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Prevalence, prescribed quantities, and trajectory of multiple prescriber episodes for benzodiazepines: A 2-year cohort study[☆]Yasuyuki Okumura^{a,*}, Sayuri Shimizu^a, Toshihiko Matsumoto^b^a Research Department, Institute for Health Economics and Policy, Association for Health Economics Research and Social Insurance and Welfare, 11 Toyo Kaiji Bldg. 2F, 1-5-11 Nishishimbashi, Minato-ku, Tokyo 105-0003, Japan^b Department of Drug Dependence Research/Center for Suicide Prevention, National Institute of Mental Health, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-Higashi cho, Kodaira, Tokyo 187-8553, Japan

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ABSTRACT

Background: Little is known about the use of multiple prescribers for benzodiazepines, which might reflect fragmented patient care and increases the risk of hospital admission for drug dependence or poisoning. Therefore, we aimed to identify the prevalence, prescribed quantities, and trajectory of multiple prescriber episodes for benzodiazepines.

Methods: We conducted a 2-year cohort study of 1178,361 recipients aged 0–74 years using a large health insurance claims database in Japan. We quantified multiple prescriber episodes for benzodiazepines occurring in ambulatory care settings in a baseline and subsequent year by (1) counting the number of unique providers within a 12-month period, (2) calculating the maximum number of unique providers within a single month, and (3) identifying consecutive overlapping prescriptions of over 30 days duration. **Results:** Among 58,314 patients with a benzodiazepine prescription during the baseline year, 282 (0.5%) filled prescriptions from four or more providers within a 12-month period, 439 (0.8%) filled prescriptions from three or more providers within a single month, and 757 (1.3%) filled consecutive overlapping prescriptions. The odds for multiple prescriber episodes were significantly higher among patients with multiple chronic conditions. Consecutive overlapping prescriptions had the best accuracy to detect patients with potentially questionable prescribed quantities as well as to predict those with multiple prescriber episodes in the subsequent year.

Conclusions: These results highlight the need for pharmacists to increase their involvement in prescription oversight and for health insurance agencies to implement a prescription monitoring program to screen for patients with multiple prescriber episodes for benzodiazepines.

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1. Introduction

Multiple prescriber behavior refers to the behavior wherein a person obtains prescriptions for the same medication from multiple healthcare providers (Jena et al., 2014). The use of multiple prescribers might reflect doctor shopping behavior, which is similarly but more specifically defined as obtaining prescriptions from several physicians for the same medication at the same time (Pradel et al., 2009). However, it might also reflect fragmented patient care that could arise when patients either substituted physicians, filled prescriptions from somewhere other than their customary provider, or received treatment from special settings (e.g., an

emergency room; Jena et al., 2014; Wilsey et al., 2010). Multiple prescriber behavior is therefore not a problem per se and is legitimate; a patient has a right to seek the best healthcare service available.

There are, however, several concerns about the potential risks of multiple prescriber behavior as well as doctor shopping behavior. Multiple prescriber behavior has been associated with an increased risk of hospital admissions owing to drug dependence or drug poisoning (Jena et al., 2014). Doctor shopping behavior in turn is regarded as not only a means of obtaining high-dose prescriptions but as the principal method of diversion of prescription medications to street markets (Inciardi et al., 2007; Pradel et al., 2009). Doctor shopping behavior has also been linked to the incidences of overdose (Okumura et al., 2015b) and death by overdose (Hall et al., 2008; Martyres et al., 2004).

In the literature on multiple prescriber episodes, most studies have focused on opioids and were conducted in the United States and France (Cepeda et al., 2012; Gilson et al., 2012; Han et al., 2012,

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2014; Jena et al., 2014; McDonald and Carlson, 2014; Nordmann et al., 2013; Pauly et al., 2011b, 2012; Pradel et al., 2009, 2004; Wilsey et al., 2011, 2010). Less attention has been paid to other medications such as benzodiazepines (Cepeda et al., 2012; Frauger et al., 2011; Ong et al., in press; Pauly et al., 2011a, 2012; Pradel et al., 2010; Wilsey et al., 2010), stimulants (Cepeda et al., 2014; Wilsey et al., 2010), and diuretics (Cepeda et al., 2012).

To investigate multiple prescriber episodes in Japan, the focus should be on benzodiazepines rather than opioids because of their consumption levels. The consumption level for opioids expressed in morphine equivalents was much lower in Japan (118 g/million inhabitants/day) than those reported in the United States (1776 g/million inhabitants/day) and France (711 g/million inhabitants/day) (Foundation for Promotion of Cancer Research, 2014). In contrast, the consumption level for benzodiazepines expressed in defined daily dose for statistical purposes [S-DDD] was much higher in Japan (46 S-DDD/1000 inhabitants/day) than those reported in the United States (8 S-DDD/1000 inhabitants/day) and France (15 S-DDD/1000 inhabitants/day) (International Narcotics Control Board, 2011). In addition, sedatives-hypnotics, most of which are benzodiazepines, were identified as the most prevalent classes of medications prescribed from three or more providers within a 1-month period for patients aged ≥ 15 years (Japan Health Insurance Association, 2012).

In Japan, there are 33 oral benzodiazepines and benzodiazepine-related drugs approved for the treatment of several symptoms such as sleep disorders, anxiety disorders, epilepsy, and muscle spasms (Supplementary Table S1). All benzodiazepines are prescription drugs and are reimbursed by public health insurance. The regulatory agency in Japan has restricted the maximum duration for a prescription of the 25 benzodiazepines controlled under the Narcotics and Psychotropics Control Law (Supplementary Table S1). However, because the healthcare system has been based on free access to any hospital with no gate keeping, patients can receive benzodiazepine prescriptions from any number of providers.

To date, most studies on multiple prescriber episodes have been conducted in Western countries, and few have quantified the differences between several criteria for multiple prescriber episodes (Pauly et al., 2011b) or have examined whether the use of multiple prescribers is associated with an increase in obtaining high-dose prescriptions (Han et al., 2014; Neutel et al., 2013). To the best of our knowledge, no study has quantified the repetition rate. Therefore, we aimed to identify the prevalence, prescribed quantities, and trajectory of multiple prescriber episodes for benzodiazepines through the quantification of multiple prescriber episodes using three distinct calculation methods.

2. Methods

2.1 Data source and study cohort

We conducted a 2-year cohort study using the large health insurance claims database developed by the Japan Medical Data Center (JMDC) Co. Ltd., Tokyo, Japan (Kimura et al., 2010; Ooba et al., 2013). The JMDC collects medical and pharmacy claims from more than 50 occupation-based public health insurance agencies for corporate employees and their family members. The database included 2258,704 recipients aged 0–74 years old as of October 2014, representing 2.0% of the population (Ministry of Health Labour and Welfare, 2015).

We included all recipients who were continuously enrolled in the database during the study period (October 1, 2012 through September 30, 2014). The study period was divided into 2 phases: baseline (between October 1, 2012 and September 30, 2013) and follow-up (between October 1, 2013 and September 30, 2014). To

validate prescriptions written before the baseline phase, all recipients were also required to have been active in their insurance plan from at least 6 months prior to the study period. Information in the database includes sex, age, medical institution codes, dispensing date, drug name, dosage, days supplied, and drug price.

2.2. Selection of benzodiazepines

We investigated 33 oral benzodiazepines and benzodiazepine-related drugs available in ambulatory care settings during the study period (Supplementary Table S1). Almost all recipients with a benzodiazepine prescription were recorded in the database, because all benzodiazepines are considered prescription rather than over-the-counter drugs and are reimbursed by public health insurance plans in Japan. During the study period, 26 drugs were listed as benzodiazepines based on the Anatomical Therapeutic Chemical (ATC) classification system (WHO Collaborating Centre for Drug Statistics Methodology, 2015): (1) benzodiazepine-derivative anxiolytics (N05BA), (2) benzodiazepine-derivative hypnotics and sedatives (N05CD), (3) benzodiazepine-derivative antiepileptics (N03AE), and (4) Z-drugs (N05CF). We also examined 7 benzodiazepines that were not covered by the ATC classification system but were approved for use by the regulatory agency in Japan including flutazolam, flutoprazepam, haloxazolam, mexazolam, nimetazepam, oxazolam, and rilmazafone.

2.3. Definition of multiple prescriber episodes

To quantify multiple prescriber episodes, we used three calculation methods, as follows.

2.3.1. Number of unique providers within a 12-month time window. We counted the number of unique benzodiazepine providers per patient within a 12-month time window. Multiple prescriber episodes were subdivided into two, three, and four or more providers. We note that this method might not necessarily reflect temporal or consecutive overlapping prescriptions from multiple providers. Rather, this might reflect fragmented patient care such as a change in the primary physician (Jena et al., 2014; Wilsey et al., 2010).

2.3.2. Maximum number of unique providers within 1-month time windows. We counted the number of unique benzodiazepine providers per patient within 1-month time windows. To identify single values for unique providers in the baseline and subsequent years, we selected for each patient the month in which the maximum value of unique providers was obtained. Multiple prescriber episodes were subdivided into groups of two and three or more providers. We note that this method is expected to reflect temporal and consecutive overlapping prescriptions from multiple providers.

2.3.3. Consecutive overlapping prescriptions lasting over a 30-day period. We identified patients with overlapping benzodiazepine prescriptions from two or more providers lasting more than a consecutive 30-day period (Fig. 1, Step 1–Step 3). To account for the delay incurred by refilling, we allowed a 7-day grace period between two consecutive prescriptions by the same provider to a single patient (i.e., between “the date of first prescription plus number of days supplied” and “the date of second prescription”). We note that this method might also reflect consecutive overlapping prescriptions from multiple providers.

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