Regular Prescriptions for Benzodiazepines: A Cross-Sectional Study of Outpatients at a University Hospital

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Abstract

Objective To investigate 1) the patterns of regular prescriptions for benzodiazepines among department clinics in a university teaching hospital, 2) the effects of patient’s characteristics on regular benzodiazepine prescriptions, and 3) the patterns of benzodiazepine prescriptions among department clinics from the perspective of pharmacological half-life.

Patients Patients were 22,099 outpatients (51% female; mean age: 56 years) who were prescribed any drug three or more times.

Methods Cross-sectional study of patient-based data (July 2002 to August 2003) from the database of a computer ordering system at a university hospital. The patterns of regular prescriptions for benzodiazepines were compared among the clinical departments (i.e., ‘Internal Medicine’, ‘Psychiatry’, and ‘Others’). A logistic regression model was used to assess the effects of patient gender and age, and the clinic visited on the issuing of regular prescriptions for benzodiazepines.

Results Regular benzodiazepine users were 3,204 (14.5%). Benzodiazepines were more likely to be prescribed for women (61.3%) than for men and were prescribed most often by psychiatrists (31.7%), followed by internists (20.1%). Multivariate logistic regression model showed that being female and elderly, and being prescribed by a psychiatrist were significantly associated with regular benzodiazepine prescriptions. With regard to the pharmacological half-life, internists were more likely to prescribe short half-life benzodiazepines than were psychiatrists (p < 0.001).

Conclusion A large number of outpatients at a Japanese university hospital appeared to be maintained on a regular supply of benzodiazepine drugs. Educational programs are needed to promote the rational prescribing of benzodiazepines.

Key words: age, benzodiazepines, female, pharmacological half-life, regular prescription, university hospital

Introduction

Benzodiazepines are known worldwide to be very useful psychotropic agents (1-4). Their therapeutic actions as anxiolytics, sedative hypnotics, anticonvulsants, and muscle relaxants have led to their use as first-line treatments, and they have become one of the most prescribed classes of drugs. About 2% of the adult populations of the USA (i.e., four million people) and UK (i.e., one million people) have been reported to use prescription benzodiazepine hypnotics or tranquilizers regularly for 12 or more months, with almost 50% of these subjects having used the drugs for five or more years (5). Benzodiazepines are remarkably useful drugs for psychological illnesses. However, with regular use, their benefits are outweighed by their adverse effects, which include the development of tolerance, psychomotor impairment, cognitive and memory changes, physical and pharmacological dependence, and withdrawal reactions upon discontinuation. Dependence usually develops within a few weeks or months of regular use, and withdrawal reactions, such as anxiety or sleep disturbance, occur when patients discontinue the drugs, making it very difficult for the majority of regular
benzodiazepine users to stop taking the medication (6-8). Those reports suggest that the patient characteristics of female gender and elderly affect the regular use of benzodia- zepines (6-8).

In 1999, the Teikyo University School of Medicine installed a computer ordering system (COS), which has been used to monitor drug prescriptions among various department clinics at the hospital. An analysis of the patterns of regular benzodiazepine prescriptions with respect to patient gender and age would enable us to compare the results with previous findings in Western countries (5-8) and to develop more rational schemes for prescribing benzodiazepines. Furthermore, given that dependency and withdrawal reactions are enhanced by the regular use of short half-life benzodiazepines (9), it is important to assess the regular prescription of benzodiazepines from the perspective of pharmacological half-life.

Hence, the purpose of the present study was three-fold: (i) to compare the patterns of regular prescriptions for benzodiazepines among department clinics at a university teaching hospital in Japan; (ii) to determine the effects of patient gender and age, and department clinic visited on regular prescriptions for benzodiazepines; and (iii) to compare the patterns of prescriptions for benzodiazepines among the different department clinics from the perspective of pharmacological half-life.

Subjects and Methods

Dataset and patients

A dataset (patient-based data) was developed from a COS database (prescription-based data) at Teikyo University Itabashi Hospital, Tokyo, Japan (1,154 hospitalized beds). This university teaching hospital has 21 department clinics, of which approximately 60,000 outpatients visit every year. Data syntheses were conducted using Access 2000 and SQL server 2000 (Microsoft, Inc., Japan). The prescriptions for benzodiazepines written for individual patients were identified according to the department clinics visited by the patients.

The subjects included in the dataset were outpatients who visited our hospital and were prescribed medicine by physicians between July 2002 and August 2003. Patients were excluded if they were younger than 15 years of age, were prescribed any drugs fewer than three times during one study year, or were prescribed benzodiazepines at two or more different clinics. Thus, the analysis included 22,099 patients (51% female) with a mean age of 56 ± 18 years (mean ± SD). For the purpose of the analyses, age was categorized into seven groups with 10-year intervals. However, because of the small sizes of their groups, the 15- to 19-year-old (y/o) subjects were combined with the 20-29 y/o subjects, and subjects >90 y/o were combined with the 80-89 y/o group.

The department clinics were categorized into three groups: ‘internal medicine’, ‘psychiatry’, and ‘others’. The psychiatry group included prescriptions by physicians at psychosomatic medicine clinic. During the study period, there were 190 prescribing physicians in the ‘internal medicine’ group, 60 in ‘psychiatry,’ and 441 in ‘others’. The number of prescriptions from the psychosomatic medicine clinic represented only 5.1% of the total number of prescriptions from the psychiatry clinic.

Benzodiazepines

The benzodiazepines included alprazolam, bro- mazepam, brotizolam, chloridiazepoxide, clotiazepam, cloza- zolam, diazepam, estazolam, ethyl loflazepate, etizolam, fludiazepam, flunitrazepam, flutoprazepam, lorazepam, lor- metazepam, medazepam, nitrazepam, oxazepam, quazepam, rilmazafone, and triazolam. The cases were defined as patients who received benzodiazepine drugs, and patients without benzodiazepine prescriptions were regarded as controls. The mean (± SD) period of a benzodiazepine prescription was 12 (± 1.9) months. Precise information on the half-life of pharmacological action was integrated into the dataset. According to the literature (6), the following benzodiazepines were categorized by half-life (range of average half-life of metabolites), i.e. short half-life (shorter than 10 hours): brotiazepam, clothiazepam, etizolam, lormetazepam, tofisopam, and triazolam; intermediate half-life (10-35 hours): alprazolam, bromazepam, estazolam, flunitrazepam, lorazepam, nitrazepam, oxazepam, and rilmazafone hydro- chloride; and long half-life (longer than 35 hours): cloxzolam, diazepam, ethyl loflazepate, flurazepam, medazepam, and quazepam.

Statistical analysis

The patterns of benzodiazepine prescriptions classified by pharmacological half-life (i.e., short, intermediate, and long) were compared between the internal medicine and psychiatry groups, between the psychiatry and other groups, and between the internal medicine and other groups, using chi-squared tests.

A logistic regression model was used to assess the effects of patient gender and age, and department group visited on regular benzodiazepine prescriptions. Univariate and adjusted odds ratios (OR) of regular prescriptions for benzodiazepines were computed along with the 95% confidence intervals (CI). With regard to p values in the multivariate models, the Cochrane-Amitage trend test was used for age, and the Wald-chi-squared test was used for department groups. The analyses were conducted with a significance level at 5% and using the SAS ver. 8.12 for Windows software.

Results

Of the 22,099 patients analyzed in the present study, 15%
Table 1. Clinical Characteristics of Regular Users of Benzodiazepines and Control Population and the Risk of Regular Use of Benzodiazepines (n=22099)

<table>
<thead>
<tr>
<th>Variables</th>
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<th>Multivariate</th>
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<tr>
<td></td>
<td>OR 95%CI</td>
<td>p value</td>
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<td>Lower</td>
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<td>80+</td>
<td>220</td>
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\*Control is defined as patients who were not prescribed benzodiazepine.
\*P values were calculated for age by using a trend test based on Cochran-Armitage method and for department clinic by using Wald chi-square test
\*Adjusting for patient gender and age, and department clinic.
\*The department of psychiatry includes psychoanalytic medicine.
\*Others include ear nose throat, orthopedics, dermatology, surgery, psychiatry, urology, obstetrics & gynecology, dentistry, neurology, neurosurgery, anesthetic surgery, ophthalmology, pediatrics, cardiosurgery, rehabilitation, anaesthesia, radiology, kidney center, emergency medicine.

Figure 1. The patterns of benzodiazepine prescription by department clinics from the perspective of pharmacological half-life. Compared with the psychiatry group, physicians in internal medicine and other groups were more likely to prescribe short half-life benzodiazepines, followed by intermediate half-life agents (p<0.0001), and internists prescribed these drugs more often than physicians in the other departments (p<0.0001).

Discussion

The present study determined the patterns of regular benzodiazepine prescriptions in both the univariate and multivariate models. Compared with patients aged 15 to 29 years, patients in the older age groups were more likely to be prescribed benzodiazepines when adjusting for patient gender and department group visited; the percentage of prescriptions for these drugs increased as age increased (p < 0.0001 in trend tests). Compared to psychiatrists, internists and other physicians were less likely to prescribe benzodiazepines.

Fig. 1 shows the patterns of benzodiazepines prescription by department clinics from the perspective of pharmacological half-life (i.e., internal medicine, psychiatry, and others). Compared with the psychiatry group, the physicians in the internal medicine and other groups were more likely to prescribe short half-life benzodiazepines, followed by intermediate half-life benzodiazepines (p < 0.0001), and internists prescribed these drugs more often than physicians in the other departments (p < 0.0001).

In the present study, female gender was a significant and...
independent risk factor for regular benzodiazepine prescriptions. Various studies suggest that the female predominance in the use of benzodiazepines refers to the fact that psychological ill health and anxiety are significantly more common in women than in men (10-12). Consequently, it is possible that women are more likely to develop psychological and physiological dependency than men, and the clinical implication is that women are the subjects in whom physicians actively intervene to provide rational prescribing for benzodiazepines. According to several reports (13, 14), an alternative explanation is that women are more likely than men to complain of psychological symptoms. Hence, being female is the cause or the result of the higher prevalence of mental ill health in women is debatable. Unfortunately, our study did not adjust for health status information, and accordingly, the interpretation of the effect of female gender on the use of benzodiazepine requires further exploration in future studies.

Although warnings have been repeatedly issued regarding the long-term use of benzodiazepines (5-9), in the present study, regular prescriptions of benzodiazepines were found to increase with age. The earlier finding showed that psychological illnesses, such as generalized anxiety disorders, are less prevalent in older adults than in younger adults (15). The discrepancy raises important questions about the evaluation of these elderly patients regarding “whether their mental statuses need to be treated with benzodiazepines”? Benzodiazepine drug use among seniors leads to serious health problems such as falls and hip fracture (16-18). One clinical implication of the results of the present study is that physicians should carefully assess the mental health status of each elderly patient, to determine the requirement for benzodiazepine medication.

The effect of department clinics on the regular prescription of benzodiazepines should be interpreted with caution. Since several physicians at each department clinic prescribed benzodiazepines during the study period, the effect of department clinics might reflect the educational influence in each department clinic regarding the prescribing of benzodiazepines. Alternatively, psychiatrists see patients who need to be treated with benzodiazepines more often than physicians at other department clinics, and therefore the effect of department clinics observed in our study might represent the characteristics of the diseases treated by the various department clinics.

Our result of pharmacological half-life among department clinics shows that internists were more likely to prescribe short half-life benzodiazepines while psychiatrists were more likely to prescribe intermediate agents. According to the literature (8, 19), short half-life compounds increase the risk of dependency, which results in the long-term use of benzodiazepines, although these compounds might decrease the frequency of falls and cognitive impairment. Therefore, we recommend that internists consider the pharmacological actions of benzodiazepines before prescribing them.

In conclusion, our results indicate that a large number of outpatients are maintained on a regular supply of benzodiazepines. For rational prescribing, primarily based on limited use (i.e., short-term or intermittent use at minimal effective doses), appropriate mental assessment is essential. In addition, the influence of patients’ characteristics (i.e., sex and age) and adverse effects related to pharmacological half-life need to be included in educational programs for rational benzodiazepine prescription.

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