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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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Manuscripts

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6 Factors associated with long-term prescription of benzodiazepine: a retrospective cohort
7 study using a health insurance database in Japan
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6 **Abstract**
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9 2 Objectives: Long-term prescriptions of benzodiazepine drugs (BZD) seem to remain,
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11 3 although clinical guidelines aim to prevent it. The aim of this study was to investigate
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13 4 the proportion of the long-term BZD prescription and its risk factors.
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18 5 Design: Retrospective cohort study using a health insurance database.
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21 6 Setting: Japan.
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24 7 Participants: A total 88,001 patients were identified outpatients aged 18 to 65 who
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26 8 started BZDs between October 1st, 2012 and April 1st, 2015. After excluding patients
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28 9 without eight months follow-up (n = 12,325), and patients who underwent surgery on
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30 10 the day of first BZD prescription (n = 3,721), 71,955 outpatients were analyzed.
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34 11 Main outcome measures: We investigated the proportion of the long-term prescription
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36 12 for ≥ 8 months among the new BZD users. We assessed patient demographics,
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38 13 diagnoses, initial BZD prescription, and prescribers as potential predictors of the long-
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40 14 term BZD prescription. Multivariable logistic regression was performed to assess the
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42 15 association between the long-term prescription and the potential predictors.
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46 16 Results: Of the new BZD users, 6,462 (9.0%) were consecutively prescribed BZD for
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48 17 ≥ 8 months. The long-term prescription was significantly associated with cancer, aging,
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50 18 mood and neurotic disorder, hypnotics, prescription by psychiatrists, and high-dose
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7 19 BZD at the initial prescription.
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9 20 Conclusion: Despite the recent clinical guidelines, 9% of new BZD users were
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12 21 prescribed for more than 8 months. Physicians should be aware of the risk factors when
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15 22 prescribing BZDs for the first time.
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21 24 **Strengths and limitations of this study**
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24 25 ● A large sample of the Japanese outpatients among the non-elderly adult population.
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27 26 ● Analyzed new benzodiazepine users to prevent prevalent user bias.
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30 27 ● A strict definition of long-term use of benzodiazepine by identifying consecutive
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33 28 monthly prescription data.
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36 29 ● Limitation of detailed and accurate information in the health insurance database
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39 30 such as the diagnosis and the severity of psychiatric disorders.
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45 32 **Introduction**
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48 33 Concerns about long-term use of benzodiazepines and benzodiazepine-related drugs
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51 34 (BZDs) have been raised over the world. Although BZDs are safer than old sedative-
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54 35 hypnotics, efficacy of their long-term use has not been demonstrated. Long-term use of
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57 36 BZD leads to dependence.¹ Patients may become dependent on BZDs to avoid
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6 37 withdrawal symptoms.¹⁻³ Studies showed several adverse consequences related to long-
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9 38 term use of BZD, including dementia among elderly people^{4,5} and fracture^{6,7} cancer⁸
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12 39 and car accident⁹ in any generation.
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15 40 Understanding prevalence of long-term use of BZDs and its risk factors is
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18 41 essential to prevent adverse consequences. However, reported prevalence of long-term
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21 42 BZD use varied widely because of variability in definition of long-term BZD prescription,
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24 43 study participants, and follow-up period^{10,11} Over a half of the studies did not provide
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27 44 plausible explanation for the definitions.¹¹ Some studies used one prescription per year
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30 45 or per several months as definition of long-term BZD prescription and others included
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33 46 prevalent users of BZDs or only the elderly as study population. These studies may have
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36 47 overestimated the proportion of long-term prescription of BZDs.
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39 48 Reported risk factors of long-term prescription have been also inconsistent. In a
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42 49 systematic review,¹¹ long-term prescription of BZDs were associated with older age,
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45 50 psychiatric disorders, and polypharmacy or high-dose BZDs at the initial prescription.
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48 51 However, association of several other factors with long term use of BZDs remains
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51 52 inconsistent, including demographic variables (e.g. gender, income), type of BZDs (e.g.
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54 53 half-life, Z-drug), or characteristics of prescriber (e.g. psychiatry). The inconsistency
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57 54 may have been affected by variability of definition of long-term use of BZD.¹¹ For
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6 55 example, in a study where long-term prescription was defined as at least one
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9 56 prescription every three months, female was a risk factor. ¹² However, in another study
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12 57 where long-term prescription was defined as lasting BZD use for 60 days, male was a
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15 58 risk factor. ¹³
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18 59 In this study, we subjected new BZDs users who continued the drugs for ≥ 8
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21 60 consecutive months. This definition was selected based on two previous studies. In a
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24 61 systematic review, long-term BZD use was commonly defined as 6-12 months. ¹¹ In
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27 62 another study, about a half of patients who used BZDs for 8 months experienced clear
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30 63 withdrawal symptoms. ¹⁴
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33 64 Using a large-scale health insurance database with detailed prescription
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36 65 information, the present study investigated the proportion of long-term BZD
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39 66 prescription among new BZD users in Japan with a retrospective cohort design. We also
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42 67 assessed examined factors associated with the long-term prescription.
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48 69 **Methods**

51 70 **Data source**

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54 71 We used a health insurance claims database provided by JMDC Inc., Tokyo, Japan.

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57 72 JMDC Inc. has collected claims information from occupation-based health insurance
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6 73 agencies for corporate employees and their dependents since 2005.¹⁵ The JMDC
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9 74 database includes anonymous data of inpatient, outpatient, and pharmacy claims and
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12 75 special health checkups from about 3,000,000 individuals by November 2014,
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15 76 representing about 2.5% of the Japanese population.¹⁶ Each record includes age, sex,
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18 77 diagnoses, prescriptions, information of medical institution, and date of the services.
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21 78 The diagnoses are based on International Classification of Diseases, 10th revision (ICD-
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24 79 10) diagnostic codes. The prescription information has the World Health Organization's
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27 80 Anatomical Therapeutic Chemical (WHO-ATC) classification system codes, drug
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30 81 name, dosage, days of supply, and mode of prescription. Date of prescriptions has been
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33 82 recorded since April 1st 2012. We thus used the data from April 1st 2012 through
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36 83 December 31st 2015. The requirement for informed consent was waived because of the
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39 84 anonymous nature of the data. The study was approved by the Institutional Review
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41
42 85 Board of The University of Tokyo.
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48 87 **Patient selection**

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51 88 We selected outpatients aged 18 to 65 years who started at least one of available oral
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54 89 BZD and BZD-related drugs between October 1st 2012 and April 1st 2015
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57 90 (Supplementary table). We chose only subjects who had been continuously enrolled in
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7 91 the JMDC database for at least six months before first prescription of BZDs. We
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9 92 defined first users as those who had not used any BZDs for this six-month baseline
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12 93 period (Figure 1). We excluded patients who were followed up for less than 8 months
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15 94 after the first BZD prescription. We also excluded those who underwent surgery on the
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18 95 day of the first BZD prescription. Surgeries were identified with Japanese original
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21 96 procedure codes. When extracting BZDs, we used the WHO-ATC codes N05BA,
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24 97 N05CD, N05CF, and N03AE.¹⁷ We added seven BZDs which were not covered by the
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27 98 WHO-ATC codes but were available in Japan. We excluded clobazam from this study
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30 99 because it was categorized as benzodiazepine-derivative anxiolytics in the WHO-ATC
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33 100 code (N05BA09) but was used as an antiepileptic in Japan. Thirty-two BZDs were
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36 101 identified.

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39 102 ---Figure 1---

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43 44 45 104 **Definition of long-term BZD prescription**

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48 105 We defined long-term BZD users as those who received at least one prescription of any
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51 106 BZDs every month for ≥ 8 consecutive months.

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55 56 57 108 **Potential predictors of long-term BZD prescription**

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7 109 We assessed the following variables at baseline period as potential predictors of long-
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10 110 term BZD use based on previous studies. Patient characteristics included sex, age,
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12 111 working status (worker or dependent), diagnosis of cancer (ICD-10 code, C\$), and
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15 112 psychiatric diagnosis (no diagnosis, mood disorders only [F3], neurotic, stress-related
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18 113 and somatic disorders only [F4], both mood disorder and neurotic disorder [F3 and F4],
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21 114 and other psychiatric disorders [F0, 1, 5-9]. Physician's specialty (psychiatry or others)
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24 115 was also evaluated. Pharmacological characteristics of the first BZD prescription
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27 116 included type of BZD (hypnotics only, anxiolytics only, or both), half-life of BZD
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30 117 (short: <12 hours, medium: 12-24 hours, long: \geq 24 hours), administration instruction
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33 118 (regular, as needed, or both), and the number of BZDs. If a patient was prescribed
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36 119 multiple BZDs with different half-lives, we selected the BZD with the longest half-life.
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41 42 121 **Statistical analyses**

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45 122 First, we calculated proportion of long-term use of BZD and compared the potential
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48 123 predictors of long-term prescription between the patients who were prescribed BZDs for
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51 124 \geq 8 and <8 months. We used Student's t-test to compare the average of continuous
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54 125 variables (such as age) and chi-squared test to compare the proportion of categorical
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57 126 variables (such as sex). Next, a multivariable logistic regression was performed to
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6 127 assess the association between the potential predictors and long-term prescription.
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9 128 The threshold for significance was $P < 0.05$. We used IBM SPSS version 23
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12 129 (IBM, Armonk, NY, USA) for all statistical analyses.
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18 131 **Results**

21 132 **Patient characteristics**

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24 133 A total 88,001 patients were identified as new BZD users during the study period
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27 134 (Figure 2). After excluding patients without eight months follow-up ($n = 12,325$), and
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30 135 patients who underwent surgery on the day of first BZD prescription ($n = 3,721$), 71,955
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33 136 patients were included in the analysis. There were 6,462 patients (9.0%) who were
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36 137 prescribed BZDs for ≥ 8 consecutive months. When stratified by gender, 10.7% of males
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39 138 and 7.2% of females continued BZD use for ≥ 8 months. As for age group, the
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42 139 proportion of long-term use was 8.9%, 9.3%, 9.5%, 8.6%, and 9.0% for subjects aged
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45 140 18-29, 30-39, 40-49, 50-59, and 60-65, respectively. Table 1 shows patient
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48 141 characteristics, information of physicians, and pharmacological characteristics of the
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51 142 initial prescription. About half of them were diagnosed with mood disorder, and
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54 143 hypnotics were more likely to be prescribed than anxiolytics.

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57 144 ---Figure 2---

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7 145 ---Table 1---

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9 146 Table 1 Demographic and clinical characteristics of the new users of benzodiazepines (N
10 147 = 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

142 148 Data presented as n (%) unless otherwise specified.

143 149 BZD, benzodiazepine-related drugs; SD, standard deviation.

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152 **Predictors of long-term prescription**

153 153 Table 2 shows the result of the multivariable logistic regression. Patients with cancer

154 154 had significantly higher risk of long-term BZD prescription than those without cancer

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

157 ---Table 2---

158 Table 2 Factors related to long-term benzodiazepine prescription among the new users of
 159 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 (\leq 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

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

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162 Discussion

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

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6 165 continued BZDs for ≥ 8 months. Long-term BZD prescription was significantly
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9 166 associated with older age, cancer, comorbidity of mood and neurotic disorder,
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12 167 hypnotics, prescription at psychiatry, and high-dose of BZD at the initial prescription.
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15 168 The half-life of BZD was not associated with long-term prescription.
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19 169 This study showed 9% of new users continued BZDs for ≥ 8 months. This figure
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21 170 was comparable to that in a previous study¹¹ but relatively lower than prevalence in
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24 171 most of previous studies.^{10,18-20} Also, previous studies using prevalent user design
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27 172 caused overestimation of the long-term BZD use. In this study, prevalence of long-term
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30 173 prescription in non-elderly population may be more reliable because we assessed BZD
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33 174 use for ≥ 8 consecutive months. Alternatively, low prevalence may be due to
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36 175 development of guidelines for BZDs. The guidelines restricting long-term BZD
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39 176 prescription, such as the UK National Institute for Health and Care Excellence
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42 177 guideline, were developed and spread around the world since 2000's. These guidelines
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45 178 may have affected physicians' prescription practice. Furthermore, the guidelines
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48 179 potentially affected patients' prescription preference because the information had been
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51 180 available on the Internet.
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54 181 Some risk factors for long-term use, including older age, psychiatric disorders,
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57 182 users of hypnotics, regular prescription, a large number of BZD, and psychiatrist-

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6 183 prescriber were consistent with those in a previous study in Japan.¹² Patients with more
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9 184 severe condition may consult psychiatrists, be diagnosed with one or more psychiatric
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12 185 disorders and be prescribed a high dose of BZD for regular use. Although severe
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15 186 conditions may cause long-term use of BZDs, BZDs should be prescribed with caution
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18 187 because there is weak evidence for efficacy of the long-term BZD use and BZD is not
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21 188 the first-line treatment for depression and anxiety. Half-life of BZD was not associated
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24 189 with long-term use in this study, although many studies illustrated risk of short-acting
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27 190 BZD.^{21,22} Since 2000, when benzodiazepine-related hypnotics became popular, studies
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30 191 had focused on effect of half-life of BZD on long-term BZD prescription, but evidence
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33 192 remained inconclusive.¹¹ Differences in population characteristics may have resulted in
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36 193 the inconsistent study results of short-acting BZD. Our results suggested that among the
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39 194 relatively young and healthy population, half-life of BZD did not play an important role
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42 195 in long-term prescription as previously considered. Further study is required to evaluate
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45 196 effect of half-life of BZD on long-term prescription in population with deferent
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48 197 characteristics.

51 198 Patients with cancer at baseline were likely to continue BZD in this study.

54 199 Patients with cancer may use and continue BZD because of pain and psychological

57 200 distress,^{10,13,23} especially among non-elderly adults.^{24,25} Moreover, patients with cancer

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6 201 likely have these symptoms during and even after cancer treatment. It is important to
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9 202 manage pain and psychological distress by other measures to prevent additional adverse
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12 203 effect from long-term use of BZD among cancer patients.
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15 204 Based on our findings, it is important to carefully prescribe BZD in accordance
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18 205 with the recommendation to avoid long-term use, especially for patients with dual
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21 206 diagnosis of mood and neurotic disorder, using hypnotics, prescribed two or more
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24 207 BZDs, and with cancer. Prescription guidelines of BZD such as NICE guideline and
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27 208 WHO recommend using BZD up to 30 days.^{26,27} In Japan, year-long prescription of
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30 209 BZD was disincentivized in 2018.²⁸ However, this may not be enough to prevent long-
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33 210 term BZD use because most of BZD users may already be dependent on BZDs by one
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36 211 year. Additional measure should be taken to restrict BZD prescription. For example, an
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39 212 option may be to disincentivize prescription of high-dose BZD at initial prescription or
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42 213 continuation BZD for more than one month based on patient' severity of psychiatric
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45 214 disorders.
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48 215 This study had several limitations related to claimed data. The data did not
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51 216 include severity of psychiatric disorders and insomnia. If people with severe condition
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54 217 quitted their job and change health insurance, they dropped out from this study cohort.
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57 218 Although rare among the new users, this may have influenced characteristics of the
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6 219 study cohort. Moreover, the elderly and unemployed people were not included in this
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13 14 15 222 **Conclusion**

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18 223 We identified several risk factors for determining long-term prescription of
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21 224 BZD among new users of BZD. Although prevalence of long-term users was relatively
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24 225 low, assessment of these risk factors is necessary to prevent long-term prescription of
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27 226 BZDs when physicians prescribe BZD at initial visit.

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31 32 33 228 **Author contributions**

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36 229 AT, SO, Hayato Y, and Hideo Y devised the study protocol. AT, SO, and Hayato Y
37
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39 230 drafted the manuscript. All authors reviewed and approved the final manuscript.

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47
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49
50
51 234 The Health Care Science Institute, Japan.

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55 56 57 236 **Competing interests**

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6 237 The authors declare no conflict of interest.
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12 239 **Data sharing statement**
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15 240 No additional data sharing available
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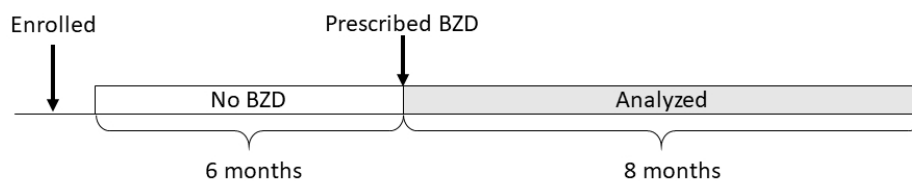


Figure 1 Patient selection

Figure 1 Patient selection

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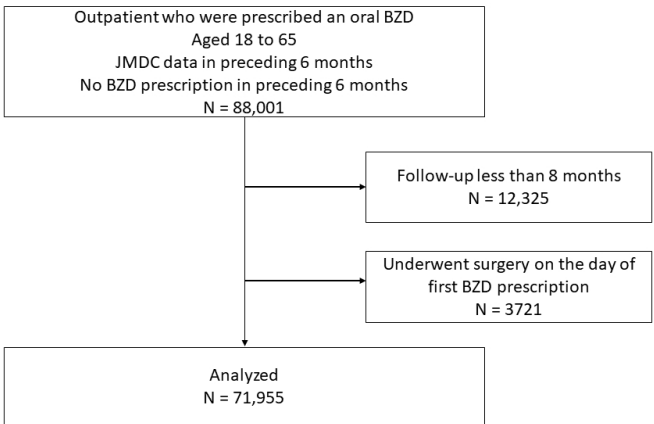


Figure 2 Participant flow

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.

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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, Gøtzsche 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

1	Background /	#2	Explain the scientific background and rationale for the	3-5
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3	rationale		investigation being reported	
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6	Objectives	#3	State specific objectives, including any prespecified	5
7			hypotheses	
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11	Study design	#4	Present key elements of study design early in the paper	5
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15	Setting	#5	Describe the setting, locations, and relevant dates, including	5-7
16			periods of recruitment, exposure, follow-up, and data collection	
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20	Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of	5-7, Fig
21			selection of participants. Describe methods of follow-up.	1
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26		#6b	For matched studies, give matching criteria and number of	NA
27			exposed and unexposed	
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31	Variables	#7	Clearly define all outcomes, exposures, predictors, potential	7-8
32			confounders, and effect modifiers. Give diagnostic criteria, if	
33			applicable	
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39	Data sources /	#8	For each variable of interest give sources of data and details of	5
40	measurement		methods of assessment (measurement). Describe	
41			comparability of assessment methods if there is more than one	
42			group. Give information separately for for exposed and	
43			unexposed groups if applicable.	
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51	Bias	#9	Describe any efforts to address potential sources of bias	6
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54	Study size	#10	Explain how the study size was arrived at	5-6
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57	Quantitative	#11	Explain how quantitative variables were handled in the	7-8
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1	variables	analyses. If applicable, describe which groupings were chosen,	
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6	Statistical	#12a Describe all statistical methods, including those used to control	8-9
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16		#12c Explain how missing data were addressed	NA
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19		#12d If applicable, explain how loss to follow-up was addressed	NA
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22		#12e Describe any sensitivity analyses	NA
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26	Participants	#13a Report numbers of individuals at each stage of study—eg	9
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38		#13b Give reasons for non-participation at each stage	NA
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41		#13c Consider use of a flow diagram	Fig 2
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44	Descriptive data	#14a Give characteristics of study participants (eg demographic,	9
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54		#14b Indicate number of participants with missing data for each	NA
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1		#14c	Summarise follow-up time (eg, average and total amount)	NA
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4	Outcome data	#15	Report numbers of outcome events or summary measures	9, Table
5			over time. Give information separately for exposed and	1
6			unexposed groups if applicable.	
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11	Main results	#16a	Give unadjusted estimates and, if applicable, confounder-	10, Tabl
12			adjusted estimates and their precision (eg, 95% confidence	e 2
13			interval). Make clear which confounders were adjusted for and	
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22		#16b	Report category boundaries when continuous variables were	9-11
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28		#16c	If relevant, consider translating estimates of relative risk into	NA
29			absolute risk for a meaningful time period	
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32	Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and	NA
33			interactions, and sensitivity analyses	
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38	Key results	#18	Summarise key results with reference to study objectives	11-12
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41	Limitations	#19	Discuss limitations of the study, taking into account sources of	14
42			potential bias or imprecision. Discuss both direction and	
43			magnitude of any potential bias.	
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48	Interpretation	#20	Give a cautious overall interpretation considering objectives,	12-14
49			limitations, multiplicity of analyses, results from similar studies,	
50			and other relevant evidence.	
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56	Generalisability	#21	Discuss the generalisability (external validity) of the study	14
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1 results

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4 Funding #22 Give the source of funding and the role of the funders for the 15
5 present study and, if applicable, for the original study on which
6 the present article is based
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10 11 Author notes

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BMJ Open

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

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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Public health
Keywords:	Benzodiazepine, Cohort study, Dependence, Long-term prescription, Risk factors

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6 Factors associated with long-term prescription of benzodiazepine: a retrospective cohort
7 study using a health insurance database in Japan
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56 Benzodiazepine, Cohort study, Dependence, Long-term prescription, Risk factors
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6 **Abstract**
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10 2 Objectives: Current clinical guidelines discourage long-term prescription of
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12 3 benzodiazepines and Z-drugs (BZD), however, the practice continues to exist.

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15 4 The aim of this study was to investigate the proportion of long-term BZD prescriptions
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18 5 and its risk factors.

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21 6 Design: Retrospective cohort study using a health insurance database.

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24 7 Setting: Japan.

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27 8 Participants: A total 86,909 patients were identified as outpatients aged 18 to 65 who
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30 9 started BZD between October 1st, 2012 and April 1st, 2015. After excluding patients
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33 10 who underwent surgery on the day of first BZD prescription (n = 762) and patients
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36 11 without eight months follow-up (n = 12,103), 74,044 outpatients were analyzed.

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39 12 Main outcome measures: We investigated the proportion of long-term prescriptions for
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42 13 ≥ 8 months among new BZD users. We assessed patient demographics, diagnoses,
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45 14 characteristics of the initial BZD prescription, and prescribers as potential predictors of
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48 15 the long-term BZD prescription. Multivariable logistic regression was performed to
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51 16 assess the association between long-term prescription and potential predictors.

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54 17 Results: Of the new BZD users, 6,687 (9.0%) were consecutively prescribed BZD for \geq
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57 18 8 months. The long-term prescription was significantly associated with mood and
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6 19 neurotic disorder, cancer, prescription by psychiatrists, multiple prescriptions,
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9 20 hypnotics, and medium half-life BZD in the initial prescription.
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12 21 Conclusion: Despite the recent clinical guidelines, 9% of new BZD users were given
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15 22 prescriptions for more than 8 months. Physicians should be aware of risk factors when
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18 23 prescribing BZDs for the first time.
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24 25 **Strengths and limitations of this study**

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

32 33 **Introduction**

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

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37 dependence. ¹ Patients may become dependent on BZDs to avoid withdrawal symptoms.

38 ¹⁻³ Studies have shown several adverse consequences related to the long-term use of
39 BZD, including fracture, ^{4,5} cancer, ⁶ and car accidents ⁷ in any age group.

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

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

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7 55 The inconsistencies may have been affected by variability in the definition of long-term
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9 56 use of BZD. ¹⁰ For example, in a study where long-term prescription was defined as at
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12 57 least one prescription every three months, female gender was a risk factor. ¹¹ However,
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15 58 in another study where long-term prescription was defined as BZD use lasting for 60
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18 59 days, male gender was a risk factor. ¹⁰

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21 60 In this study, we followed new BZDs users who continued the drugs for ≥ 8
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24 61 consecutive months. This definition was selected based on two previous studies. ^{9, 12} In a
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27 62 systematic review, long-term BZD use was commonly defined as 6-12 months. ⁹ In
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30 63 another study, about a half of patients who used BZDs for 8 months experienced clear
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33 64 withdrawal symptoms. ¹²

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36 65 Using a large-scale health insurance database with detailed prescription
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39 66 information, the present study investigated the proportion of long-term BZD
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42 67 prescriptions among new BZD users in Japan with a retrospective cohort design. We
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45 68 also assessed examined factors associated with the long-term prescription.

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70 **Methods**

71 **Data source**

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

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6 73 JMDC Inc. has collected claims information from occupation-based health insurance
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9 74 agencies for corporate employees and their dependents since 2005.¹³ The JMDC
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12 75 database includes anonymous data of inpatient, outpatient, and pharmacy claims and
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15 76 special health checkups from about 3,000,000 individuals as of November 2014,
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18 77 representing about 2.5% of the Japanese population.¹⁴ Each record includes age, sex,
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21 78 diagnoses, prescriptions, information about the medical institution, and date of the
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24 79 services. The diagnoses are based on International Classification of Diseases, 10th
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27 80 revision (ICD-10) diagnostic codes. The prescription information has the World Health
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30 81 Organization's Anatomical Therapeutic Chemical (WHO-ATC) classification system
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33 82 codes, drug name, dosage, days of supply, and mode of prescription. Date of
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36 83 prescriptions has been recorded since April 1st 2012. As such, we used data from April
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39 84 1st 2012 through December 31st 2015. The requirement for informed consent was
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42 85 waived because of the anonymous nature of the data. The study was approved by the
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45 86 Institutional Review Board of The University of Tokyo (No. 10862).

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50 51 88 **Patient selection**

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54 89 We selected outpatients aged 18 to 65 years who started at least one of the available oral
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57 90 BZDs between October 1st 2012 and April 1st 2015 (Supplementary Table 1). We
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7 91 chose only subjects who had been continuously enrolled in the JMDC database for at
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10 92 least six months before the first prescription of BZDs. We defined new users as those
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13 93 who had not used any BZDs for this six-month baseline period (Figure 1). We excluded
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16 94 patients who were followed up for less than 8 months after the first BZD prescription.
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19 95 We also excluded those who underwent surgery on the day of the first BZD
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22 96 prescription. Surgeries were identified with original Japanese procedure codes. When
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25 97 extracting BZDs, we used the WHO-ATC codes N05BA, N05CD, and N05CF.¹⁵ We
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28 98 added seven BZDs which were not covered by the WHO-ATC codes, but were available
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31 99 in Japan. We excluded clobazam (N05BA09), which is categorized as an anti-epileptic
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34 100 drug in Japan, from this study because this drug is likely to be needed as a BZD for a
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37 101 long-term. Finally, 31 BZDs were included in this study.

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39 102 ---Figure 1---

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43 44 45 104 **Definition of long-term BZD prescription**

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48 105 We defined long-term BZD users as those who received at least one prescription of any
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51 106 BZD every month for ≥ 8 consecutive months. This definition was based on the time of
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54 107 experiencing withdrawal symptoms.¹² The prescription of most BZDs (23/31, 74.2%)
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57 108 are restricted to 30 days in Japan (Supplementary Table 1) and most first-time
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6 109 prescriptions are usually for a short-term.
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11 111 **Potential predictors of long-term BZD prescription**

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15 112 We assessed the following variables at the baseline period as potential predictors of
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18 113 long-term BZD use based on previous studies. Patient characteristics at the first BZD
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21 114 prescription included sex, age, occupational status (employed or dependent), diagnosis
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23
24 115 of cancer (ICD-10 code, C\$) during the prior 6 months, and psychiatric diagnosis (no
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27 116 diagnosis, mood disorders only [F3], neurotic, stress-related and somatic disorders only
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30 117 [F4], both mood disorder and neurotic disorder, but without other disorders [F3 and F4],
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33 118 and those with other psychiatric disorders [F0, 1, 5-9]. For example, if a patient had
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36 119 alcohol use disorder (F1) and depressive episode (F3), the person was categorized in
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39 120 other psychiatric disorders. Physician's specialty (psychiatry or other) at the first BZD
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42 121 prescription was also evaluated. Pharmacological characteristics of the first BZD
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45 122 prescription included multiple BZDs (1 or ≥ 2), type of BZD (hypnotics only,
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48 123 anxiolytics only, or both), administration instructions (as needed, regular prescription: 1
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51 124 week (1-7 days), regular prescription: 2 weeks (8-14 days), and regular prescription:
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54 125 more than 2 weeks (≥ 15 days)), and half-life of BZD (short: < 12 hours, medium:
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57 126 12-24 hours, long: ≥ 24 hours). Multiple BZD was derived from the number of BZD
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6 127 ingredients in the first prescription. As for the variables of type of BZD, administration
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9 128 instruction and half-life of BZD, we selected the BZD with the longest prescription days
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12 129 if a patient was prescribed multiple BZDs.
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18 131 **Statistical analyses**

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21 132 First, we calculated the proportion for long-term use of BZD and compared potential
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24 133 predictors of long-term prescription between patients who were prescribed BZDs for ≥ 8
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27 134 and < 8 months. We used Student's t-test to compare the average of continuous
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30 135 variables (such as age) and chi-squared test to compare the proportion of categorical
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33 136 variables (such as sex). Next, a multivariable logistic regression was performed to
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36 137 assess the association between potential predictors and long-term prescription.
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39 138 Additionally, we compared participant characteristics at the first BZD
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42 139 prescription between those who were followed up for 8 months and those who were
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45 140 censored from this study cohort. Moreover, we conducted sensitivity analysis by
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48 141 changing the definition of long-term prescription to consecutive monthly prescription
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51 142 for 6 months or 12 months to confirm the proportion of long-term prescriptions and risk
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54 143 factors for different definitions. Finally, we stratified the participants by prescription
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57 144 status (as needed or regular prescription) and then performed a multivariable logistic
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6 145 regression.

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9 146 The threshold for significance was $p < 0.05$. We used IBM SPSS version 23
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12 147 (IBM, Armonk, NY, USA) for all statistical analyses.

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16 17 18 149 **Patient and public involvement**

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21 150 Patients or members of the public were not involved in the design or implementation of
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23
24 151 this study. Patients and the general public will be informed of the study results via
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27 152 publication.

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31 32 33 154 **Results**

34 35 36 155 **Patient characteristics**

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39 156 A total 86,909 patients were identified as new BZD users during the study period
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42 157 (Figure 2). After excluding patients without eight months follow-up ($n = 12,103$), and
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45 158 patients who underwent surgery on the day of first BZD prescription ($n = 762$), the
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48 159 remaining 74,044 patients were included in our analysis. At the first prescription, of
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51 160 74,044 patients, 58,404 (86.7%) were prescribed BZDs for 14 days or less and 73,526
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54 161 (99.3%) were prescribed BZDs for less than 30 days. There were 6,687 patients (9.0%)
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57 162 who were prescribed BZDs over a period of ≥ 8 consecutive months. When stratified by
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7 163 gender, 10.8% of males and 7.1% of females continued BZD use for ≥ 8 months. As for
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10 164 age group, the proportion of long-term use was 8.9%, 9.3%, 9.6%, 8.7%, and 7.2% for
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12 165 subjects aged 18-29, 30-39, 40-49, 50-59, and 60-65, respectively. Table 1 shows
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15 166 patient characteristics, information about physicians, and pharmacological
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18 167 characteristics of the initial prescription. About half of patients were diagnosed with
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21 168 mood disorder, and hypnotics were more likely to be prescribed than anxiolytics.

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24 169 ---Figure 2---

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27 170 ---Table 1---

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30 171 Table 1 Demographics and clinical characteristics for new users of benzodiazepines (N
31 172 = 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 speciality, 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)	

173 Data presented as n (%) unless otherwise specified.

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

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

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177 A comparison of the baseline characteristics between the analyzed patients and

178 12,103 patients who were censored is presented in Supplementary Table 2. Censored

179 patients were more likely to be given prescriptions by psychiatrists. Otherwise, the

180 baseline characteristics were comparable between the groups.

181

182 Predictors of long-term prescription

183 Table 2 shows the results of the multivariable logistic regression. For patient

184 characteristics, comorbidity of mood and neurotic disorders had the strongest

185 association with long-term prescription compared to no psychiatric diagnosis (odds

186 ratio: OR, 3.53; 95% confidence interval: CI, 3.19-3.90; $p < 0.001$). Patients with cancer

187 had a significantly higher risk of long-term BZD prescription than those without cancer

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

191

192 ---Table 2---

193 Table 2 Factors related to long-term benzodiazepine prescription among new users of
 194 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 (\geq 24 h)	0.96 0.89 to 1.04 0.32

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

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

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

207

208 Discussion

209 Using a large health insurance claims database, we investigated the proportion of
 210 long-term BZD prescriptions among new BZD users aged 18 to 65 years old. A total of
 211 9.0% continued BZDs for \geq 8 months. Long-term BZD prescription was significantly
 212 associated with older age, cancer, comorbidity of mood and neurotic disorder, multiple

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6 213 BZD prescriptions, hypnotics, prescription by psychiatry, regular prescription, and
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9 214 medium half-life of BZD at the initial prescription.
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12 215 This study showed 6.1%, 9.0%, and 11.8% of new users continued BZDs for \geq
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15 216 6 months, \geq 8 months, and \geq 12 months, respectively. These figures were comparable to
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18 217 results in a previous study ⁹, but relatively lower than prevalence in most previous
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21 218 studies. ^{8,16-18} This may be because previous studies used a prevalent user design or
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24 219 were conducted in an elderly population and resulted in an overestimation of long-term
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27 220 BZD use. In this study, prevalence of long-term prescription in a non-elderly population
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30 221 may be more reliable because we used a new-user design and assessed BZD use for \geq 8
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33 222 consecutive months. As another possible reason, low prevalence may be due to the
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36 223 development of guidelines for BZDs. Guidelines restricting long-term BZD
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39 224 prescription, such as the UK National Institute for Health and Care Excellence
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42 225 guideline, were developed and have spread around the world since the 2000s. These
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45 226 guidelines may have affected physicians' prescription practice. Furthermore, the
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48 227 guidelines potentially affected the prescription preferences of patients because the
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51 228 information became available on the Internet.
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54 229 Risk factors for long-term use, including older age, psychiatric disorders, users
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57 230 of hypnotics, regular prescription, multiple prescriptions, and psychiatrist-prescriber
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6 231 were consistent with those in a previous study in Japan.¹¹ Patients with a more severe
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9 232 condition may consult psychiatrists, be diagnosed with one or more psychiatric
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12 233 disorders, and be prescribed a high dose of BZD for regular use. Although severe
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15 234 conditions may cause long-term use of BZDs, BZDs should be prescribed with caution
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18 235 because there is weak evidence for the efficacy of long-term BZD use and BZD is not
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21 236 the first-line treatment for depression and anxiety. The medium half-life of BZD was
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24 237 associated with long-term use in the present study. This result was consistent with that
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27 238 of other research using the same database.¹¹ However, other studies suggested the risk
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30 239 of short-acting BZD,^{19,20} and evidence regarding the association between half-life and
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33 240 long-term use remains inconclusive in the literature.⁹ Since 2000, Z-drug hypnotics
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36 241 have become popular, and temporal differences in population characteristics may have
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39 242 resulted in the inconsistent study results. Further study is required to evaluate the effect
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42 243 of the half-life of BZD on long-term prescription in a population with different
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45 244 characteristics.

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48 245 In this study, patients with cancer at the baseline were more likely to continue
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51 246 BZD. Patients with cancer may use and continue BZD because of pain and
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54 247 psychological distress,^{8,10,21} especially among non-elderly adults.^{22,23} Moreover,
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57 248 patients with cancer likely have these symptoms during and even after cancer treatment.
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6 249 It is important to manage pain and psychological distress by other measures to prevent
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9 250 additional adverse effects from long-term use of BZD among cancer patients.

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12 251 Based on our findings, it is important to carefully prescribe BZD in accordance
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15 252 with the recommendation to avoid long-term use, especially for patients with a dual
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18 253 diagnosis of mood and neurotic disorder, using hypnotics, prescribed two or more
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21 254 BZDs, and with cancer. Prescription guidelines of BZD such as the NICE guideline and
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24 255 WHO recommend using BZD for up to 30 days.^{24,25} In Japan, the year-long prescription
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27 256 of BZD was disincentivized in 2018.²⁶ However, this may not be sufficient to prevent
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30 257 long-term BZD use because most BZD users may already be dependent on BZDs by
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33 258 one year. Additional measures should be taken to restrict BZD prescriptions. For
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36 259 example, an option may be to disincentivize prescriptions of high-dose BZD at the
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39 260 initial prescription or continuation of BZD for more than one month based on the
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42 261 patient's severity of psychiatric disorders.

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45 262 The sensitivity analysis showed the risk factors were almost the same when
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48 263 using different definitions of long-term prescription (≥ 6 or ≥ 12 months). This finding
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51 264 suggested the robustness of the analysis. However, the stratified analysis revealed that
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54 265 risk factors varied with a different prescription status (prescription as needed or regular
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57 266 prescription). Frequency of symptoms and physicians' manner of prescription may
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6 267 influence prescription status. Further studies using detailed patient information and
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9 268 physicians' intention of prescription is necessary to identify risk factors of long-term
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12 269 prescription in specific patient groups.
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15 270 This study had several limitations related to claims data. First, the data did not
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18 271 include severity of psychiatric disorders and insomnia symptoms. Although we adjusted
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21 272 for diagnosis using ICD-10 codes, there may be residual confounding due to patient
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24 273 conditions. Second, the analyzed cohort might not be representative of all included
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27 274 patients because censored patients were more likely to be prescribed first BZDs by
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30 275 psychiatrists. These patients might have had a relatively severe condition and tended to
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33 276 quit their job and change health insurance. Third, our definition of long-term
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36 277 prescription may also cause an underestimation of long-term prescription because
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39 278 people who received BZDs every two or three months were not counted as long-term.
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45 280 **Conclusion**

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48 281 We identified several risk factors for determining long-term prescription of
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51 282 BZD among new users of BZD. Although the prevalence of long-term users was
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54 283 relatively low, assessment of these risk factors is necessary to prevent long-term
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57 284 prescription of BZDs when physicians prescribe BZD at an initial visit.
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9 286 **Author contributions**

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12 287 AT, SO, Hayato Y, TM, Hideo Y, and NK devised the study protocol. AT, SO, Hayato
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15 288 Y, HM, and Hideo Y contributed to data collection and analysis and drafted the
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18 289 manuscript. All authors have contributed to interpretation and critically reviewed the
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21 290 manuscript. All authors approved the final version of the manuscript.
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23
24 291 **Funding statement**

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28
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30 293 The Health Care Science Institute, Japan.
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36 295 **Competing interests**

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39 296 The authors declare no conflict of interest.
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45 298 **Data sharing statement**

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48 299 No data are available.
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54 373 **Figure legend/caption**

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57 374 Figure 1. Patient selection
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6 375 BZD: benzodiazepines and Z-drug
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12 377 Figure 2. Participant flow diagram
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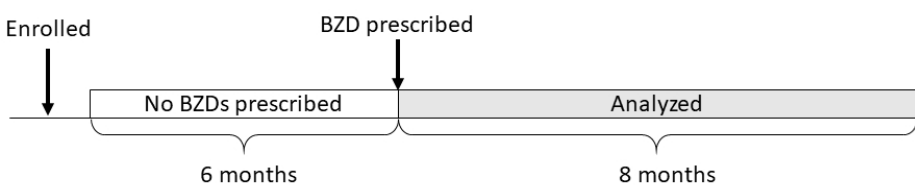


Figure 1
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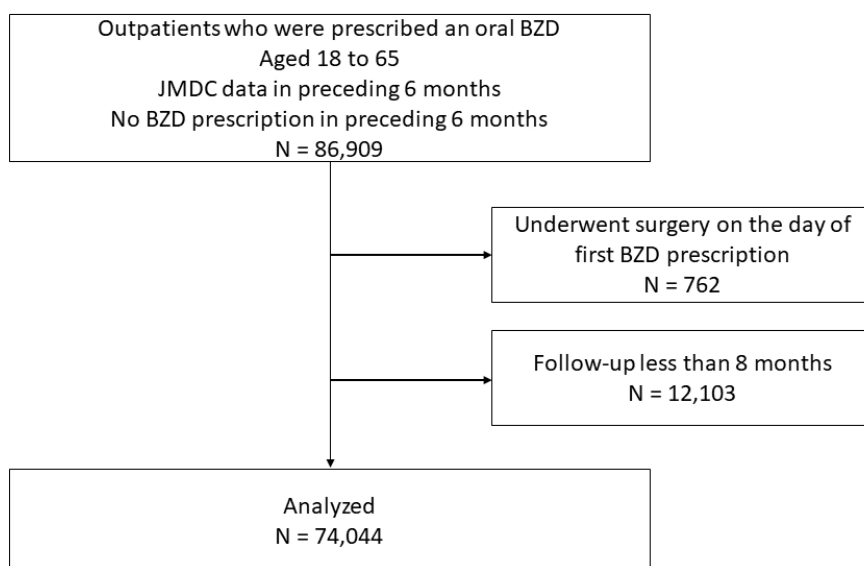


Figure 2

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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 (\geq 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 (\geq 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 (N=81409)	BZD ≥ 6 months		BZD < 12 months (N=61857)	BZD ≥ 12 months	
	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, Gøtzsche 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

1		#6b	For matched studies, give matching criteria and number of	NA
2			exposed and unexposed	
3				
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5	Variables	#7	Clearly define all outcomes, exposures, predictors, potential	7-9
6			confounders, and effect modifiers. Give diagnostic criteria, if	
7			applicable	
8				
9				
10	Data sources /	#8	For each variable of interest give sources of data and details	5-9
11	measurement		of methods of assessment (measurement). Describe	
12			comparability of assessment methods if there is more than one	
13			group. Give information separately for for exposed and	
14			unexposed groups if applicable.	
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18	Bias	#9	Describe any efforts to address potential sources of bias	6-7
19				
20				
21	Study size	#10	Explain how the study size was arrived at	6-7
22				
23	Quantitative	#11	Explain how quantitative variables were handled in the	8-9
24	variables		analyses. If applicable, describe which groupings were	
25			chosen, and why	
26				
27				
28	Statistical	#12a	Describe all statistical methods, including those used to control	9-10
29	methods		for confounding	
30				
31				
32		#12b	Describe any methods used to examine subgroups and	9-10
33			interactions	
34				
35				
36		#12c	Explain how missing data were addressed	NA
37				
38		#12d	If applicable, explain how loss to follow-up was addressed	9
39				
40				
41		#12e	Describe any sensitivity analyses	9
42				
43	Participants	#13a	Report numbers of individuals at each stage of study—eg	10
44			numbers potentially eligible, examined for eligibility, confirmed	
45			eligible, included in the study, completing follow-up, and	
46			analysed. Give information separately for for exposed and	
47			unexposed groups if applicable.	
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51		#13b	Give reasons for non-participation at each stage	10
52				
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54		#13c	Consider use of a flow diagram	Fig 2
55				
56	Descriptive data	#14a	Give characteristics of study participants (eg demographic,	10-11
57			clinical, social) and information on exposures and potential	Table1
58				
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1		confounders. Give information separately for exposed and	
2		unexposed groups if applicable.	
3			
4		#14b Indicate number of participants with missing data for each	NA
5		variable of interest	
6			
7		#14c Summarise follow-up time (eg, average and total amount)	10, 14
8			
9			
10	Outcome data	#15 Report numbers of outcome events or summary measures	10-11,
11		over time. Give information separately for exposed and	Table 1
12		unexposed groups if applicable.	
13			
14			
15	Main results	#16a Give unadjusted estimates and, if applicable, confounder-	12-13,
16		adjusted estimates and their precision (eg, 95% confidence	Table 2
17		interval). Make clear which confounders were adjusted for and	
18		why they were included	
19			
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21			
22		#16b Report category boundaries when continuous variables were	8-9
23		categorized	
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26		#16c If relevant, consider translating estimates of relative risk into	NA
27		absolute risk for a meaningful time period	
28			
29			
30	Other analyses	#17 Report other analyses done—e.g., analyses of subgroups and	12, 14
31		interactions, and sensitivity analyses	
32			
33			
34	Key results	#18 Summarise key results with reference to study objectives	14-15
35			
36	Limitations	#19 Discuss limitations of the study, taking into account sources of	18
37		potential bias or imprecision. Discuss both direction and	
38		magnitude of any potential bias.	
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40			
41	Interpretation	#20 Give a cautious overall interpretation considering objectives,	14-19
42		limitations, multiplicity of analyses, results from similar studies,	
43		and other relevant evidence.	
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45			
46	Generalisability	#21 Discuss the generalisability (external validity) of the study	18
47		results	
48			
49			
50	Funding	#22 Give the source of funding and the role of the funders for the	19
51		present study and, if applicable, for the original study on which	
52		the present article is based	
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Author notes

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2 CC-BY. This checklist was completed on 03. February 2019 using <https://www.goodreports.org/>, a
3 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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