiazepine prescriptions across various periods. A Bonferroni correction was used to control Type I error rates in multiple comparisons.

A logistic regression model was employed to analyze factors influencing benzodiazepine prescriptions in MDD patients, adjusting for variables including age, gender, marital status, educational and occupational status, MDD duration, somatic comorbidities, hospital stay length, HAMD-17 scores, and benzodiazepine prescription duration. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Variables for the final model were selected using a stepwise method with an inclusion significance level of < 0.1 and an exclusion significance level of ≥ 0.05. A p-value below 0.05 was statistically significant. Statistical analyses were conducted using SPSS version 23.0.

Results

A total of 309 inpatients with MDD were initially identified from the Affiliated Kangning Hospital of Ningbo University. Of these, 31 patients were excluded (Figure 1) for the following reasons: a subsequent diagnosis of bipolar disorder (n=17), obsessive-compulsive disorder (n=5), schizophrenia (n=3), Alzheimer's disease (n=1), or alcohol-induced mental disorders (n=1); and death (n=4). The final cohort consisted of 278 patients. Data on benzodiazepine prescriptions were collected for this cohort at baseline and at 3, 6, 12, 18, 24, 30, and 36 months during the follow-up period.

Demographics and Clinical Characteristics of Patients

The final study cohort comprised 278 patients with MDD. The sample had a mean age of 52.2 years (SD = 15.3) and was 71.2% female (n=198) and 28.8% male (n=80). The majority of participants were married (76.6%, n=213). Educational attainment was distributed as follows: primary school (27.3%), junior high school (37.4%), high school (16.2%), and university (19.1%). In terms of employment status, 39.9% (n=111) were employed and 60.1% (n=167) were unemployed. Clinically, the mean disease duration was 80.7 months (SD = 101.8), and the mean HAMD-17 score at baseline was 24.8 (SD = 9.8). The mean duration of hospitalization was 27.9 days (SD = 16.5). Comorbid physical diseases were present in 30.6% (n=85) of patients. The mean patient height was 162.7 cm (SD = 9.5), and the mean weight was 59.4 kg (SD = 13.0) (Table 1).

Prescription Patterns of Benzodiazepines in Patients with MDD

At baseline, 84.9% (n=236) of the study patients with MDD were prescribed benzodiazepines. The distribution was as follows: one benzodiazepine (50.7%, n=141), two benzodiazepines (32.4%, n=90), and three benzodiazepines (1.8%, n=5). By the 36-month follow-up, the overall prescription rate had declined to 36.7% (n=102), with 28.8% (n=80) prescribed one type, 7.6% (n=21) prescribed two types, and 0.4% (n=1) prescribed three types. The overall prevalence of benzodiazepine use decreased

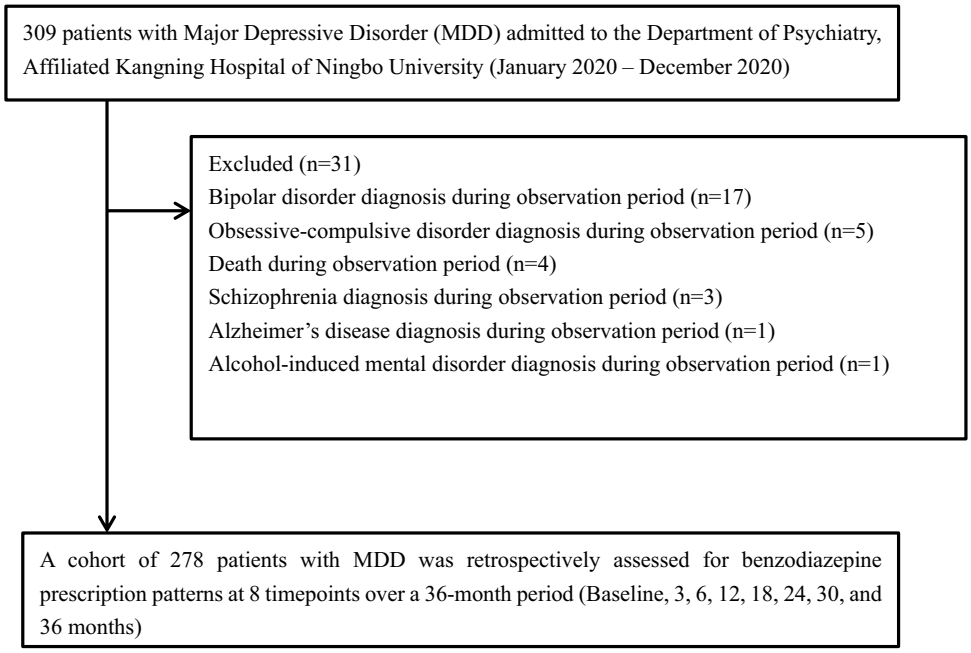

Figure 1 The patient inclusion and exclusion process.

significantly over the study period ($P < 0.001$). This decline was statistically significant for regimens involving one or two benzodiazepines ($P < 0.001$ for both), but not for regimens involving three benzodiazepines ($P > 0.05$) (Table 2). The most pronounced reduction occurred within the first 12 months (Figure 2).

Table 1 Presents the Demographics and Clinical Characteristics of the Patients

Demographic and Clinical Variables	**Total Patients (n = 278)**
Age, mean (SD), years	52.17 ± 15.29
Gender, n (%)	
Male	80(28.8)
Female	198(71.2)
Marital status, n (%)	
Married	213(76.6)
Single/Divorced/Separated/Widowed	65(23.4)
Educational status, n (%)	
University education	53(19.1)
High level general education/Technical education	45(16.2)
General secondary education	104(37.4)
Elementary school/None	76(27.3)

(*Continued*)

Table 1 (Continued).

Demographic and Clinical Variables	Total Patients (n = 278)
Occupational status, n (%)	
Employed	111(39.9)
Unemployed	167(60.1)
Duration of MDD, mean (SD), months	80.74±101.82
Height, mean (SD), cm	162.66±9.45
Weight, mean (SD), kg	59.36±12.96
Somatic comorbidities, n (%)	
Yes	85(30.6)
No	193(69.4)
Length of hospital stay, mean (SD), days	27.94±16.49
HAMD total 17-item, mean (SD)	24.76±9.79

Table 2 Displays the Count and Percentage of Benzodiazepine Prescriptions for Patients Undergoing Treatment for Major Depressive Disorder (MDD)

Number of BZD	Baseline	3 months	6 Months	12 Months	18 Months	24 Months	30 Months	36 Months	χ^2	P-value
Total	236(84.9)	173(62.2)	132(47.5)	98(35.3)	99(35.6)	96(34.5)	98(35.3)	102(36.7)	260.758	<0.001
1	141(50.7)	115(41.4)	90(32.4)	68(24.5)	68(24.5)	73(26.3)	70(25.2)	80(28.8)	82.321	<0.001
2	90(32.4)	53(19.1)	37(13.3)	27(9.7)	27(9.7)	22(7.9)	26(9.4)	21(7.6)	118.016	<0.001
3	5(1.8)	5(1.8)	5(1.8)	3(1.1)	4(1.4)	1(0.4)	2(0.7)	1(0.4)	6.700	0.444

Prescription Patterns of Different Types of Benzodiazepines in Patients with MDD

At baseline, the most prescribed non-selective benzodiazepines were lorazepam (39.6%, n=110), oxazepam (23.7%, n=66), and clonazepam (16.2%, n=45), followed by estazolam (4.3%, n=12) and alprazolam (2.5%, n=7). Prescription

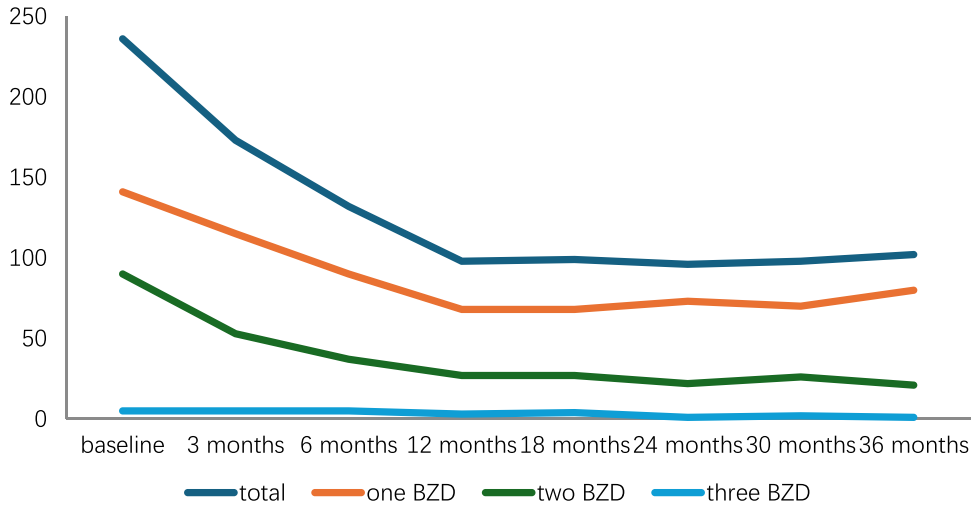

Figure 2 Illustrates the quantity of benzodiazepine prescriptions for patients undergoing treatment for Major Depressive Disorder (MDD).

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Table 3 Prescription Patterns of Different Types of Benzodiazepines in Patients with MDD, Expressed as n (%)

Number of BZD	Baseline	3 Months	6 Months	12 Months	18 Months	24 Months	30 Months	36 Months	χ^2	P-value
BZD										
Lorazepam	110(39.6)	83(29.9)	52(18.7)	34(12.2)	37(13.3)	40(14.4)	46(16.5)	42(15.1)	113.823	<0.001
Oxazepam	66(23.7)	39(14.0)	25(9.0)	18(6.5)	17(6.1)	2(0.7)	0(0.0)	2(0.7)	182.015	<0.001
Clonazepam	45(16.2)	34(12.2)	37(13.3)	30(10.8)	28(10.1)	34(12.2)	34(12.2)	32(11.5)	6.177	0.519
Estazolam	12(4.3)	17(6.1)	19(6.8)	13(4.7)	16(5.8)	13(4.7)	15(5.4)	18(6.5)	3.158	0.870
Alprazolam	7(2.5)	3(1.1)	4(1.4)	5(1.8)	5(1.8)	6(2.2)	5(1.8)	5(1.8)	2.037	0.958
sBZRA										
Zopiclone	81(29.1)	57(20.5)	38(13.7)	26(9.4)	26(9.4)	21(7.6)	22(7.9)	17(6.1)	110.153	<0.001
Zolpidem	8(2.9)	1(0.4)	2(0.7)	3(1.1)	4(1.4)	3(1.1)	5(1.8)	5(1.8)	8.604	0.282
Zaleplon	2(0.7)	2(0.7)	2(0.7)	2(0.7)	1(0.4)	1(0.4)	0(0.0)	0(0.0)	4.420	0.730
Eszopiclone	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.4)	4(1.4)	18.049	0.025

rates for all agents declined by the 36-month follow-up: lorazepam (15.1%), clonazepam (11.5%), estazolam (6.5%), alprazolam (1.8%), and oxazepam (0.7%). Longitudinal analysis revealed statistically significant changes in the usage of lorazepam and oxazepam over time ($P < 0.001$). In contrast, the changes in prescription rates for clonazepam, estazolam, and alprazolam were not statistically significant ($P > 0.05$ for all).

At baseline, zopiclone was the most prescribed selective benzodiazepine receptor agonist (29.1%, n=81), followed by zolpidem (2.9%, n=8), zaleplon (0.7%, n=2), and eszopiclone (0.4%, n=1). By the 36-month follow-up, prescription rates had declined to 6.1% (n=17) for zopiclone, 1.8% (n=5) for zolpidem, and 1.4% (n=4) for eszopiclone; zaleplon was not prescribed. Longitudinal analysis showed a statistically significant decrease in zopiclone use over time ($P < 0.001$). In contrast, usage trends for zolpidem, zaleplon, and eszopiclone were not statistically significant ($P > 0.05$ for all) (Table 3).

The prescription rates for both non-selective and selective benzodiazepines showed a declining trend, primarily concentrated within the first 12 months of follow-up (Figure 3).

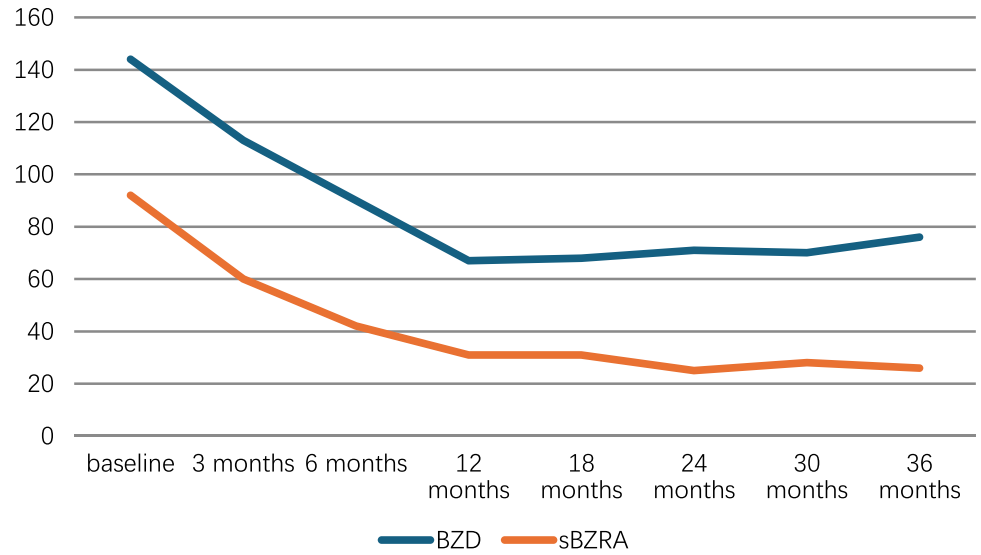

Figure 3 Prescription Patterns of Different Types of Benzodiazepines in Patients with MDD.

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Table 4 Presents a Logistic Regression Analysis Examining Factors Linked to Benzodiazepine Use at the 36-month Follow-Up

Model Variables	B	SE	Wald	P	OR	95% CI
Number of siblings	1.192	0.053	515.324	0.000	3.294	2.972–3.652
Gender	−0.296	0.164	3.258	0.071	0.744	0.540–1.026
Age	−0.158	0.009	337.239	0.000	0.854	0.839–0.868
Duration of MDD	−0.007	0.001	151.663	0.000	0.993	0.992–0.994
Length of hospital stay	−0.110	0.007	258.941	0.000	0.896	0.884–0.908
Constant	9.273	0.561	273.492	0.000	10649.629	

Logistic Regression Analysis of Factors Influencing Benzodiazepine Prescription at 36-Month Follow-Up

Table 4 presents the results of the logistic regression analysis identifying factors associated with benzodiazepine prescription at the 36-month follow-up. Benzodiazepine use at 36 months was significantly associated with the number of siblings, patient age, disease duration, and length of hospital stay. A lower number of siblings was associated with a higher likelihood of benzodiazepine prescription (OR = 3.294, 95% CI: 2.972–3.652). In contrast, older age (OR = 0.854, 95% CI: 0.839–0.868), a longer disease duration (OR = 0.993, 95% CI: 0.992–0.994), and a longer hospital stay (OR = 0.896, 95% CI: 0.884–0.908) were associated with a reduced likelihood of prescription.

Discussion

This study conducted a retrospective review of benzodiazepine prescriptions among MDD patients over a 3-year period. At baseline, 84.9% of MDD patients were prescribed a benzodiazepine, indicating a very high initial prevalence. By the 36th month of follow-up, 36.7% of patients were still prescribed benzodiazepines, indicating that more than one-third of MDD patients received long-term benzodiazepine prescriptions. The most common benzodiazepines prescribed to MDD patients were lorazepam (39.6%), zopiclone (29.1%), oxazepam (23.7%), and clonazepam (16.2%). At 36 months, the most commonly prescribed benzodiazepines were lorazepam (15.1%), clonazepam (11.5%), estazolam (6.5%), and zopiclone (6.1%). Over the 3-year period, prescriptions for lorazepam, oxazepam, and zopiclone declined significantly, while prescriptions for clonazepam remained relatively stable The study also revealed that the most significant reduction in benzodiazepine prescriptions occurred during the first year of follow-up, with no notable decline in subsequent years. Therefore, the study suggests that the optimal window for benzodiazepine dose reduction in MDD patients is within the first year of treatment. Interestingly, the optimal window for initiating dose reduction in MDD patients appears to be within the first year of treatment. Besides, regression analysis indicated that long-term benzodiazepine prescriptions were associated with the number of siblings, age, duration of illness, and length of hospitalization.

A European multicenter cross-sectional study involving 1410 inpatients and outpatients with MDD examined benzodiazepine prescription patterns as an adjunct in psychopharmacotherapy. The adjunctive benzodiazepine prescription rate was 31.35%, with lorazepam (11.13%), clonazepam (6.74%), and alprazolam (6.60%) being the most frequently prescribed benzodiazepines. Benzodiazepine use was linked to factors such as older age, unemployment, inpatient treatment, suicide risk, psychotic and melancholic features, and comorbid conditions, including panic disorder, agoraphobia, social phobia, and obsessive-compulsive disorder.[26] Notably, outpatient samples in other large-scale studies have reported substantially lower benzodiazepine prescription prevalence; for example, in a US registry study of depressed patients treated in specialty mental health outpatient settings, approximately 36% filled a benzodiazepine prescription during a year of care, suggesting that benzodiazepine prescribing practices and patient illness severity differ between inpatient and outpatient contexts.[27] Our results revealed a significantly higher proportion of benzodiazepine prescriptions, which may be related to our selection of hospitalized patients with MDD. Several prior studies have

examined the use of benzodiazepines in the treatment of MDD. In a study conducted in Finland with 288 MDD patients interviewed between 2000 and 2001, 16% reported using sedatives or hypnotics.[28] A secondary analysis of the STAR*D study, involving over 3700 patients, revealed that 84.7% experienced insomnia symptoms, yet only 27% were using hypnotics at the start of the study, suggesting potential under-treatment.[8] A Swedish study found that 41% of 182 patients over 60 years old with depression, either minor or major, and without dementia, used hypnotics.[29] A comprehensive cohort study found no link between benzodiazepine use and later development of dementia, regardless of cumulative exposure or classification into long- and short-acting drugs; some findings even suggested a protective effect.[30] Taken together, these findings indicate that benzodiazepine prescribing rates vary substantially by clinical setting (inpatient vs outpatient), patient characteristics, and study design, with inpatient status and greater illness severity likely contributing to higher usage rates observed in our cohort.

Moreover, comparisons of prescribing patterns across other major psychiatric inpatient populations reveal that high rates of hypnotic/benzodiazepine use are prevalent across different diagnostic groups: A nationwide Japanese study reported that the proportion of inpatients prescribed any hypnotic medication was 56.5% for schizophrenia and 64.9% for major depressive disorder.[31] A further cohort study of inpatients diagnosed with bipolar disorder revealed that acute-phase benzodiazepine use was observed in approximately 34% of cases, while maintenance-phase use was documented in approximately 23%.[32] These findings suggest that there are variations in medication patterns across different disorders and disease stages within the inpatient setting. To summarise, the results of inpatient studies of schizophrenia, bipolar disorder, and MDD consistently indicate that the prescription rates of benzodiazepines and hypnotics in hospital settings often exceed those reported in some outpatient settings. This finding lends further support to the hypothesis that the relatively high baseline prescription rate (84.9%) may be partially attributable to inpatient status, disease severity, and local inpatient prescribing practices.[33] A Japanese retrospective study of 351 patients with depression who were prescribed benzodiazepines found that 66.1% continued to receive them after a 12-month follow-up period, indicating a high rate of long-term benzodiazepine prescriptions. Long-term prescriptions were significantly associated with the dosage of benzodiazepines, chronic insomnia preceding depression, and whether the patients had been hospitalized.[34] In another three-year follow-up study, the quarterly prevalence of benzodiazepines prescribed was still 19.2%, demonstrating that benzodiazepine use remains high even years after diagnosis.[35] Inadequate improvement in insomnia symptoms was also related to long-term use. These findings on long-term benzodiazepine prescription were consistent with our study results. Our study also identified associations with the number of siblings, age, illness duration, and length of hospitalization. Furthermore, we observed a significant decline in benzodiazepine prescriptions among MDD patients during the first year of follow-up, with no notable decrease in subsequent follow-up periods. This study strengthens the existing evidence on long-term benzodiazepine prescribing practices.

A study in Japan collected comprehensive prescription data for 2,946 eligible patients prescribed hypnotics. Hypnotic monotherapy was prescribed to 70.8% of patients, while 29.2% received combination therapy. The most common prescriptions were benzodiazepine monotherapy (26.2%), non-benzodiazepine monotherapy (28.9%), and dual-drug combination therapy (21.1%). Benzodiazepines are the predominant hypnotics prescribed to Japanese patients with MDD, despite the common practice of prescribing combination hypnotic therapy. Current evidence suggests that while the specific pattern of hypnotic prescribing does not directly affect MDD recurrence, the selection of a particular agent is a critical clinical decision. This decision must be informed by the pronounced differences in therapeutic effectiveness and risk profiles across different classes of hypnotics.[36] Research involving 1,031 hospitalized individuals with MDD revealed a high prevalence of benzodiazepine use (64.9%), with a significant proportion (23.1%) receiving two or more concurrent agents.[37] Our results, which demonstrate an even higher baseline rate of concurrent prescriptions (34.2%), highlight a critical need for more careful and monitored prescribing strategies for hospitalized MDD patients.

Epidemiological research indicates that a significant proportion of long-term benzodiazepine users are patients with MDD. The findings of this study aligned with these observations. A French study of 4,425 long-term benzodiazepine users, which employed the Mini International Neuropsychiatric Interview (MINI) to establish DSM-IV diagnoses, found that MDD was the most common diagnosis, affecting 60% of participants.[38] McCall et al reported that hypnotic medications were more frequently linked to Depressive Disorder than to insomnia symptoms.[39] While the prescription of benzodiazepines for MDD patients is crucial, there is a significant need for effective long-term therapeutic strategies

for their pharmacotherapy.[31] For instance, a five-year follow-up study suggested that prescribing benzodiazepines to patients with MDD could reduce all-cause and cardiovascular disease-related mortality. Besides, a 5-year retrospective cohort study found that benzodiazepine use was linked to a heightened long-term risk of mood and substance use disorders.[40]

Evidence for the efficacy of hypnotic medication during the treatment of MDD is limited. Clinical studies indicate that for patients with MDD, combining benzodiazepines with antidepressants significantly enhances the improvement of insomnia and depressive symptoms.[41–43] Data on long-term symptom outcomes for psychiatric patients remain limited. Research has identified several side effects of hypnotic medications, such as benzodiazepines, including falls, delirium, acute respiratory failure, dependence, withdrawal symptoms, and an elevated suicide risk among psychiatric patients.[44–47] The likelihood of side effects rises with high-dose or long-term benzodiazepine prescriptions.[25] While short-term benzodiazepine prescriptions can effectively alleviate distress, insomnia, and behavioral disturbances related to psychosis, clinical guidelines in Japan[48,49] and Western countries[50,51] advise against their long-term use in MDD patients. According to the American Psychiatric Association's depression treatment guidelines, adjunctive use of hypnotic drugs can accelerate symptom relief, though there is no evidence supporting long-term benefits, and tapering off these medications may be challenging.[52] The Royal Australian and New Zealand College of Psychiatrists[53] advises that hypnotics should be used solely for short-term sleep issues.

This study is subject to several methodological limitations that should be acknowledged. Indeed, its single-center design, which relies on data from a single hospital, may limit the generalizability of the findings to broader clinical settings. Furthermore, the relatively modest sample size precluded the possibility of conducting subgroup analyses, which might have revealed additional insights with a larger cohort. Finally, the investigation did not account for the specific dosages of benzodiazepines prescribed, a variable that could plausibly influence patterns of long-term use. Consequently, the present study was unable to assess the dose-response relationship or determine whether higher doses were associated with longer-term medication use or adverse outcomes. It is recommended that future prospective studies collect detailed dose information to fill this critical gap. Despite these constraints, this three-year retrospective analysis of electronic medical records provides valuable evidence of a high baseline benzodiazepine prescription rate among hospitalized MDD patients and a marked reduction within the first year, offering clinically relevant insights for their application.

Conclusion

In this study, our findings suggest that benzodiazepine prescriptions are highly prevalent among inpatients diagnosed with MDD. It is advisable to limit benzodiazepine prescriptions for MDD patients to within 12 months. However, it should be noted that due to the observational nature of this study, the findings should be interpreted as descriptive conclusions. The first year should be viewed as a critical window for clinical reassessment and deprescribing, rather than a strict 12-month permissible duration. Discontinuing benzodiazepines becomes more challenging after prolonged use beyond this period.

Data Sharing Statement

The data supporting the results of this study are available upon request from the corresponding author.

Ethics Approval and Consent to Participate

This study was approved by the Ethical Committee of Ningbo Kangning Hospital (NBKNYY-2022-LC-29). All participants received verbal and written information about the study and provided written consent to participate in this study. All procedures carried out in studies conformed to the 1964 Helsinki Declaration and its subsequent amendments or similar ethical standards.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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