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# Continuation and discontinuation of benzodiazepine prescriptions: A cohort study based on A large claims database in Japan

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## ABSTRACT

Although benzodiazepines (BZDs) are often prescribed to treat a wide range of psychiatric and neurological conditions, they are also associated with various harms and risks including dependence. However the frequency of its continued use in the real world has not been well studied, especially at longer follow-ups. The aim of this study was to clarify the frequency of long-term BZD use among new BZD users over longer follow-ups and to identify its predictors. We conducted a cohort study to examine how frequently new BZD users became chronic users, based on a large claims database in Japan from January 2005 to June 2014. We used Cox proportional hazards models to identify potential predictors. A total 84,412 patients with new BZD prescriptions were included in our cohort. Among them, 35.8% continued to use BZD for three months, 15.2% for one year and 4.9% for eight years without ever attaining three months of no BZD prescription. The confirmed predictors for long-term BZD use were older age, psychiatrist-prescriber, regular use, high dose of BZD, and concomitant prescription of psychotropic drugs. When we consider BZD use, we have to keep in mind these figures and avoid these predictors as much as possible.

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## 1. Introduction

Benzodiazepines (BZDs) are widely prescribed around the world to treat anxiety, insomnia, agitation, seizures, muscle spasms and non-specific physical complaints (Lader, 2011). Their short-term efficacy has been confirmed in some systematic reviews for generalized anxiety disorder (Martin et al., 2007), panic disorder (van Balkom et al., 1997), chronic insomnia (Holbrook et al., 2001), alcohol withdrawal (Amato et al., 2010) and akathisia (Lima et al., 2002). BZDs are also often used in conjunction with other psychotropic drugs. For example, the combination of BZD and antidepressant led to greater response and to less drop-out than antidepressant alone in the acute phase treatment of depression (Furukawa et al., 2001). However, the long-term continued efficacy of BZDs has been examined in only a few studies to date (Roth et al., 2005; Nardi et al., 2012), and, therefore, remains largely untested and unknown even for the above indications for which short-term efficacy has been confirmed.

On the other hand, various adverse effects of BZDs have been reported in the literature, including cognitive impairment, psychomotor disturbance, withdrawal and dependence (Lader, 2011). Some studies revealed that BZD increased the risk for falls and

fractures (Cumming and Le Couteur, 2003) and the risk for road traffic accidents (Rapoport et al., 2009; Smink et al., 2010). Long-term use of BZD is especially likely to lead to dependence and withdrawal symptoms. Recent studies suggested that BZDs may be associated with the incidence of dementia (Billioti de Gage et al., 2012, 2014) and increased mortality (Weich et al., 2014).

The risk-benefit balance of BZD use, especially in the long-term, is therefore likely to be negative. In fact, NICE guidelines recommend only short-term prescription of BZDs for insomnia (NICE April, 2004), generalized anxiety disorder or panic disorder (NICE January, 2011). A WHO guideline for traumatic stress in non-specialized settings suggests that, when psychotherapy is not feasible, short-term treatment with BZD may be considered (WHO, 2013). Other guidelines also make similar recommendations (Baldwin et al., 2005; Schutte-Rodin et al., 2008; Schaffer et al., 2012). These guidelines seem to imply that in practice many doctors use BZD over long periods despite lack of demonstrated merit of such use.

However, it is not clear what proportion of new BZD users become long-term BZD users. In other words, it is not known how frequently new BZD users can stop BZD in the real world. Although there are several cohort studies of new BZD users, the frequency of BZD use at about one-year follow-up obtained from these studies range extremely widely (10–87%) (Isacson, 1997; Veronese et al., 2007; Kjosavik et al., 2012) and the frequency at longer follow-up is even less well elucidated. In addition, predictors for long-term BZD use have not been well understood. The reported variation in

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the frequency of long-term use suggests the importance of examining such predictors. Although there seems to be general agreement that older age and high dose of BZD predict long-term BZD use, other factors have not been established by previous studies (Mant et al., 1988; Veronese et al., 2007; Kjosavik et al., 2012). These suggested but unconfirmed factors include female sex, low level of education, hypnotic (rather than anxiolytic only), alcohol dependence, severity of symptom, and prescription by psychiatrists, regular (rather than as needed) use (Neutel et al., 2003; van Hulst et al., 2003; Barnas et al., 1993; Veronese et al., 2007; Luijendijk et al., 2008). Some of the uncertainty regarding these predictors is due to the fact that most of these studies were cross-sectional and included not only new BZDs user but also chronic BZD user. We therefore need a well-designed prospective study with a larger sample size and with a longer follow-up to clarify these important issues concerning BZD prescriptions.

The aim of this study was therefore (1) to determine the frequency of long-term BZDs use among new BZD users over longer follow-ups and (2) to identify its predictors in a large cohort of medical and psychiatric outpatients based on a nationwide claims database.

## 2. Methods

### 2.1. Data source

We used the claims database provided by the Japan Medical Data Center (JMDC) Ltd., Tokyo, Japan. The JMDC database consists of the claims information submitted to several health insurance societies by multiple medical institutions for both corporate employees and their dependents, starting from January 1st, 2005 (Kimura et al., 2010). The JMDC database contains the claims data from about 3,000,000 individuals in Japan (approximately 2.5% of the country's entire population) by June 30th, 2014. For each person, the JMDC database includes an encrypted personal identifier, age, gender, diagnoses and prescriptions. Diagnoses are specified with International Classification of Diseases, 10th Revision (ICD-10) diagnostic codes. Prescriptions include the Anatomical Therapeutic Chemical (ATC) Classification System codes, days of supply, dosage information and mode of prescription (*pro re nata* or not). The date of service information is specified up to the month and year.

This study has been approved by the Ethics Committee of Kyoto University Graduate School of Medicine, Kyoto, Japan.

### 2.2. Study cohort

Based on this JMDC database, we defined our study cohort as follows in order to focus on new BZD users.

- i) The patients were registered with health insurance societies contributing claims to the JMDC database at least once between January 1st 2005 to June 30th 2014.
- ii) Outpatients
- iii) Aged 18 or older
- iv) They were prescribed BZD *per os* after they had not used any type of BZD for at least one year.
- v) Prescription of any one of the following BZDs and BZD-related drugs such as Z-drugs: alprazolam, bromazepam, chlordiazepoxide, clorazepate dipotassium, clonazepam, clobazepam, diazepam, ethyl loflazepate, etizolam, fludiazepam, flutazolam, flutoprazepam, hydroxyzine, hydroxyzine pamoate, lorazepam, medazepam, mexazolam, oxazolam, prazepam, tandospirone citrate, tofisopam, brotizolam, estazolam, flunitrazepam, flurazepam, haloxazolam, lormetazepam,

nimetazepam, nitrazepam, quazepam, rilmazafone, triazolam, zolpidem, zopiclone and eszopiclone. These drugs are categorized according to the ATC system as ATC-codes N03A, N05B and N05C and represent all the relevant drugs that have been approved for medical prescription in Japan.

### 2.3. Continuation of BZD use

We used two definitions of BZD continuation. The first definition of BZD continuation was at least one prescription for BZD within three months (Ishigooka et al., 1998; Veronese et al., 2007). This definition focused on heavy users who were likely to use BZD continuously and regularly. The three-month time window was chosen because prescription of BZD is restricted to 30 days or 90 days, depending on the product, of supply in Japan. The second definition of BZD continuation was at least one prescription of oral BZD within 12 months (Isacson, 1997; van Hulst et al., 2003). This definition would include not only heavy users but also non-continuous but repeated *prn* users. Not satisfying this definition would mean that the patients were able to stop BZD completely.

We followed the patients up to June 30th, 2014.

### 2.4. Potential predictors of long-term BZD use

We examined the following potential predictors for each of the above two definitions: sex, age (18–34, 35–49, 50–64, 65≤) (Olsson et al., 2015), medical specialty (psychiatrist-prescriber or non-psychiatrist-prescriber), diagnosis with any psychiatric disorder, dose of BZD (defined daily dose (DDD); 0.1, 0.1–0.5, 0.5≤), type of BZD (anxiolytic, hypnotic, or both), half-life of BZD (short (< 12 h), medium (12–24 h), or long (24 h≤)) (Barbone et al., 1998; Passaro et al., 2000), regular vs as needed, and concomitant psychotropic drugs (antipsychotic drug, antidepressant or mood stabilizer). When one patient had multiple diagnoses of mental disorders, we employed the diagnostic hierarchy giving preference to psychotic disorders over affective disorders, and affective disorders over anxiety disorders. In order to obtain DDD, we first converted the total dose divided by prescription days in the index month into diazepam equivalent according to Inada et al. (Inada and Inagaki, 2015), because some BZDs are unique to the Japanese market and do not have defined DDD. Then this diazepam equivalent was divided by 10 mg, which is the DDD of diazepam, and the results were expressed as DDD for each drug. We obtained the data on half-life of BZD from a drug information booklet called the interview form provided by the pharmaceutical companies. When patients used more than one BZD with different half-lives at the index month, the longest half-life was chosen. When patients used BZDs both regularly and as needed, they were classified as regular use.

In order to examine the differences among BZD drugs, we also investigated the time to discontinuation of the 15 most frequency prescribed BZD.

### 2.5. Statistical analyses

The following two analyses were conducted for each of the two definitions of BZD continuation. First, we generated Kaplan-Meier survival curves for continuation of BZD. Time zero was the first month of the BZD prescription. The event was discontinuation of BZD prescription. When the participants were not prescribed BZD during the course of three months or one year, we took the month of last BZD prescription as the BZD discontinuation date. An observation was censored if no event had occurred by the end of the observation period.

Next, we used Cox proportional hazards regression models to examine associations between the potential predictors and the

incidence of discontinuation. We used univariate Cox proportional hazards models to obtain unadjusted hazard ratio (HR) for each potential predictor. In addition, we used multivariate Cox proportional hazards models to calculate HR for prescription patterns of BZD while adjusting for patient's age, sex and psychiatric morbidity as well as the medical specialty, in order to examine which prescription patterns were contributing to chronic use. All the identified potential predictors were then entered simultaneously into a multivariate model to ascertain mutually independently influential predictors. Multicollinearity among the included variables was examined through variance inflation factors (VIF). VIFs greater than 4 are usually interpreted to indicate excessive or serious multicollinearity (O'Brien, 2007). We tested the proportional hazards assumption for the model by examination of the log minus log plots for all potential predictors. We also obtained unadjusted and adjusted estimates for each BZD in comparison with all the other BZDs. Statistical significance was set at two-sided  $P < 0.05$ . We undertook all analyses by using SPSS version 22.0 and Stata/IC 12.1. There were no missing data.

### 3. Results

#### 3.1. Patient characteristics

A total of 138,599 people were identified as new BZD user. When we excluded children less than 18 years old or inpatients, 84,412 people were included in our cohort. Table 1 presents the baseline demographic and clinical characteristics of our patients. 88.5% of the patients were received their BZD prescriptions from non-psychiatrists. About half the patients (49.6%) had psychiatric diagnoses, and a quarter (23.7%) received concomitant psychotropic medications. The most often prescribed BZD was etizolam, followed by zolpidem, brotizolam, clonazepam, and alprazolam.

#### 3.2. Continuation of BZD use

Fig. 1 illustrates Kaplan–Meier curve of the probability of continuing receiving at least one BZD prescription within three months. Follow-up periods ranged from one month to 107 months. 16,813 (19.9%) people were censored, of whom 246 (0.3%) died, 8317 (9.9%) were disenrolled from the health insurance before stopping BZD or before end of the observation, and 8250 (9.8%) reached the end of the observation before stopping BZD. 46.1% of new BZD users continued in the second month. The proportion of the BZD continuation was 35.8% in the third month, 19.8% in the sixth month, and 15.2% in the first year, respectively. 4.7% developed long-term use for a duration of eight years.

Fig. 2 illustrates Kaplan–Meier curve of the probability of continuing receiving at least one BZD prescription within one year. 39,803 (47.2%) people were censored, of whom 397 (0.5%) people died and 18,685 (22.1%) were disenrolled from the health insurance before stopping BZD or before end of the observation, and 20,721 (24.5%) people still continued to use BZD at the end of the observation period. 65.5% of new BZD user continued in the second month. The proportion of the BZD continuation was 58.6% in the third month, 46.7% in the sixth month, and 39.5% in the first year, respectively. 19.6% developed long-term use for a duration of eight years. In other words, 34.5% of new BZD users were able to stop BZD use completely by two months, 41.4% by three months, 53.3% by six months, 60.5% by one year, and 80.4% by eight years.

#### 3.3. Potential predictors

Table 2 shows factors associated with time to BZD discontinuation. Based on both unadjusted and adjusted Cox

**Table 1**  
Demographic and clinical characteristics of the cohort.

Characteristic (n=84412)			
Sex, no. (%)			
	Female	43559	(51.6)
	Male	40853	(48.4)
Age, year			
	Mean (SD)	42	(12.7)
	Range	18–75	
Age group, no. (%)			
	18–35	28081	(33.2)
	35–50	33919	(40.2)
	50–65	19479	(23.1)
	65≤	2933	(3.5)
Medical specialty, no. (%)			
	Non-psychiatry	74716	(88.5)
	Psychiatry	9696	(11.5)
Setting, no (%)			
	Hospital	29512	(35.0)
	Clinic	54900	(65.0)
Psychiatric diagnosis, no. (%)			
	Non-psychiatric disorders	42502	(50.4)
	Any psychiatric disorders	41910	(49.6)
	Alcohol use disorders	189	(0.2)
	Psychotic disorders	1629	(1.9)
	Affective disorders	18043	(21.3)
	Anxiety disorders	21048	(24.9)
Dose of BZD, n (%)			
	DDD < 0.1	33033	(39.1)
	0.1≤DDD < 0.5	38909	(46.1)
	0.5≤DDD < 1	9207	(10.1)
	1≤DDD	3263	(3.7)
Type of BZD, no. (%)			
	Anxiolytic	48555	(57.5)
	Hypnotic	27682	(32.8)
	Both	8175	(9.7)
Half-life of BZD <sup>†</sup> , n. (%)			
	Short (< 12 h)	52612	(62.3)
	Medium (12–24 h)	9041	(10.7)
	Long (24 h≤)	22759	(27.0)
Regular vs as needed, no. (%)			
	As needed	21037	(24.9)
	Regular use	63375	(75.1)
Concomitant psychotropic drug, no.			
	No psychotropic drug	64447	(76.3)
	Any psychotropic drug	19965	(23.7)
	Antipsychotic drug <sup>**</sup>	9211	(10.9)
	Antidepressants <sup>**</sup>	13602	(16.1)
	Mood stabilizers <sup>**</sup>	1549	(1.8)

BZD, benzodiazepine; DDD, daily defined dose.

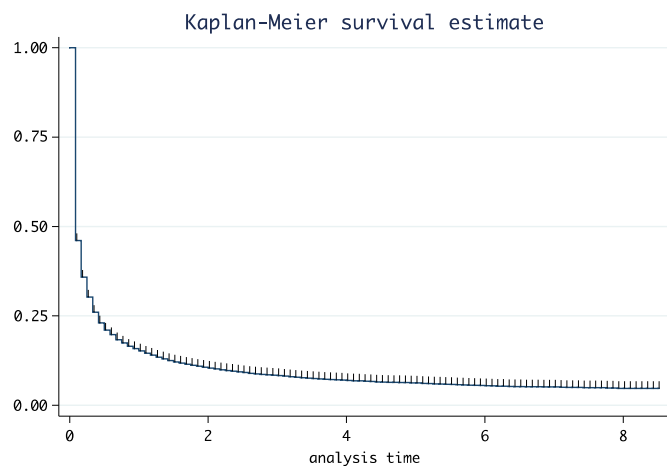
<sup>†</sup> When patients used more than one BZD with different half-lives, the longest one was chosen.

<sup>\*\*</sup> Due to some patients, receiving two or more drugs, the sum is greater than 23.7%.

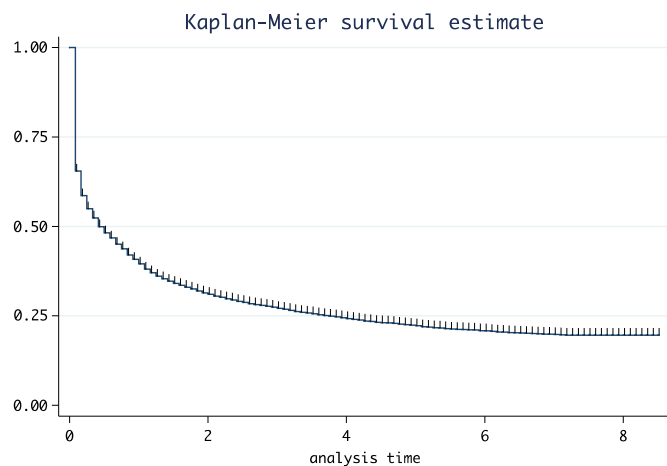
regression analysis, male, at least 65 years old, psychiatrist-prescriber (rather than non-psychiatrist-prescriber), any psychiatric disorders (rather than non-psychiatric disorders), high dose of BZD, hypnotic (rather than anxiolytic only), medium or long half-life of BZD, regular use (rather than as needed), and concomitant psychotropic drugs were significantly associated with continued use without ever attaining three months of no prescription.

The same predictors emerged for continued use without ever attaining 12 months of no prescription, both in the unadjusted and adjusted Cox regression analyses.

Furthermore, we entered all the identified potential predictors simultaneously into multivariate Cox regression analyses in order to examine mutually independent predictors. In the two definitions of BZD continuation, at least 65 years old, psychiatrist-prescriber, any psychiatric disorders, high dose of BZD, hypnotic, medium or long half-life of BZD, concomitant psychotropic drugs and clinic setting remained statistically significant. Only male and



**Fig. 1.** Kaplan–Meier survival estimate indicates the probability of receiving at least one BZD prescription within three months. Unit of the horizontal axis is year. Censored patients are marked as a vertical line.



**Fig. 2.** Kaplan–Meier survival estimate indicates the probability of receiving at least one BZD prescription within one year. Unit of the horizontal axis is year. Censored patients are marked as a vertical line.

regular use did not remain statistically significant. Therefore the confirmed predictors were at least 65 years old, psychiatrist-prescriber, any psychiatric disorders, high dose of BZD, hypnotic, medium or long half-life of BZD, concomitant psychotropic drugs and clinic setting.

In order to examine the potential correlations among the entered variables, we calculated variance inflation factors (VIFs), all of which were below 3 (max=1.77, mean=1.34) and did not suggest multicollinearity (O'Brien, 2007).

Log-minus-log plot for all potential predictors indicated that the analyses did not violate the proportionality assumption.

#### 3.4. Subgroup analyses limited to psychiatric disorders

Because having psychiatric disorders was the confirmed predictors, we excluded non-psychiatric disorders and further analyzed BZD chronic use.

The number of the participants with psychiatric disorders was 41910. 6.1% turned out to be continuous BZD users over eight years without ever attaining three months of no BZD prescription. 22.6% turned out to be continuous users over eight years without ever attaining one year of no BZD prescription.

Based on both unadjusted and adjusted Cox regression analyses, male, 35–50 years old, psychiatrist-prescriber, clinic setting, any psychiatric disorders, high dose of BZD, hypnotic, medium or

long half-life of BZD, regular use, and concomitant psychotropic drugs were significantly associated with continued use without ever attaining three months of no prescription. On the other hand, the same predictors other than age were significantly associated with continued use without ever attaining 12 months of no prescription. In this definition of the BZD continuation, the predictors of the age group were 35 to 50, 50–65 and at least 65 years old (Supplementary Table 1).

Furthermore, we compared the differences among psychiatric disorders (including psychotic disorders, affective disorders, anxiety disorders, and alcohol use disorders) directly (Supplementary Table 2).

#### 3.5. Differences among BZDs

The 15 most frequently used BZD and these unadjusted and adjusted HR were listed in Table 3. Diazepam, rilmazafone and tofisopam were more likely to be discontinued than the other BZDs, while the others, in particular flunitrazepam, were less likely so.

## 4. Discussion

To the best of our knowledge, this is the first cohort study to focus on new onset long-term BZD use in a nationwide sample extending over several years. 19.8% of the new BZD users continued use of BZD up to 6 months, 15.2% up to 1 year, and 4.9% turned out to be continuous users over eight years without ever attaining three months of no BZD prescription. On the other hand, excluding both continuous and occasional users, we saw that 34.5% of new BZD users were able to stop BZD use completely by two months, 53.3% by six months, 60.5% by one year and 80.4% by eight years. For both definitions of BZD use, we identified the following predictors for long term BZD use: older age, psychiatrist-prescriber (rather than non-psychiatrist-prescriber), any psychiatric disorders (rather than non-psychiatric disorders), high dose of BZD, hypnotic (rather than anxiolytic only), medium or long half-life of BZD, regular use (rather than as needed), and concomitant psychotropic drugs.

#### 4.1. Comparison with the previous literature

The frequencies of continued BZD use at around one follow-up year reported in previous studies ranged widely for two reasons (Isacson, 1997; Veronese et al., 2007; Kjosavik et al., 2012). Firstly, there were various definitions of long-term BZD use in previous studies. For example, Simon et al. defined long-term BZD use as use for at least 60 days at a rate of at least one pill per day (Simon et al., 1996), while Isacson defined a BZD user as an individual who obtained at least one prescription for benzodiazepines during the course of one year (Isacson, 1997). Secondly, the demographic characteristics of the included subjects in previous studies also differed widely. Veronese et al. focused on both inpatients and outpatients in South Verona only and defined new BZD user as a prescription without any recorded benzodiazepine treatment in the previous 3 months (Veronese et al., 2007). Gray et al. focused on elderly people (Gray et al., 2003). In the following we compare our findings with those of previous studies with similar characteristics. From the perspective of heavy BZD use, there is one nationwide study which used a definition similar to ours (Kjosavik et al., 2012). The result of this study was close to our figure at one-year follow-up (15.2% in our study vs 11.8% in the previous study). From the perspective of both regular and non-regular continued BZD users, one study used the same definition as ours (Isacson 1997). The result of this study was also similar to our figure at one-



**Table 2**  
Factors associated with time to BZD discontinuation (Cox regression analysis).

Factor	No BZD prescription within 3 months				No BZD prescription within 1 year			
	Unadjusted		Adjusted <sup>b</sup>		Unadjusted		Adjusted <sup>b</sup>	
	HR <sup>a</sup>	P value	HR <sup>a</sup>	P value	HR <sup>a</sup>	P value	HR <sup>a</sup>	P value
Sex								
Female	(Reference)				(Reference)			
Male	0.91 (0.89–0.92)	< 0.001*			0.96 (0.95–0.98)	< 0.001*		
Age group								
18–35	(Reference)				(Reference)			
35–50	1.00 (0.98–1.01)	0.648			1.01 (0.99–1.03)	0.294		
50–65	1.00 (0.98–1.02)	0.849			0.92 (0.89–0.94)	< 0.001*		
65≤	0.89 (0.86–.94)	< 0.001*			0.68 (0.64–.72)	< 0.001*		
Medical Specialty								
Non-psychiatry	(Reference)				(Reference)			
Psychiatry	0.65 (0.63–0.66)	< 0.001*			0.62 (0.60–0.64)	< 0.001*		
Setting								
Hospital	(Reference)				(Reference)			
Clinic	0.83 (0.82–0.85)	< 0.001*			0.81 (0.80–0.83)	< 0.001*		
Psychiatric diagnosis								
Non-psychiatric disorders	(Reference)				(Reference)			
Any psychiatric disorders	0.70 (0.69–0.71)	< 0.001*			0.71 (0.69–0.72)	< 0.001*		
Alcohol use Disorders	0.59 (0.49–0.70)	< 0.001*			0.57 (0.45–0.72)	< 0.001*		
Psychotic Disorders	0.52 (0.49–0.56)	< 0.001*			0.50 (0.46–0.54)	< 0.001*		
Affective Disorders	0.58 (0.56–0.59)	< 0.001*			0.60 (0.58–0.61)	< 0.001*		
Anxiety Disorders	0.85 (0.84–0.87)	< 0.001*			0.85 (0.83–0.86)	< 0.001*		
Dose of BZD								
DDD < 0.1	(Reference)		(Reference)		(Reference)		(Reference)	
0.1≤DDD < 0.5	0.68 (0.67–0.69)	< 0.001*	0.73 (0.72–0.75)	< 0.001*	0.67 (0.66–0.69)	< 0.001*	0.73 (0.72–0.75)	< 0.001*
0.5≤DDD	0.42 (0.41–0.43)	< 0.001*	0.48 (0.47–0.50)	< 0.001*	0.42 (0.41–0.44)	< 0.001*	0.48 (0.47–0.50)	< 0.001*
Type of BZD								
anxiolytic	(Reference)		(Reference)		(Reference)		(Reference)	
hypnotic	0.95 (0.94–0.97)	< 0.001*	0.86 (0.85–0.88)	< 0.001*	0.88 (0.86–0.89)	< 0.001*	0.78 (0.77–0.80)	< 0.001*
both	0.60 (0.58–0.61)	< 0.001*	0.68 (0.66–0.70)	< 0.001*	0.60 (0.58–0.62)	< 0.001*	0.70 (0.67–0.72)	< 0.001*
Half-life of BZD								
short (< 12 h)	(Reference)		(Reference)		(Reference)		(Reference)	
medium (12–24 h)	0.64 (0.63–0.66)	< 0.001*	0.74 (0.72–0.76)	< 0.001*	0.61 (0.59–0.63)	< 0.001*	0.70 (0.68–0.73)	< 0.001*
long (24 h≤)	0.76 (0.75–0.78)	< 0.001*	0.82 (0.81–0.84)	< 0.001*	0.77 (0.75–0.79)	< 0.001*	0.82 (0.80–0.84)	< 0.001*
Regular vs as needed								
As needed	(Reference)		(Reference)		(Reference)		(Reference)	
Regular use	0.78 (0.77–0.80)	< 0.001*	0.82 (0.81–0.84)	< 0.001*	0.86 (0.84–0.88)	< 0.001*	0.91 (0.89–0.93)	< 0.001*
Concomitant psychotropic drug								
No psychotropic drug	(Reference)		(Reference)		(Reference)		(Reference)	
Any psychotropic drug	0.62 (0.60–0.63)	< 0.001*	0.70 (0.69–0.72)	< 0.001*	0.62 (0.60–0.63)	< 0.001*	0.73 (0.71–0.75)	< 0.001*
Antipsychotic drug	0.63 (0.61–0.64)	< 0.001*	0.74 (0.72–0.76)	< 0.001*	0.65 (0.63–0.67)	< 0.001*	0.77 (0.75–0.80)	< 0.001*
Antidepressants	0.57 (0.56–0.58)	< 0.001*	0.67 (0.65–0.69)	< 0.001*	0.59 (0.58–0.61)	< 0.001*	0.70 (0.68–0.73)	< 0.001*
Mood Stabilizers	0.64 (0.60–0.68)	< 0.001*	0.71 (0.67–0.76)	< 0.001*	0.59 (0.54–0.64)	< 0.001*	0.65 (0.60–0.71)	< 0.001*

BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval; DDD, daily defined dose

\*Significant when  $P < 0.05$ .

<sup>a</sup> HR is a relative speed toward discontinuation of BZD, small number indicates that patients are likely to continue BZD.

<sup>b</sup> Adjusted for age, sex, medical speciality, setting, psychiatric diagnosis.

year follow-up (39.5% in our study vs 43.5% in the previous study).

On the other hand, there are few studies with more than three years of follow-up. Only one study had an eight-year follow-up and examined both regular and non-regular continuous BZD users defined as: our figure was nearly twice their figure (19.6% in our study vs 11.5% at eight years) (9194248). This is probably because many patients in this study were lost to follow-up and the study was limited to a semi-rural areas. There is no study focusing on heavy BZD users with more than three years of follow-up.

As expected, we confirmed that incident long-term BZD use was associated with older age, high dose of BZD and regular use at first prescription. Two former predictors were consistent with earlier researches (Holm, 1990; Ishigooka et al., 1998; Manthey et al., 2011). One previous study also found regular prescription to be a predictor of continuous use (Isacson, 1997).

We also found psychiatrist-prescriber, diagnosis with any psychiatric disorder and concomitant psychotropic drugs were predictors for long term BZD use. Patients with more severe

symptoms may go to psychiatry specialist and be diagnosed with a psychiatric disorder and be prescribed concomitant psychotropic drugs more often. It is possible that severe symptoms would be related with long term BZD use. One study did not find concomitant psychotropic drug use to be a predictor (Veronese et al., 2007). This is probably due to the fact that this study focused on psychiatrists only.

Hypnotics posed a higher risk of long-term BZD use than anxiolytics, consistent with an earlier study (Barnas et al., 1993). However, we found that different BZDs were associated with different risks even when they were of the same type. The particularity for diazepam remains puzzling. In the present study, diazepam was more likely to be discontinued. Diazepam is an anxiolytic BZD with long half-life. This may suggest that the half-life of BZD is a weaker, albeit independently significant, predictor of chronic use than the type of BZD. Clinicians therefore should pay heed to the characteristics of each BZD.

**Table 3**  
Time to BZD discontinuation for the 15 most frequency prescribed BZD, in the decreasing order of frequency (Cox regression analysis).

	Type	Half-life	No BZD prescription within 3 months						No BZD prescription within 1 year					
			Unadjusted			Adjusted <sup>b</sup>			Unadjusted			Adjusted <sup>b</sup>		
			HR <sup>a</sup>	95% CI	P value	HR <sup>a</sup>	95% CI	P value	HR <sup>a</sup>	95% CI	P value	HR <sup>a</sup>	95% CI	P value
Etizolam	Anxiolytic	Short	0.99	(0.98–1.01)	0.395	1.00	(0.98–1.02)	0.773	1.02	(1.00–1.05)	0.040	1.02	(1.00–1.05)	0.034 <sup>*</sup>
Zolpidem	Hypnotic	Short	0.93	(0.92–0.95)	< 0.001 <sup>*</sup>	0.87	(0.86–0.89)	< 0.001 <sup>*</sup>	0.86	(0.84–0.88)	< 0.001 <sup>*</sup>	0.82	(0.79–0.84)	< 0.001 <sup>*</sup>
Brotizolam	Hypnotic	Short	0.82	(0.80–0.83)	< 0.001 <sup>*</sup>	0.83	(0.81–0.85)	< 0.001 <sup>*</sup>	0.81	(0.78–0.83)	< 0.001 <sup>*</sup>	0.82	(0.80–0.85)	< 0.001 <sup>*</sup>
Clotiazepam	Anxiolytic	Short	0.96	(0.94–0.98)	0.001 <sup>*</sup>	1.03	(1.00–1.05)	0.04 <sup>*</sup>	1.00	(0.97–1.03)	0.925	1.07	(1.04–1.10)	< 0.001 <sup>*</sup>
Alprazolam	Anxiolytic	Short	0.82	(0.80–0.84)	< 0.001 <sup>*</sup>	0.96	(0.93–0.99)	0.003 <sup>*</sup>	0.81	(0.78–0.84)	< 0.001 <sup>*</sup>	0.93	(0.90–0.97)	< 0.001 <sup>*</sup>
Diazepam	Anxiolytic	Long	1.28	(1.24–1.31)	< 0.001 <sup>*</sup>	1.19	(1.16–1.22)	< 0.001 <sup>*</sup>	1.38	(1.34–1.43)	< 0.001 <sup>*</sup>	1.29	(1.25–1.33)	< 0.001 <sup>*</sup>
Ethyl loflazepate	Anxiolytic	Long	0.79	(0.77–0.82)	< 0.001 <sup>*</sup>	0.92	(0.89–0.95)	< 0.001 <sup>*</sup>	0.83	(0.80–0.86)	< 0.001 <sup>*</sup>	0.95	(0.91–0.99)	0.006 <sup>*</sup>
Lorazepam	Anxiolytic	Medium	0.75	(0.72–0.78)	< 0.001 <sup>*</sup>	0.90	(0.87–0.94)	< 0.001 <sup>*</sup>	0.70	(0.67–0.74)	< 0.001 <sup>*</sup>	0.83	(0.78–0.87)	< 0.001 <sup>*</sup>
Zopiclone	Hypnotic	Short	0.98	(0.94–1.02)	0.300	0.92	(0.87–0.96)	< 0.001 <sup>*</sup>	0.90	(0.85–0.94)	< 0.001 <sup>*</sup>	0.85	(0.80–0.89)	< 0.001 <sup>*</sup>
Rilmazafone	Hypnotic	Short	1.20	(1.15–1.25)	< 0.001 <sup>*</sup>	1.06	(1.02–1.11)	0.008 <sup>*</sup>	1.22	(1.16–1.29)	< 0.001 <sup>*</sup>	1.08	(1.03–1.14)	0.003 <sup>*</sup>
Triazolam	Hypnotic	Short	0.82	(0.78–0.85)	< 0.001 <sup>*</sup>	0.82	(0.78–0.86)	< 0.001 <sup>*</sup>	0.79	(0.73–0.82)	< 0.001 <sup>*</sup>	0.79	(0.74–0.83)	< 0.001 <sup>*</sup>
Tofisopam	Anxiolytic	Short	1.18	(1.13–1.24)	< 0.001 <sup>*</sup>	1.04	(0.99–1.09)	0.092	1.24	(1.18–1.31)	< 0.001 <sup>*</sup>	1.12	(1.06–1.18)	0.034 <sup>*</sup>
Bromazepam	Anxiolytic	Short	0.71	(0.67–0.75)	< 0.001 <sup>*</sup>	0.86	(0.81–0.90)	< 0.001 <sup>*</sup>	0.70	(0.65–0.74)	< 0.001 <sup>*</sup>	0.82	(0.77–0.88)	< 0.001 <sup>*</sup>
Flunitrazepam	Hypnotic	Medium	0.56	(0.53–0.59)	< 0.001 <sup>*</sup>	0.66	(0.62–0.70)	< 0.001 <sup>*</sup>	0.55	(0.51–0.59)	< 0.001 <sup>*</sup>	0.64	(0.59–0.69)	< 0.001 <sup>*</sup>
Clonazepam	Anxiolytic	Long	0.81	(0.76–0.86)	< 0.001 <sup>*</sup>	0.81	(0.76–0.86)	< 0.001 <sup>*</sup>	0.77	(0.72–0.83)	< 0.001 <sup>*</sup>	0.77	(0.72–0.83)	< 0.001 <sup>*</sup>

BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval.

<sup>\*</sup>Significant when  $P < 0.05$ .

<sup>a</sup> HR is a relative speed toward discontinuation of BZD, small number indicates that patients are likely to continue BZD. Each BZD was compared with all other drugs except each BZD.

<sup>b</sup> Adjusted for age, sex, medical speciality, setting, psychiatric diagnosis

#### 4.2. Limitations and strengths

This cohort study is not without some methodological problems. First of all, JMDC's data included very few people 75 years and older because in Japan most of such elderly people enroll in the Late Elders' Health Insurance of their local government that JMDC does not cover (Ikegami et al., 2011). In view of our finding that older age was a predictor of BZD continuation, the frequency of overall BZD continued use may be underestimated in our study. Second, in the claims database analyses, we were unable to evaluate the severity of symptoms and their course. Nevertheless presence of any psychiatric disorder, concomitant psychotropic drug or psychiatrist-prescriber, which may be taken as a proxy indicator of the severity of symptom at the index month, were found to predict longer BZD use. Third, our data concern dispensed prescriptions and not necessarily actually consumed prescriptions. The patients may not consume BZD as instructed. We had to use the data in the JMDC database as proxy measures for drugs consumed by the patients. Fourth, we were not able to investigate all potential predictors such as socioeconomic status and substance dependence. Socioeconomic status of the subjects in our dataset may be considered relatively homogeneous as they are all company employees and their dependents. Fifth, there is a possibility that the potential predictors such as dose of BZD and type of BZD change gradually over time. However, from the clinical point of view, we analyzed the relationship between how to prescribe BZD for the first time and subsequent chronic BZD use. In the future, we need further studies to consider time-varying factors including changes in dose and type of BZD, concomitant use of other psychotropic drugs, prescriber/setting or diagnosis. Sixth, Painful and/or stressful physical comorbidities may contribute to the long term use of BZD. However, the claims database we used only lists the names of physical diagnoses as variable as psoriasis, nasal sinusitis, heart failure, cancers, or hypertension, just to mention a few of thousands of diagnostic terms, and it is almost impossible to distinguish painful and/or stressful conditions based on these descriptions only.

The strength of our research is its high generalizability for three reasons. First, our study is based on a large nationwide claims database extending over long time periods. Second, thanks to the

nature of the claims being associated with health insurance with the company, we were able to follow up patients even if they changed clinics or hospitals so long as their health insurance was registered with the same company. Lastly, our cohort contained both psychiatric and non-psychiatric patients. We therefore assume that our results apply to various conditions and situations.

#### 4.3. Clinical and research implications

We were able to estimate the frequency of continuous BZD use at longer follow-up with more precision and to confirm some predictors, particularly, older age, regular use, high dose of BZD, and concomitant psychotropic drug, for the continued BZD use. When short-term benefits appear to outweigh short-term harms and long-term risks, doctors would be advised to take into consideration the predictors as to type of medications and mode of prescriptions as confirmed in the present study in making their first prescriptions of BZD for each patient.

From a research perspective, it must be remembered that the predictors as elucidated in the present study are only observational in nature and we need intervention studies to establish which medications by which modes of prescription would maximize the benefit-risk ratio for which types of patients, both in the short term and in the long term.

#### 4.4. Conclusions

Over the course of 8-year follow-up after first BZD prescription, 1 in 20 new-onset BZD users continued to use BZD as continuous user, while 4 in 5 new-onset BZD users were able to stop BZD use completely. The strong predictors for long-term BZD use included older age, regular use, high dose of BZD, and concomitant psychotropic drug prescription.

#### Contributors

N.T and T.A.F conceived and designed the study. N.T ran the analyses. N.T, T.A.F, Y.O, Y.H interpreted the data. N.T drafted the manuscript. T.A.F, Y.O and Y.H commented on drafts of the

manuscript. N.T and T.A.F revised the manuscript. N.T takes responsibility for the overall integrity of the data and the accuracy of the data analysis. T.A.F is the guarantor.

### Conflict of interest

TAF reported having received lecture fees from Eli Lilly and Co, Meiji, Mochida, MSD, Pfizer, and TanabeMitsubishi, consultancy fees from Sekisui and Takeda Science Foundation, royalties from Igaku-Shoin, Seiwa-Shoten, and Nihon Bunka Kagaku-sha, and research project funding from the Japanese Ministry of Education, Science, and Technology, the Japanese Ministry of Health, Labor, and Welfare, and the Japan Foundation for Neuroscience and Mental Health, and he is a diplomate of the Academy of Cognitive Therapy.

Other authors declare no conflict of interest.

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### Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.psychres.2016.01.040>.

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