Psychiatry Research 237 (2016) 201–207

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

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

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ARTICLE INFO

Article history:
Received 29 March 2015
Received in revised form
15 October 2015
Accepted 15 January 2016
Available online 16 January 2016

Keywords:
Benzodiazepine
Long-term use
Longitudinal study
Kaplan-Meier survival analysis

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.

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, λ). 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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http://dx.doi.org/10.1016/j.psychres.2016.01.040
0165-1781/

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 Hulten 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, clotiazepam, cloxazolam, 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 Hulten 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≦) (Olfson 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 the15 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