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Factors associated with long-term prescription of benzodiazepine: a retrospective cohort study using a health insurance database in Japan

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Abstract

Objectives: Long-term prescriptions of benzodiazepine drugs (BZD) seem to remain, although clinical guidelines aim to prevent it. The aim of this study was to investigate the proportion of the long-term BZD prescription and its risk factors.

Design: Retrospective cohort study using a health insurance database.

Setting: Japan.

Participants: A total 88,001 patients were identified outpatients aged 18 to 65 who started BZDs between October 1st, 2012 and April 1st, 2015. After excluding patients without eight months follow-up (n = 12,325), and patients who underwent surgery on the day of first BZD prescription (n = 3,721), 71,955 outpatients were analyzed.

Main outcome measures: We investigated the proportion of the long-term prescription for ≥8 months among the new BZD users. We assessed patient demographics, diagnoses, initial BZD prescription, and prescribers as potential predictors of the long-term BZD prescription. Multivariable logistic regression was performed to assess the association between the long-term prescription and the potential predictors.

Results: Of the new BZD users, 6,462 (9.0%) were consecutively prescribed BZD for ≥8 months. The long-term prescription was significantly associated with cancer, aging, mood and neurotic disorder, hypnotics, prescription by psychiatrists, and high-dose

BZD at the initial prescription.

Conclusion: Despite the recent clinical guidelines, 9% of new BZD users were prescribed for more than 8 months. Physicians should be aware of the risk factors when prescribing BZDs for the first time.

Strengths and limitations of this study

- A large sample of the Japanese outpatients among the non-elderly adult population.
- Analyzed new benzodiazepine users to prevent prevalent user bias.
- A strict definition of long-term use of benzodiazepine by identifying consecutive monthly prescription data.
- Limitation of detailed and accurate information in the health insurance database such as the diagnosis and the severity of psychiatric disorders.

Introduction

Concerns about long-term use of benzodiazepines and benzodiazepine-related drugs (BZDs) have been raised over the world. Although BZDs are safer than old sedative-hypnotics, efficacy of their long-term use has not been demonstrated. Long-term use of BZD leads to dependence. [1] Patients may become dependent on BZDs to avoid

withdrawal symptoms. [1–3] Studies showed several adverse consequences related to long-term use of BZD, including dementia among elderly people [4,5] and fracture [6,7] cancer [8] and car accident [9] in any generation.

Understanding prevalence of long-term use of BZDs and its risk factors is essential to prevent adverse consequences. However, reported prevalence of long-term BZD use varied widely because of variability in definition of long-term BZD prescription, study participants, and follow-up period [10,11] Over a half of the studies did not provide plausible explanation for the definitions. [11] Some studies used one prescription per year or per several months as definition of long-term BZD prescription and others included prevalent users of BZDs or only the elderly as study population. These studies may have overestimated the proportion of long-term prescription of BZDs.

Reported risk factors of long-term prescription have been also inconsistent. In a systematic review, [11] long-term prescription of BZDs were associated with older age, psychiatric disorders, and polypharmacy or high-dose BZDs at the initial prescription. However, association of several other factors with long term use of BZDs remains inconsistent, including demographic variables (e.g. gender, income), type of BZDs (e.g. half-life, Z-drug), or characteristics of prescriber (e.g. psychiatry). The inconsistency may have been affected by variability of definition of long-term use of BZD. [11] For

example, in a study where long-term prescription was defined as at least one prescription every three months, female was a risk factor. [12] However, in another study where long-term prescription was defined as lasting BZD use for 60 days, male was a risk factor. [13]

In this study, we subjected new BZDs users who continued the drugs for ≥8 consecutive months. This definition was selected based on two previous studies. In a systematic review, long-term BZD use was commonly defined as 6-12 months. [11] In another study, about a half of patients who used BZDs for 8 months experienced clear withdrawal symptoms. [14]

Using a large-scale health insurance database with detailed prescription information, the present study investigated the proportion of long-term BZD prescription among new BZD users in Japan with a retrospective cohort design. We also assessed examined factors associated with the long-term prescription.

Methods

Data source

We used a health insurance claims database provided by JMDC Inc., Tokyo, Japan. JMDC Inc. has collected claims information from occupation-based health insurance

agencies for corporate employees and their dependents since 2005. [15] The JMDC database includes anonymous data of inpatient, outpatient, and pharmacy claims and special health checkups from about 3,000,000 individuals by November 2014, representing about 2.5% of the Japanese population. [16] Each record includes age, sex, diagnoses, prescriptions, information of medical institution, and date of the services. The diagnoses are based on International Classification of Diseases, 10th revision (ICD-10) diagnostic codes. The prescription information has the World Health Organization's Anatomical Therapeutic Chemical (WHO-ATC) classification system codes, drug name, dosage, days of supply, and mode of prescription. Date of prescriptions has been recorded since April 1st 2012. We thus used the data from April 1st 2012 through December 31st 2015. The requirement for informed consent was waived because of the anonymous nature of the data. The study was approved by the Institutional Review Board of The University of Tokyo.

Patient selection

We selected outpatients aged 18 to 65 years who started at least one of available oral BZD and BZD-related drugs between October 1st 2012 and April 1st 2015 (Supplementary table). We chose only subjects who had been continuously enrolled in

the JMDC database for at least six months before first prescription of BZDs. We defined first users as those who had not used any BZDs for this six-month baseline period (Figure 1). We excluded patients who were followed up for less than 8 months after the first BZD prescription. We also excluded those who underwent surgery on the day of the first BZD prescription. Surgeries were identified with Japanese original procedure codes. When extracting BZDs, we used the WHO-ATC codes N05BA, N05CD, N05CF, and N03AE.[17] We added seven BZDs which were not covered by the WHO-ATC codes but were available in Japan. We excluded clobazam from this study because it was categorized as benzodiazepine-derivative anxiolytics in the WHO-ATC code (N05BA09) but was used as an antiepileptic in Japan. Thirty-two BZDs were identified.

---Figure 1---

Definition of long-term BZD prescription

We defined long-term BZD users as those who received at least one prescription of any BZDs every month for ≥8 consecutive months.

Potential predictors of long-term BZD prescription

We assessed the following variables at baseline period as potential predictors of long-term BZD use based on previous studies. Patient characteristics included sex, age, working status (worker or dependent), diagnosis of cancer (ICD-10 code, C$), and psychiatric diagnosis (no diagnosis, mood disorders only [F3], neurotic, stress-related and somatic disorders only [F4], both mood disorder and neurotic disorder [F3 and F4], and other psychiatric disorders [F0, 1, 5-9]. Physician's specialty (psychiatry or others) was also evaluated. Pharmacological characteristics of the first BZD prescription included type of BZD (hypnotics only, anxiolytics only, or both), half-life of BZD (short: <12 hours, medium: 12-24 hours, long: ≥24 hours), administration instruction (regular, as needed, or both), and the number of BZDs. If a patient was prescribed multiple BZDs with different half-lives, we selected the BZD with the longest half-life.

Statistical analyses

First, we calculated proportion of long-term use of BZD and compared the potential predictors of long-term prescription between the patients who were prescribed BZDs for ≥8 and <8 months. We used Student's t-test to compare the average of continuous variables (such as age) and chi-squared test to compare the proportion of categorical variables (such as sex). Next, a multivariable logistic regression was performed to

assess the association between the potential predictors and long-term prescription.

The threshold for significance was $P < 0.05$. We used IBM SPSS version 23 (IBM, Armonk, NY, USA) for all statistical analyses.

Results

Patient characteristics

A total 88,001 patients were identified as new BZD users during the study period (Figure 2). After excluding patients without eight months follow-up (n = 12,325), and patients who underwent surgery on the day of first BZD prescription (n = 3,721), 71,955 patients were included in the analysis. There were 6,462 patients (9.0%) who were prescribed BZDs for ≥8 consecutive months. When stratified by gender, 10.7% of males and 7.2% of females continued BZD use for ≥8 months. As for age group, the proportion of long-term use was 8.9%, 9.3%, 9.5%, 8.6%, and 9.0% for subjects aged 18-29, 30-39, 40-49, 50-59, and 60-65, respectively. Table 1 shows patient characteristics, information of physicians, and pharmacological characteristics of the initial prescription. About half of them were diagnosed with mood disorder, and hypnotics were more likely to be prescribed than anxiolytics.

---Figure 2---

---Table 1---

Table 1 Demographic and clinical characteristics of the new users of benzodiazepines (N = 71,955)

	BZD < 8 month n = 65,493 (91.0 %)	BZD ≥8 month n = 6462 (9.0 %)	P value
Age, mean (SD)	42.3 (11.8)	42.0 (11.3)	0.016
Sex, male	33,072 (50.5)	3959 (61.3)	< 0.001
Working status, workers	42,131 (64.3)	4649 (71.9)	< 0.001
Cancer	6875 (10.5)	673 (10.4)	0.853
Medical specialty, psychiatry	6876 (10.5)	3887 (60.2)	< 0.001
Psychiatric diagnosis			< 0.001
None	28,175 (43.0)	1275 (19.7)	
Mood disorders	8958 (13.7)	2170 (33.6)	
Neurotic, stress-related and somatic disorders	20,891 (31.9)	1386 (21.4)	
Mood and neurotic disorders	6262 (9.6)	1433 (22.2)	
Other disorders	1207 (1.8)	198 (3.1)	
Type of BZD			< 0.001
Hypnotic	18,413 (28.1)	2187 (33.8)	
Anxiolytic	42,809 (65.4)	3038 (47.0)	
Both	4271 (6.5)	1237 (19.1)	
Half-life of BZD			< 0.001
Short (< 12 h)	42,392 (64.7)	3609 (55.8)	
Medium (12-24 h)	10,233 (15.6)	1512 (23.4)	
Long (≦ 24 h)	12,868 (19.6)	1341 (20.8)	
Administration instruction			< 0.001
Regular	45,959 (70.2)	4926 (76.2)	
As needed	17,122 (26.1)	938 (14.5)	
Both	2412 (3.7)	598 (9.3)	
Number of BZD, mean (SD)	1.1 (0.4)	1.3 (0.6)	< 0.001

Data presented as n (%) unless otherwise specified.

BZD, benzodiazepine-related drugs; SD, standard deviation.

Predictors of long-term prescription

Table 2 shows the result of the multivariable logistic regression. Patients with cancer had significantly higher risk of long-term BZD prescription than those without cancer

(odds ratio, 1.19; 95% confidence interval, 1.09-1.31; p < 0.001). Half-life of BZDs was not associated with long-term BZD prescription.

---Table 2---

Table 2 Factors related to long-term benzodiazepine prescription among the new users of benzodiazepines (N = 71,955)

Variables	OR	95% CI			P value
Age	1.02	1.01	to	1.02	<0.001
Sex, male	1.12	1.04	to	1.21	<0.001
Working status, workers	0.98	0.90	to	1.05	0.53
Cancer	1.19	1.09	to	1.31	<0.001
Medical specialty, psychiatry	2.04	1.88	to	2.20	<0.001
Psychiatric diagnosis					
None	Ref.				
Mood disorders	2.98	2.70	to	3.29	<0.001
Neurotic, stress-related and somatic disorders	1.42	1.30	to	1.55	<0.001
Mood and neurotic disorders	3.22	2.90	to	3.58	<0.001
Other disorders	2.26	1.91	to	2.69	<0.001
Type of BZD					
Hypnotic	Ref.				
Anxiolytic	0.61	0.57	to	0.66	<0.001
Both	0.86	0.76	to	0.98	0.02
Half-life of BZD					
Short (< 12 h)	Ref.				
Medium (12-24 h)	1.04	0.96	to	1.12	0.34
Long (≦ 24 h)	0.95	0.88	to	1.03	0.22
Administration instruction					
Regular	Ref.				
As needed	0.53	0.49	to	0.57	<0.001
Both	0.93	0.82	to	1.05	0.23
Number of BZD	1.32	1.21	to	1.45	<0.001

BZD, benzodiazepine-related drugs; CI, confidence interval; OR, odds ratio

Discussion

Using a large health insurance claims database, we investigated the proportion of long-term BZD prescription among new BZD users aged 18 to 65 years. A total of 9.0%

continued BZDs for ≥8 months. Long-term BZD prescription was significantly associated with older age, cancer, comorbidity of mood and neurotic disorder, hypnotics, prescription at psychiatry, and high-dose of BZD at the initial prescription. The half-life of BZD was not associated with long-term prescription.

This study showed 9% of new users continued BZDs for ≥8months. This figure was comparable to that in a previous study [11] but relatively lower than prevalence in most of previous studies. [10,18–20] Also, previous studies using prevalent user design caused overestimation of the long-term BZD use. In this study, prevalence of long-term prescription in non-elderly population may be more reliable because we assessed BZD use for ≥8 consecutive months. Alternatively, low prevalence may be due to development of guidelines for BZDs. The guidelines restricting long-term BZD prescription, such as the UK National Institute for Health and Care Excellence guideline, were developed and spread around the world since 2000's. These guidelines may have affected physicians' prescription practice. Furthermore, the guidelines potentially affected patients' prescription preference because the information had been available on the Internet.

Some risk factors for long-term use, including older age, psychiatric disorders, users of hypnotics, regular prescription, a large number of BZD, and psychiatrist-

prescriber were consistent with those in a previous study in Japan. [12] Patients with more severe condition may consult psychiatrists, be diagnosed with one or more psychiatric disorders and be prescribed a high dose of BZD for regular use. Although severe conditions may cause long-term use of BZDs, BZDs should be prescribed with caution because there is weak evidence for efficacy of the long-term BZD use and BZD is not the first-line treatment for depression and anxiety. Half-life of BZD was not associated with long-term use in this study, although many studies illustrated risk of short-acting BZD. [21,22] Since 2000, when benzodiazepine-related hypnotics became popular, studies had focused on effect of half-life of BZD on long-term BZD prescription, but evidence remained inconclusive. [11] Differences in population characteristics may have resulted in the inconsistent study results of short-acting BZD. Our results suggested that among the relatively young and healthy population, half-life of BZD did not play an important role in long-term prescription as previously considered. Further study is required to evaluate effect of half-life of BZD on long-term prescription in population with deferent characteristics.

Patients with cancer at baseline were likely to continue BZD in this study. Patients with cancer may use and continue BZD because of pain and psychological distress, [10,13,23] especially among non-elderly adults. [24, 25] Moreover, patients with cancer

likely have these symptoms during and even after cancer treatment. It is important to manage pain and psychological distress by other measures to prevent additional adverse effect from long-term use of BZD among cancer patients.

Based on our findings, it is important to carefully prescribe BZD in accordance with the recommendation to avoid long-term use, especially for patients with dual diagnosis of mood and neurotic disorder, using hypnotics, prescribed two or more BZDs, and with cancer. Prescription guidelines of BZD such as NICE guideline and WHO recommend using BZD up to 30 days. [26,27] In Japan, year-long prescription of BZD was disincentivized in 2018. [28] However, this may not be enough to prevent long-term BZD use because most of BZD users may already be dependent on BZDs by one year. Additional measure should be taken to restrict BZD prescription. For example, an option may be to disincentivize prescription of high-dose BZD at initial prescription or continuation BZD for more than one month based on patient' severity of psychiatric disorders.

This study had several limitations related to claimed data. The data did not include severity of psychiatric disorders and insomnia. If people with severe condition quitted their job and change health insurance, they dropped out from this study cohort. Although rare among the new users, this may have influenced characteristics of the

study cohort. Moreover, the elderly and unemployed people were not included in this study.

Conclusion

We identified several risk factors for determining long-term prescription of BZD among new users of BZD. Although prevalence of long-term users was relatively low, assessment of these risk factors is necessary to prevent long-term prescription of BZDs when physicians prescribe BZD at initial visit.

Author contributions

AT, SO, Hayato Y, and Hideo Y devised the study protocol. AT, SO, and Hayato Y drafted the manuscript. All authors reviewed and approved the final manuscript.

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Competing interests

The authors declare no conflict of interest.

Data sharing statement

No additional data sharing available

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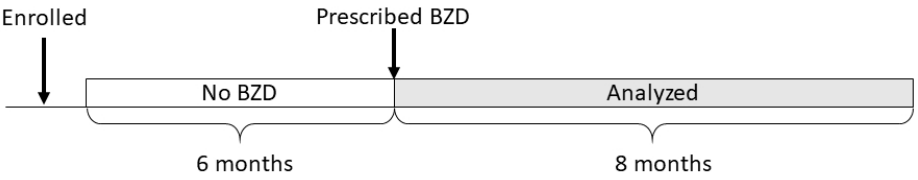

Figure 1 Patient selection

Figure 1 Patient selection

254x190mm (96 x 96 DPI)

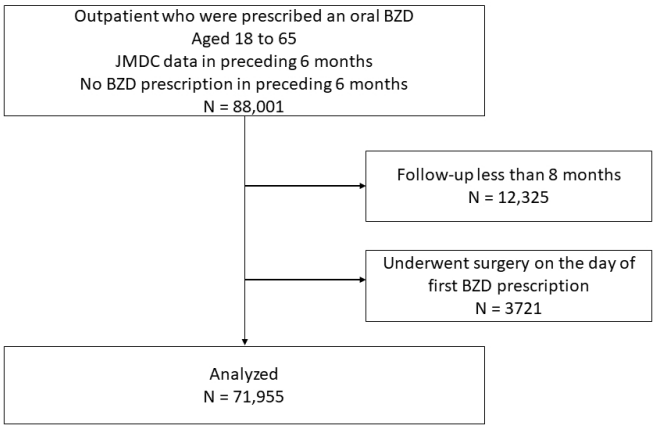

Figure 2 Participant flow

Figure 2 Patient flow

338x190mm (96 x 96 DPI)

Supporting Table 1 List of benzodiazepine and benzodiazepine-related drugs included in this study

	ATC code	Generic name
benzodiazepine-derivative anxiolytics		
1	N05BA01	diazepam
2	N05BA02	chlordiazepoxide
3	N05BA03	medazepam
4	N05BA05	potassium clorazepate
5	N05BA06	lorazepam
6	N05BA08	bromazepam
7	N05BA12	alprazolam
8	N05BA17	fludiazepam
9	N05BA18	ethyl loflazepate
10	N05BA19	etizolam
11	N05BA21	clotiazepam
12	N05BA22	cloxazolam
13	N05BA23	tofisopam
benzodiazepine-derivative hypnotics and sedatives		
14	N05CD01	flurazepam
15	N05CD02	nitrazepam
16	N05CD03	flunitrazepam
17	N05CD04	estazolam
18	N05CD05	triazolam
19	N05CD06	lormetazepam
20	N05CD09	brotizolam
21	N05CD10	quazepam
Z-drugs		
22	N05CF01	zopiclone
23	N05CF02	zolpidem
24	N05CF04	eszopiclone
benzodiazepine-derivative antiepileptics		
25	N03AE01	clonazepam
Other (not covered by the WHO-ATC code)		
26	anxiolytics	flutazolam
27	anxiolytics	flutoprazepam
28	anxiolytics	mexazolam
29	anxiolytics	oxazolam
30	hypnotics	nimetazepam
31	hypnotics	haloxazolam
32	hypnotics	rilmazafone

WHO-ATC: the World Health Organization's Anatomical Therapeutic Chemical

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2-3

Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3-5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5-7, Fig 1
	#6b	For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5
Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	5-6
Quantitative	#11	Explain how quantitative variables were handled in the	7-8

variables		analyses. If applicable, describe which groupings were chosen, and why	
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8-9
	#12b	Describe any methods used to examine subgroups and interactions	NA
	#12c	Explain how missing data were addressed	NA
	#12d	If applicable, explain how loss to follow-up was addressed	NA
	#12e	Describe any sensitivity analyses	NA
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	9
	#13b	Give reasons for non-participation at each stage	NA
	#13c	Consider use of a flow diagram	Fig 2
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	9
	#14b	Indicate number of participants with missing data for each variable of interest	NA

	#14c	Summarise follow-up time (eg, average and total amount)	NA
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	9, Table 1
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10, Table 2
	#16b	Report category boundaries when continuous variables were categorized	9-11
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	NA
Key results	#18	Summarise key results with reference to study objectives	11-12
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	14
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	12-14
Generalisability	#21	Discuss the generalisability (external validity) of the study	14

		results	
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

Author notes

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Factors associated with long-term prescription of benzodiazepine: a retrospective cohort study using a health insurance database in Japan

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Factors associated with long-term prescription of benzodiazepine: a retrospective cohort study using a health insurance database in Japan

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Abstract

Objectives: Current clinical guidelines discourage long-term prescription of benzodiazepines and Z-drugs (BZD), however, the practice continues to exist. The aim of this study was to investigate the proportion of long-term BZD prescriptions and its risk factors.

Design: Retrospective cohort study using a health insurance database.

Setting: Japan.

Participants: A total 86,909 patients were identified as outpatients aged 18 to 65 who started BZD between October 1st, 2012 and April 1st, 2015. After excluding patients who underwent surgery on the day of first BZD prescription (n = 762) and patients without eight months follow-up (n = 12,103), 74,044 outpatients were analyzed.

Main outcome measures: We investigated the proportion of long-term prescriptions for ≥ 8 months among new BZD users. We assessed patient demographics, diagnoses, characteristics of the initial BZD prescription, and prescribers as potential predictors of the long-term BZD prescription. Multivariable logistic regression was performed to assess the association between long-term prescription and potential predictors.

Results: Of the new BZD users, 6,687 (9.0%) were consecutively prescribed BZD for ≥ 8 months. The long-term prescription was significantly associated with mood and

neurotic disorder, cancer, prescription by psychiatrists, multiple prescriptions, hypnotics, and medium half-life BZD in the initial prescription.

Conclusion: Despite the recent clinical guidelines, 9% of new BZD users were given prescriptions for more than 8 months. Physicians should be aware of risk factors when prescribing BZDs for the first time.

Strengths and limitations of this study

- A large sample of Japanese outpatients among the non-elderly adult population.
- Analyzed new benzodiazepine users to prevent prevalent user bias.
- A strict definition of long-term use of benzodiazepine by identifying consecutive monthly prescription data.
- Limitations in detailed and accurate information in the health insurance database such as diagnosis and severity of psychiatric disorders.

Introduction

Globally, there is increasing concern about the long-term use of benzodiazepines and Z-drugs (BZD). Although BZDs are safer than old sedative-hypnotics, the efficacy of their long-term use has not been demonstrated. Long-term use of BZD leads to

dependence. [1] Patients may become dependent on BZDs to avoid withdrawal symptoms. [1–3] Studies have shown several adverse consequences related to the long-term use of BZD, including fracture, [4,5] cancer, [6] and car accidents [7] in any age group.

An understanding about the prevalence of long-term use of BZDs and its risk factors is essential for preventing adverse consequences. However, the reported prevalence of long-term BZD use varies widely because of variability in the definition of a long-term BZD prescription, study participants, and follow-up period [8,9] Over half of previous studies did not provide an adequate explanation for the definitions. [9] Some studies used one prescription per year or per several months as the definition of a long-term BZD prescription and others included prevalent users of BZDs or only the elderly as the study population. These studies may have overestimated the proportion of long-term prescription of BZDs.

The reported risk factors of a long-term prescription have been also inconsistent. In a systematic review, [9] long-term prescription of BZDs were associated with an older age, psychiatric disorders, and polypharmacy or high-dose BZDs at the initial prescription. However, the association of several other factors with long-term use of BZDs remains inconsistent, including demographic variables (e.g., gender, income), type of BZDs (e.g., half-life, Z-drug), or characteristics of prescriber (e.g., psychiatry).

The inconsistencies may have been affected by variability in the definition of long-term use of BZD. [10] For example, in a study where long-term prescription was defined as at least one prescription every three months, female gender was a risk factor. [11] However, in another study where long-term prescription was defined as BZD use lasting for 60 days, male gender was a risk factor. [10]

In this study, we followed new BZDs users who continued the drugs for ≥ 8 consecutive months. This definition was selected based on two previous studies. [9, 12] In a systematic review, long-term BZD use was commonly defined as 6-12 months. [9] In another study, about a half of patients who used BZDs for 8 months experienced clear withdrawal symptoms. [12]

Using a large-scale health insurance database with detailed prescription information, the present study investigated the proportion of long-term BZD prescriptions among new BZD users in Japan with a retrospective cohort design. We also assessed examined factors associated with the long-term prescription.

Methods

Data source

We used a health insurance claims database provided by JMDC Inc., Tokyo, Japan.

JMDC Inc. has collected claims information from occupation-based health insurance agencies for corporate employees and their dependents since 2005. [13] The JMDC database includes anonymous data of inpatient, outpatient, and pharmacy claims and special health checkups from about 3,000,000 individuals as of November 2014, representing about 2.5% of the Japanese population. [14] Each record includes age, sex, diagnoses, prescriptions, information about the medical institution, and date of the services. The diagnoses are based on International Classification of Diseases, 10th revision (ICD-10) diagnostic codes. The prescription information has the World Health Organization's Anatomical Therapeutic Chemical (WHO-ATC) classification system codes, drug name, dosage, days of supply, and mode of prescription. Date of prescriptions has been recorded since April 1st 2012. As such, we used data from April 1st 2012 through December 31st 2015. The requirement for informed consent was waived because of the anonymous nature of the data. The study was approved by the Institutional Review Board of The University of Tokyo (No. 10862).

Patient selection

We selected outpatients aged 18 to 65 years who started at least one of the available oral BZDs between October 1st 2012 and April 1st 2015 (Supplementary Table 1). We

chose only subjects who had been continuously enrolled in the JMDC database for at least six months before the first prescription of BZDs. We defined new users as those who had not used any BZDs for this six-month baseline period (Figure 1). We excluded patients who were followed up for less than 8 months after the first BZD prescription. We also excluded those who underwent surgery on the day of the first BZD prescription. Surgeries were identified with original Japanese procedure codes. When extracting BZDs, we used the WHO-ATC codes N05BA, N05CD, and N05CF.[15] We added seven BZDs which were not covered by the WHO-ATC codes, but were available in Japan. We excluded clobazam (N05BA09), which is categorized as an anti-epileptic drug in Japan, from this study because this drug is likely to be needed as a BZD for a long-term. Finally, 31 BZDs were included in this study.

---Figure 1---

Definition of long-term BZD prescription

We defined long-term BZD users as those who received at least one prescription of any BZD every month for ≥ 8 consecutive months. This definition was based on the time of experiencing withdrawal symptoms. [12] The prescription of most BZDs (23/31, 74.2%) are restricted to 30 days in Japan (Supplementary Table 1) and most first-time

prescriptions are usually for a short-term.

Potential predictors of long-term BZD prescription

We assessed the following variables at the baseline period as potential predictors of long-term BZD use based on previous studies. Patient characteristics at the first BZD prescription included sex, age, occupational status (employed or dependent), diagnosis of cancer (ICD-10 code, C$) during the prior 6 months, and psychiatric diagnosis (no diagnosis, mood disorders only [F3], neurotic, stress-related and somatic disorders only [F4], both mood disorder and neurotic disorder, but without other disorders [F3 and F4], and those with other psychiatric disorders [F0, 1, 5-9]. For example, if a patient had alcohol use disorder (F1) and depressive episode (F3), the person was categorized in other psychiatric disorders. Physician's specialty (psychiatry or other) at the first BZD prescription was also evaluated. Pharmacological characteristics of the first BZD prescription included multiple BZDs (1 or ≥ 2), type of BZD (hypnotics only, anxiolytics only, or both), administration instructions (as needed, regular prescription: 1 week (1-7 days), regular prescription: 2 weeks (8-14 days), and regular prescription: more than 2 weeks (≥ 15 days)), and half-life of BZD (short: < 12 hours, medium: 12-24 hours, long: ≥ 24 hours). Multiple BZD was derived from the number of BZD

ingredients in the first prescription. As for the variables of type of BZD, administration instruction and half-life of BZD, we selected the BZD with the longest prescription days if a patient was prescribed multiple BZDs.

Statistical analyses

First, we calculated the proportion for long-term use of BZD and compared potential predictors of long-term prescription between patients who were prescribed BZDs for ≥ 8 and < 8 months. We used Student's t-test to compare the average of continuous variables (such as age) and chi-squared test to compare the proportion of categorical variables (such as sex). Next, a multivariable logistic regression was performed to assess the association between potential predictors and long-term prescription.

Additionally, we compared participant characteristics at the first BZD prescription between those who were followed up for 8 months and those who were censored from this study cohort. Moreover, we conducted sensitivity analysis by changing the definition of long-term prescription to consecutive monthly prescription for 6 months or 12 months to confirm the proportion of long-term prescriptions and risk factors for different definitions. Finally, we stratified the participants by prescription status (as needed or regular prescription) and then performed a multivariable logistic

regression.

The threshold for significance was $p < 0.05$. We used IBM SPSS version 23 (IBM, Armonk, NY, USA) for all statistical analyses.

Patient and public involvement

Patients or members of the public were not involved in the design or implementation of this study. Patients and the general public will be informed of the study results via publication.

Results

Patient characteristics

A total 86,909 patients were identified as new BZD users during the study period (Figure 2). After excluding patients without eight months follow-up (n = 12,103), and patients who underwent surgery on the day of first BZD prescription (n = 762), the remaining 74,044 patients were included in our analysis. At the first prescription, of 74,044 patients, 58,404 (86.7%) were prescribed BZDs for 14 days or less and 73,526 (99.3%) were prescribed BZDs for less than 30 days. There were 6,687 patients (9.0%) who were prescribed BZDs over a period of ≥ 8 consecutive months. When stratified by

gender, 10.8% of males and 7.1% of females continued BZD use for ≥ 8 months. As for age group, the proportion of long-term use was 8.9%, 9.3%, 9.6%, 8.7%, and 7.2% for subjects aged 18-29, 30-39, 40-49, 50-59, and 60-65, respectively. Table 1 shows patient characteristics, information about physicians, and pharmacological characteristics of the initial prescription. About half of patients were diagnosed with mood disorder, and hypnotics were more likely to be prescribed than anxiolytics.

---Figure 2---

---Table 1---

Table 1 Demographics and clinical characteristics for new users of benzodiazepines (N = 74,004)

	BZD < 8 months n=67357 (91.0)	BZD ≥ 8 months n=6687 (9.0)	p
Age (mean, SD)	42.3 (11.8)	41.9 (11.2)	0.02
Sex, male	33851 (50.3)	4111 (61.5)	<0.001
Occupational status, employed	43315 (64.3)	4827 (72.2)	<0.001
Cancer	7073 (10.5)	690 (10.3)	0.66
Medical spatiality, psychiatry	17986 (26.7)	3845 (57.5)	<0.001
Psychiatric diagnosis			<0.001
None	28705 (42.6)	1286 (19.2)	
Mood disorder (F3)	9487 (14.1)	2301 (34.4)	
Neurotic, stress-related and somatic disorder (F4)	21370 (31.7)	1415 (21.2)	
Mood and neurotic disorders (F3 and F4)	6537 (9.7)	1489 (22.3)	
Other disorders	1258 (1.9)	196 (2.9)	
Multiple BZDs on first prescription	6460 (9.6)	1719 (25.7)	<0.001
Type of BZD [a]			<0.001
Hypnotic	20025 (29.7)	2469 (36.9)	
Anxiolytic	44027 (65.4)	3184 (47.6)	
Both	3305 (4.9)	1034 (15.5)	

Administration instructions [a]			<0.001
As needed	17968 (26.7)	969 (14.5)	
Regular prescription: 1 week (1-7 days)	20535 (30.5)	2323 (34.7)	
Regular prescription: 2 weeks (8-14 days)	19901 (29.5)	2423 (36.2)	
Regular prescription: more than 2 weeks (≥ 15 days)	8953 (13.3)	972 (14.5)	
Half-life of BZD [a]			<0.001
Short (< 12 h)	44968 (66.8)	3924 (58.7)	
Medium (12-24 h)	10567 (15.7)	1531 (22.9)	
Long (≥ 24 h)	11822 (17.6)	1232 (18.4)	

Data presented as n (%) unless otherwise specified.

BZD, benzodiazepines and Z-drugs; SD, standard deviation.

a: Characteristics of BZD with the longest prescription days in the first prescription

A comparison of the baseline characteristics between the analyzed patients and 12,103 patients who were censored is presented in Supplementary Table 2. Censored patients were more likely to be given prescriptions by psychiatrists. Otherwise, the baseline characteristics were comparable between the groups.

Predictors of long-term prescription

Table 2 shows the results of the multivariable logistic regression. For patient characteristics, comorbidity of mood and neurotic disorders had the strongest association with long-term prescription compared to no psychiatric diagnosis (odds ratio: OR, 3.53; 95% confidence interval: CI, 3.19-3.90; $p < 0.001$). Patients with cancer had a significantly higher risk of long-term BZD prescription than those without cancer

(OR, 1.18; 95% CI, 1.08-1.29; p < 0.001). As for characteristics of the first BZD prescription, prescription by psychiatry, hypnotics, regular prescription, and medium half-life were associated with long-term prescription.

---Table 2---

Table 2 Factors related to long-term benzodiazepine prescription among new users of benzodiazepines (N = 74,044)

	OR	95% CI			p
Age	1.02	1.01	to	1.02	<0.001
Sex, male	1.14	1.06	to	1.23	<0.001
Occupational status, employed	0.98	0.91	to	1.06	0.58
Cancer	1.18	1.08	to	1.29	<0.001
Medical specialty, psychiatry	1.80	1.68	to	1.94	<0.001
Psychiatric diagnosis					
None	Ref.				
Mood disorder (F3)	3.30	3.01	to	3.62	<0.001
Neurotic, stress-related and somatic disorder (F4)	1.49	1.36	to	1.62	<0.001
Mood and neurotic disorders (F3 and F4)	3.53	3.19	to	3.90	<0.001
Other disorders	2.37	2.00	to	2.80	<0.001
Multiple BZDs on first prescription	1.41	1.28	to	1.54	<0.001
Type of BZD [a]					
Hypnotic	Ref.				
Anxiolytic	0.61	0.57	to	0.66	<0.001
Both	0.93	0.83	to	1.05	0.27
Administration instructions [a]					
As needed	Ref.				
Regular prescription: 1 week (1-7 days)	1.98	1.82	to	2.15	<0.001
Regular prescription: 2 weeks (8-14 days)	1.91	1.76	to	2.07	<0.001
Regular prescription: more than 2 weeks (≥ 15 days)	1.83	1.67	to	2.02	<0.001
Half-life of BZD [a]					

Short (< 12 h)	Ref.				
Medium (12-24 h)	1.08	1.01	to	1.16	0.03
Long (≥ 24 h)	0.96	0.89	to	1.04	0.32

BZD, benzodiazepines and Z-drugs; OR, odds ratio; CI, confidence interval

a: Characteristics of BZD with the longest prescription days in the first prescription

When changing the definition of long-term prescription, 11.8% and 6.1% of the participants continued to be prescribed BZDs for 6 months and 12 months, respectively (Supplementary Table 3). The risk factors for a long-term prescription were similar to the results when the definition was long-term prescription for 8 months (Supplementary Table 4). As for the results of the stratified analysis, risk factors of long-term prescription among those with a regular prescription were the same as the results for all participants (Supplementary Table 5). In patients who were prescribed BZDs as needed, sex, medical specialty, multiple BZDs prescription, and half-life were not associated with long-term prescription.

Discussion

Using a large health insurance claims database, we investigated the proportion of long-term BZD prescriptions among new BZD users aged 18 to 65 years old. A total of 9.0% continued BZDs for ≥ 8 months. Long-term BZD prescription was significantly associated with older age, cancer, comorbidity of mood and neurotic disorder, multiple

BZD prescriptions, hypnotics, prescription by psychiatry, regular prescription, and medium half-life of BZD at the initial prescription.

This study showed 6.1%, 9.0%, and 11.8% of new users continued BZDs for ≥ 6 months, ≥ 8 months, and ≥ 12 months, respectively. These figures were comparable to results in a previous study [9], but relatively lower than prevalence in most previous studies. [8,16–18] This may be because previous studies used a prevalent user design or were conducted in an elderly population and resulted in an overestimation of long-term BZD use. In this study, prevalence of long-term prescription in a non-elderly population may be more reliable because we used a new-user design and assessed BZD use for ≥ 8 consecutive months. As another possible reason, low prevalence may be due to the development of guidelines for BZDs. Guidelines restricting long-term BZD prescription, such as the UK National Institute for Health and Care Excellence guideline, were developed and have spread around the world since the 2000s. These guidelines may have affected physicians' prescription practice. Furthermore, the guidelines potentially affected the prescription preferences of patients because the information became available on the Internet.

Risk factors for long-term use, including older age, psychiatric disorders, users of hypnotics, regular prescription, multiple prescriptions, and psychiatrist-prescriber

were consistent with those in a previous study in Japan. [11] Patients with a more severe condition may consult psychiatrists, be diagnosed with one or more psychiatric disorders, and be prescribed a high dose of BZD for regular use. Although severe conditions may cause long-term use of BZDs, BZDs should be prescribed with caution because there is weak evidence for the efficacy of long-term BZD use and BZD is not the first-line treatment for depression and anxiety. The medium half-life of BZD was associated with long-term use in the present study. This result was consistent with that of other research using the same database. [11] However, other studies suggested the risk of short-acting BZD, [19,20] and evidence regarding the association between half-life and long-term use remains inconclusive in the literature. [9] Since 2000, Z-drug hypnotics have become popular, and temporal differences in population characteristics may have resulted in the inconsistent study results. Further study is required to evaluate the effect of the half-life of BZD on long-term prescription in a population with different characteristics.

In this study, patients with cancer at the baseline were more likely to continue BZD. Patients with cancer may use and continue BZD because of pain and psychological distress, [8,10,21] especially among non-elderly adults. [22, 23] Moreover, patients with cancer likely have these symptoms during and even after cancer treatment.

It is important to manage pain and psychological distress by other measures to prevent additional adverse effects from long-term use of BZD among cancer patients.

Based on our findings, it is important to carefully prescribe BZD in accordance with the recommendation to avoid long-term use, especially for patients with a dual diagnosis of mood and neurotic disorder, using hypnotics, prescribed two or more BZDs, and with cancer. Prescription guidelines of BZD such as the NICE guideline and WHO recommend using BZD for up to 30 days. [24,25] In Japan, the year-long prescription of BZD was disincentivized in 2018. [26] However, this may not be sufficient to prevent long-term BZD use because most BZD users may already be dependent on BZDs by one year. Additional measures should be taken to restrict BZD prescriptions. For example, an option may be to disincentivize prescriptions of high-dose BZD at the initial prescription or continuation of BZD for more than one month based on the patient's severity of psychiatric disorders.

The sensitivity analysis showed the risk factors were almost the same when using different definitions of long-term prescription (≥ 6 or ≥ 12 months). This finding suggested the robustness of the analysis. However, the stratified analysis revealed that risk factors varied with a different prescription status (prescription as needed or regular prescription). Frequency of symptoms and physicians' manner of prescription may

influence prescription status. Further studies using detailed patient information and physicians' intention of prescription is necessary to identify risk factors of long-term prescription in specific patient groups.

This study had several limitations related to claims data. First, the data did not include severity of psychiatric disorders and insomnia symptoms. Although we adjusted for diagnosis using ICD-10 codes, there may be residual confounding due to patient conditions. Second, the analyzed cohort might not be representative of all included patients because censored patients were more likely to be prescribed first BZDs by psychiatrists. These patients might have had a relatively severe condition and tended to quit their job and change health insurance. Third, our definition of long-term prescription may also cause an underestimation of long-term prescription because people who received BZDs every two or three months were not counted as long-term.

Conclusion

We identified several risk factors for determining long-term prescription of BZD among new users of BZD. Although the prevalence of long-term users was relatively low, assessment of these risk factors is necessary to prevent long-term prescription of BZDs when physicians prescribe BZD at an initial visit.

Author contributions

AT, SO, Hayato Y, TM, Hideo Y, and NK devised the study protocol. AT, SO, Hayato Y, HM, and Hideo Y contributed to data collection and analysis and drafted the manuscript. All authors have contributed to interpretation and critically reviewed the manuscript. All authors approved the final version of the manuscript.

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Competing interests

The authors declare no conflict of interest.

Data sharing statement

No data are available.

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Figure legend/caption

Figure 1. Patient selection

BZD: benzodiazepines and Z-drug

Figure 2. Participant flow diagram

BZD: benzodiazepines and Z-drug

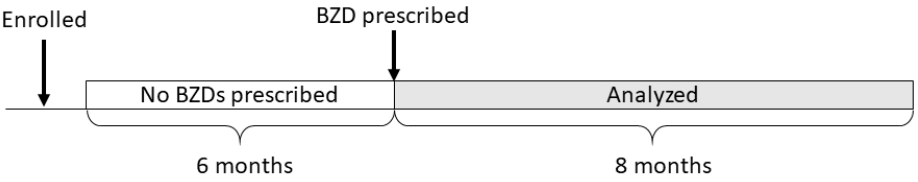

Figure 1

254x190mm (96 x 96 DPI)

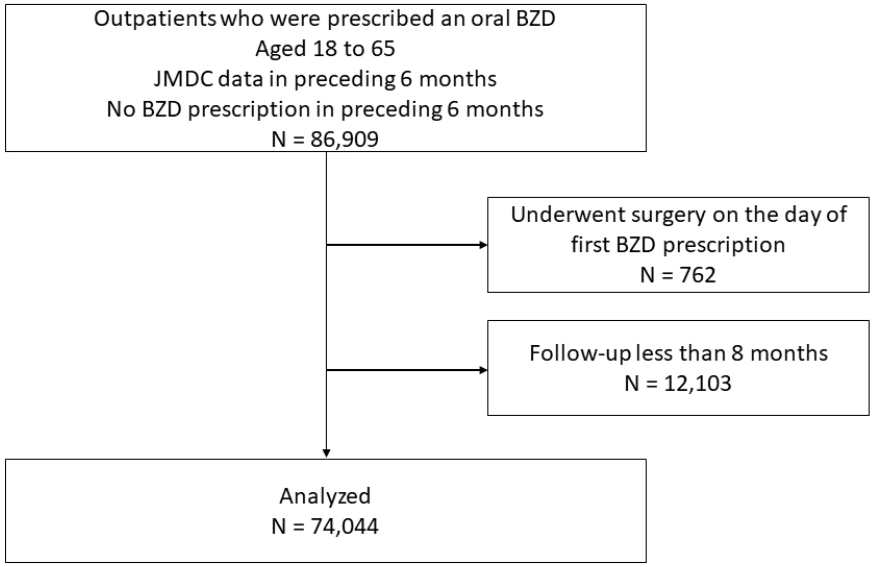

Figure 2

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Supplementary Table 1

List of benzodiazepine and benzodiazepine-related drugs included in this study

	ATC code	Generic name	Maximum number of prescription days
benzodiazepine-derivative anxiolytics			
1	N05BA01	diazepam	90
2	N05BA02	chlordiazepoxide	30
3	N05BA03	medazepam	30
4	N05BA05	potassium clorazepate	14
5	N05BA06	lorazepam	30
6	N05BA08	bromazepam	30
7	N05BA12	alprazolam	30
8	N05BA17	fludiazepam	30
9	N05BA18	ethyl loflazepate	30
10	N05BA19	etizolam	30
11	N05BA21	clotiazepam	30
12	N05BA22	cloxazolam	30
13	N05BA23	tofisopam	-
benzodiazepine-derivative hypnotics and sedatives			
14	N05CD01	flurazepam	30
15	N05CD02	nitrazepam	90
16	N05CD03	flunitrazepam	30
17	N05CD04	estazolam	30
18	N05CD05	triazolam	30
19	N05CD06	lormetazepam	30
20	N05CD09	brotizolam	30
21	N05CD10	quazepam	30
Z-drugs			
22	N05CF01	zopiclone	30
23	N05CF02	zolpidem	30
24	N05CF04	eszopiclone	-
Other (not covered by the WHO-ATC code)			
25	anxiolytics	flutazolam	-
26	anxiolytics	flutoprazepam	-
27	anxiolytics	mexazolam	-
28	anxiolytics	oxazolam	30
29	hypnotics	nimetazepam	30
30	hypnotics	haloxazolam	30
31	hypnotics	rilmazafone	-

WHO-ATC: World Health Organization Anatomical Therapeutic Chemical

Supplementary Table 2

Comparison of the characteristics between those who were followed up for 8 months and those who were censored from this study cohort (N=86147)

	Censored n=12103 (14.0)	Followed up for 8 months n=74044 (86.0)	Standardized difference
Age (mean, SD)	41.0 (13.1)	42.2 (11.8)	-0.096
Sex, male	5740 (47.4)	37962 (51.3)	-0.078
Occupational status, employed	8101 (66.9)	48142 (65.0)	0.040
Cancer	1365 (11.3)	7763 (10.5)	0.026
Medical specialty, psychiatry	4277 (35.3)	21831 (29.5)	0.124
Psychiatric diagnosis			
None	4306 (35.6)	29991 (40.5)	-0.101
Mood disorder (F3)	2196 (18.1)	11788 (15.9)	0.059
Neurotic, stress-related and somatic disorder (F4)	3747 (31.0)	22785 (30.8)	0.004
Mood and neurotic disorders (F3 and F4)	1582 (13.1)	8026 (10.8)	0.071
Other disorders	272 (2.2)	1454 (2.0)	0.014
Multiple BZDs on first prescription	1515 (12.5)	8179 (11.0)	0.047
Type of BZD [a]			
Hypnotic	3918 (32.4)	22494 (30.4)	0.043
Anxiolytic	7353 (60.8)	47211 (63.8)	-0.062
Both	832 (6.9)	4339 (5.9)	0.041
Administration instructions [a]			
As needed	2992 (24.7)	18937 (25.6)	-0.021
Regular prescription: 1 week (1-7 days)	3815 (31.5)	22858 (30.9)	0.013
Regular prescription: 2 weeks (8-14 days)	3808 (31.5)	22324 (30.1)	0.030
Regular prescription: more than 2 weeks (≥ 15 days)	1488 (12.3)	9925 (13.4)	-0.033
Half-life of BZD [a]			
Short (< 12 h)	7858 (64.9)	48892 (66.0)	-0.023
Medium (12-24 h)	2236 (18.5)	12098 (16.3)	0.058
Long (≥ 24 h)	2009 (16.6)	13054 (17.6)	-0.027

Data presented as n (%) unless otherwise specified.

BZD, benzodiazepines and Z-drugs; SD, standard deviation.

a: Characteristics of BZD with the longest prescription days in the first prescription

Supplementary Table 3

Demographics and clinical characteristics of new users of BZD when using different definitions for long-term prescription

	BZD < 6 months	BZD ≥ 6 months		BZD < 12 months	BZD ≥ 12 months	
	(N=81409)			(N=61857)		
	71770 (88.2)	9639 (11.8)	p	58061 (93.9)	3796 (6.1)	p
Age (mean, SD)	42.2 (11.9)	41.9 (11.4)	0.01	42.3 (11.7)	42.2 (11.0)	0.83
Sex, male	35731 (49.8)	5821 (60.4)	<0.001	29468 (50.8)	2338 (61.6)	<0.001
Occupational status, employed	46011 (64.1)	6902 (71.6)	<0.001	37458 (64.5)	2735 (72.0)	<0.001
Cancer	7481 (10.4)	1079 (11.2)	0.02	6075 (10.5)	379 (10.0)	0.36
Medical specialty, psychiatry	18922 (26.4)	5401 (56.0)	<0.001	15645 (26.9)	2206 (58.1)	<0.001
Psychiatric diagnosis			<0.001			<0.001
None	30772 (42.9)	1958 (20.3)		24701 (42.5)	709 (18.7)	
Mood disorder (F3)	9839 (13.7)	3211 (33.3)		8385 (14.4)	1338 (35.2)	
Neurotic, stress-related and somatic disorder (F4)	22978 (32.0)	2119 (22.0)		18203 (31.4)	777 (20.5)	
Mood and neurotic disorders (F3 and F4)	6840 (9.5)	2093 (21.7)		5711 (9.8)	857 (22.6)	
Other disorders	1341 (1.9)	258 (2.7)		1061 (1.8)	115 (3.0)	
Multiple BZDs on first prescription	6650 (9.3)	2339 (24.3)	<0.001	5798 (10.0)	1023 (26.9)	<0.001
Type of BZD [a]			<0.001			<0.001
Hypnotic	21290 (29.7)	3550 (36.8)		17411 (30.0)	1428 (37.6)	
Anxiolytic	47097 (65.6)	4707 (48.8)		37659 (64.9)	1754 (46.2)	
Both	3383 (4.7)	1382 (14.3)		2991 (5.2)	614 (16.2)	
Administration instructions [a]			<0.001			<0.001
As needed	19365 (27.0)	1481 (15.4)		15277 (26.3)	543 (14.3)	
Regular prescription: 1 week (1-7 days)	21902 (30.5)	3296 (34.2)		17699 (30.5)	1347 (35.5)	
Regular prescription: 2 weeks (8-14 days)	21089 (29.4)	3493 (36.2)		17285 (29.8)	1360 (35.8)	
Regular prescription: more than 2 weeks (≥ 15 days)	9414 (13.1)	1369 (14.2)		7800 (13.4)	546 (14.4)	
Half-life of BZD [a]			<0.001			<0.001
Short (< 12 h)	48097 (67.0)	5655 (58.7)		38801 (66.8)	2207 (58.1)	
Medium (12-24 h)	11210 (15.6)	2191 (22.7)		9100 (15.7)	882 (23.2)	
Long (≥ 24 h)	12463 (17.4)	1793 (18.6)		10160 (17.5)	707 (18.6)	

Data presented as n (%) unless otherwise specified.

BZD, benzodiazepines and Z-drugs; SD, standard deviation.

a: Characteristics of BZD with the longest prescription days in the first prescription

Supplementary Table 4

Factors related to long-term BZD prescription among new BZD users when using different definitions for long-term prescription

	long-term: ≥ 6 months (N=81409)				long-term: ≥ 12 months (N=61857)			
	OR	95% CI		p	OR	95% CI		p
Age	1.01	1.01	to 1.02	<0.001	1.02	1.02	to 1.02	<0.001
Sex, male	1.13	1.06	to 1.20	<0.001	1.11	1.01	to 1.22	0.03
Occupational status, employed	0.98	0.92	to 1.05	0.64	0.97	0.88	to 1.08	0.58
Cancer	1.32	1.23	to 1.42	<0.001	1.11	0.99	to 1.25	0.07
Medical specialty, psychiatry	1.78	1.68	to 1.89	<0.001	1.77	1.61	to 1.94	<0.001
Psychiatric diagnosis								
None	Ref.				Ref.			
Mood disorder (F3)	3.20	2.96	to 3.46	<0.001	3.44	3.04	to 3.88	<0.001
Neurotic, stress-related and somatic disorder (F4)	1.46	1.36	to 1.57	<0.001	1.53	1.36	to 1.72	<0.001
Mood and neurotic disorders (F3 and F4)	3.37	3.10	to 3.67	<0.001	3.71	3.25	to 4.23	<0.001
Other disorders	2.06	1.77	to 2.39	<0.001	2.60	2.09	to 3.24	<0.001
Multiple BZDs on first prescription	1.40	1.29	to 1.52	<0.001	1.43	1.27	to 1.61	<0.001
Type of BZD [a]								
Hypnotic	Ref.				Ref.			
Anxiolytic	0.61	0.58	to 0.64	<0.001	0.59	0.54	to 0.64	<0.001
Both	0.89	0.80	to 0.99	0.04	0.90	0.77	to 1.04	0.14
Administration instructions [a]								
As needed	Ref.				Ref.			
Regular prescription: 1 week (1-7 days)	1.87	1.75	to 2.00	<0.001	1.98	1.78	to 2.20	<0.001
Regular prescription: 2 weeks (8-14 days)	1.86	1.74	to 1.99	<0.001	1.83	1.65	to 2.04	<0.001
Regular prescription: more than 2 weeks (≥ 15 days	1.75	1.61	to 1.90	<0.001	1.76	1.55	to 1.99	<0.001
Half-life of BZD [a]								
Short (< 12 h)	Ref.				Ref.			
Medium (12-24 h)	1.12	1.05	to 1.19	<0.001	1.11	1.01	to 1.22	0.03
Long (≥ 24 h)	1.02	0.95	to 1.09	0.62	0.997	0.900	to 1.10	0.95

BZD, benzodiazepines and Z-drugs; OR, odds ratio; CI, confidence interval

a: Characteristics of BZD with the longest prescription days in the first prescription

Supplementary Table 5

Factors related to long-term BZD prescription (≥ 8 months) among the new BZD users with as-needed prescription or regular prescription

	As needed (n=18937)				Regular (n=55107)			
	OR	95% CI		p	OR	95% CI		p
Age	1.01	1.00	to 1.02	<0.01	1.02	1.01	to 1.02	<0.001
Sex, male	1.13	0.95	to 1.35	0.17	1.14	1.05	to 1.23	<0.01
Occupational status, employed	0.97	0.81	to 1.17	0.75	0.98	0.90	to 1.06	0.61
Cancer	1.41	1.17	to 1.71	<0.001	1.11	1.00	to 1.22	0.04
Medical specialty, psychiatry	1.18	0.98	to 1.42	0.08	1.96	1.81	to 2.11	<0.001
Psychiatric diagnosis								
None	Ref.							
Mood disorder (F3)	3.00	2.36	to 3.82	<0.001	3.41	3.08	to 3.77	<0.001
Neurotic, stress-related and somatic disorder (F4)	1.53	1.24	to 1.89	<0.001	1.52	1.38	to 1.67	<0.001
Mood and neurotic disorders (F3 and F4)	4.16	3.24	to 5.34	<0.001	3.53	3.16	to 3.95	<0.001
Other disorders	2.13	1.44	to 3.15	<0.001	2.48	2.05	to 2.99	<0.001
Multiple BZDs on first prescriptions [a]	1.45	0.79	to 2.65	0.23	1.37	1.25	to 1.51	<0.001
Type of BZD [a]								
Hypnotic	Ref.							
Anxiolytic	0.44	0.37	to 0.52	<0.001	0.67	0.62	to 0.72	<0.001
Both	0.70	0.36	to 1.39	0.31	0.99	0.88	to 1.12	0.90
Half-life of BZD [a]								
Short (< 12 h)	Ref.							
Medium (12-24 h)	1.11	0.92	to 1.33	0.28	1.10	1.02	to 1.19	0.02
Long (≥ 24 h)	0.80	0.60	to 1.07	0.13	0.95	0.87	to 1.03	0.22

BZD, benzodiazepines and Z-drugs; OR, odds ratio; CI, confidence interval

a: Characteristics of BZD with the longest prescription days in the first prescription

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3-5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-8
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5-8, Fig 1

	#6b	For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5-9
Bias	#9	Describe any efforts to address potential sources of bias	6-7
Study size	#10	Explain how the study size was arrived at	6-7
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8-9
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	9-10
	#12b	Describe any methods used to examine subgroups and interactions	9-10
	#12c	Explain how missing data were addressed	NA
	#12d	If applicable, explain how loss to follow-up was addressed	9
	#12e	Describe any sensitivity analyses	9
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	10
	#13b	Give reasons for non-participation at each stage	10
	#13c	Consider use of a flow diagram	Fig 2
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	10-11 Table1

		confounders. Give information separately for exposed and unexposed groups if applicable.	
	#14b	Indicate number of participants with missing data for each variable of interest	NA
	#14c	Summarise follow-up time (eg, average and total amount)	10, 14
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	10-11, Table 1
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13, Table 2
	#16b	Report category boundaries when continuous variables were categorized	8-9
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	12, 14
Key results	#18	Summarise key results with reference to study objectives	14-15
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	18
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	14-19
Generalisability	#21	Discuss the generalisability (external validity) of the study results	18
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

Author notes