The Long-Term Prescription of Benzodiazepines, Psychotropic Agents, to the Elderly at a University Hospital in Japan

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Benzodiazepines are useful and effective psychotropic agents used worldwide. Their therapeutic actions as anxiolytics, sedative hypnotics, anticonvulsants, and muscle relaxants have led to their use as first-line treatments. In addition, they are less toxic than barbiturates when they are used in overdose and have thus become one of the most prescribed classes of drugs. A literature (Woods et al. 1992) reported that about 2% of the adult populations in the United States (4 million peo-
is unclear if previous risk profiles are being considered in light of the long-term prescription of these drugs to this age group. Therefore, we investigated long-term benzodiazepine prescriptions especially to the elderly at a university teaching hospital in Japan.

In 1999, the Teikyo University School of Medicine installed a computer ordering system (COS), which has been used to monitor drug prescriptions in every clinical department at the hospital. Using data available through the COS, the university has launched several research projects to study evidence-based health care services at the hospital (Nakao et al. 2007). This study was part of a project to assist physicians in developing more rational protocols for appropriate drug prescription.

**Materials and Methods**

**Data set**

We created a new data set of patient information using Access 2000 (Microsoft Japan, Tokyo) based on the original COS database accumulated at Teikyo University Itabashi Hospital, Tokyo, Japan (1,154 hospital beds). This university teaching hospital has 19 department clinics, with approximately 60,000 outpatients visiting annually. The variables retrieved from the COS database were patient gender and age, prescribing department, benzodiazepine pharmacological half-life, and the date of benzodiazepine prescription.

**Patients**

Fig. 1 is a flow chart of our study subjects. The subjects consisted of 5,959 adult outpatients who had
visited the hospital and were prescribed benzodiazepines by physicians between July 2002 and June 2003. After excluding 1,720 patients who were prescribed benzodiazepines at two or more different clinics, 4,239 patients (59% female, mean age 57 years) receiving benzodiazepines were selected for the analyses. The patients were divided into two groups depending on the prescription length based on previous studies (WHO Collaborating Centre for Drugs 1996; Zandstra et al. 2002): the long-term group consisted of those with prescription periods of 3 months or more (mean ± s.d.: 8.0 ± 2.7 months) and the short-term group had prescription periods of 2 months or less (1.4 ± 0.5 months). In Japan, according to the Health Insurance Law, physicians can write a prescription for hypnotics for up to 14 days; hence, patients who take the drug continuously have to see a physician at least twice a month. The data set used in this study contained the date of prescription, and we defined the prescription time period based on this date.

Benzodiazepines

Referring to the Anatomical Therapeutic Chemical Classification System (WHO Collaborating Centre for Drugs 1996) index groups, including N05BA (N = nervous system, N05B = anxiolytics, 01 = diazepam, 02 = medazepam, 04 = oxazolam, 06 = lorazepam, 08 = bromazepam, 12 = alprazolam, 18 = ethyl loflazepate, 19 = etizolam, 21 = clotiazepam, 22 = cloxazolam, 23 = tofisopam), N05CD (N05C = hypnotics and sedatives, 01 = flurazepam, 02 = nitrazepam, 03 = flunitrazepam, 05 = triazolam, 06 = lormetazepam, 09 = brotizolam, 10 = quazepam), and N5CM (others, rilmazafone hydrochloride). The following benzodiazepines were categorized by pharmacological half-life. The short half-life (< 10 hrs) group comprised brotiazepam, clotiazepam, etizolam, lormetazepam, tofisopam, and triazolam; the intermediate half-life (10–30 hrs) group included alprazolam, bromazepam, estazolam, flunitrazepam, lorazepam, nitrazepam, oxazolam, and rilmazafone hydrochloride; and the long half-life (> 30 hrs) group consisted of cloxazolam, diazepam, ethyl loflazepate, flurazepam, medazepam, and quazepam.

Department clinics

The department clinics were categorized into four groups: surgery, internal medicine, psychiatry, and “other”. The surgery group included the departments of general surgery, orthopedic surgery, urology, ophthalmology, otorhinolaryngology, neurosurgery, the emergency room, plastic surgery, and cardiovascular surgery. The internal medicine group consisted of the general internal medicine and neurology departments. The psychiatry group was composed of the psychiatry and mind/body medicine departments, and the “other” group included the pediatrics, dermatology, radiology, anesthesiology, and rehabilitation departments and the hemodialysis center.

Although the diagnostic information was preliminary during the study period (the annual report of the hospital, unpublished), the major ICD-10 diagnoses in internal medicine were angina pectoris, followed by chronic renal failure, primary lung cancer, old myocardial infarction, and hepatocellular carcinoma, while those in surgery were inguinal hernia, followed by gastric cancer, breast cancer, pancreatic cancer, and hepatocellular carcinoma. The total number of new outpatients in the psychiatry group was 1,549, of which 19.5% had depressive disorders. During the study period, the numbers of physicians employed in the aforementioned groups were 190 in the internal medicine group, 354 in the surgery group, 60 in the psychiatry group and 84 in the other department group.

Statistical analysis

Chi-square tests were used to compare patient gender, department group, and pharmacological half-life between the long- and short-term groups, and the t-test was applied to compare age between the two groups. To clarify the patient characteristics in each age category, patient age was transformed into four groups (15–40, 41–59, 60–70, and 71 years or older) relying on the distribution quartiles, and a logistic regression model was applied to assess whether the categorized age was associated with long-term benzodiazepine prescription after adjusting for patient gender, department group, and pharmacological half-life (Model I). In the same logistic regression model, the statistical interaction effect of the oldest age group with the department group was also assessed. In order to evaluate the independent effects of patient gender, department group, and pharmacological half-life on long-term prescription in the elderly, the same logistic model was also calculated using these stratified age groups (Model II).

Univariate and adjusted odds ratios (OR) for long-term benzodiazepine prescriptions were computed along with the 95% confidence intervals (CI). The Cochrane–Armitage trend test was applied to assess the age group trends, and the Wald chi-square test was used to deter-
mine the significance of the department group. $P < 0.05$ was considered significant, and SAS ver. 8.12 for Windows (SAS Institute, Cary, NC, USA) was used for the analyses.

**RESULTS**

Table 1 shows the differences in patient age and gender, department group, and pharmacological half-life between the long- and short-term prescription groups. The mean age was 9 years older in the long-term group than in the short-term group. The patients given prescriptions in the internal medicine or psychiatry department groups were more likely to be assigned to the long-term prescription group than those given prescriptions in the surgery and “other” department groups.

Table 2 shows the results of Model I, estimating the OR for long-term benzodiazepine prescription in association with the age categories. Patient age was significantly associated with long-term prescriptions; as patient age increased, the proportion of long-term prescriptions also increased. The relationship between long-term benzodiazepine prescription and age remained significant after controlling for patient gender, department group, and pharmacological half-life ($p < 0.0001$ in trend tests). The department group was also significantly associated with long-term benzodiazepine prescription in the multivariate model (data not included in Table 2). Benzodiazepines were more frequently prescribed by internal medicine group (adjusted OR, 1.93; 95% CI, 1.58–2.36) and psychiatry group (adjusted OR, 2.14; 95% CI, 1.67–2.73) than by surgery group. Gender and pharmacological half-life were not significantly associated with long-term prescription. Statistical interactions between the elderly ($\geq 71$ years old) and long-term prescription were observed with internal medicine ($p = 0.003$); benzodiazepines were more frequently prescribed for long term in the elderly by internal medicine group.

**Table 1.** Patient age and gender, and clinical departments between long- and short-term prescription groups ($n = 4,239$).

<table>
<thead>
<tr>
<th>Age (y/o)</th>
<th>Long-term group ($n = 3,240$) prescribed 3 months or longer</th>
<th>Short-term group ($n = 999$) prescribed 2 months or shorter</th>
<th>$p$ value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Means</td>
<td>s.d.</td>
<td>Means</td>
</tr>
<tr>
<td></td>
<td>$n$</td>
<td>%</td>
<td>$n$</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male ($n = 1,748$)</td>
<td>1,358</td>
<td>78</td>
<td>390</td>
</tr>
<tr>
<td>Female ($n = 2,491$)</td>
<td>1,882</td>
<td>76</td>
<td>609</td>
</tr>
<tr>
<td>Department group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery ($n = 988$)</td>
<td>680</td>
<td>69</td>
<td>308</td>
</tr>
<tr>
<td>Internal medicine ($n = 1,714$)</td>
<td>1,398</td>
<td>82</td>
<td>316</td>
</tr>
<tr>
<td>Psychiatry ($n = 1,419$)</td>
<td>1,082</td>
<td>76</td>
<td>337</td>
</tr>
<tr>
<td>Others ($n = 118$)</td>
<td>80</td>
<td>68</td>
<td>38</td>
</tr>
<tr>
<td>Pharmacological half-life b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long ($n = 718$)</td>
<td>512</td>
<td>71</td>
<td>206</td>
</tr>
<tr>
<td>Intermediate ($n = 950$)</td>
<td>726</td>
<td>76</td>
<td>224</td>
</tr>
<tr>
<td>Short ($n = 1,515$)</td>
<td>1,130</td>
<td>75</td>
<td>385</td>
</tr>
</tbody>
</table>

* Based on chi-square test for gender, department group, and pharmacological half-life, and t-test for age.

b 1,056 patients who were prescribed more than one different pharmacological half-life benzodiazepines were excluded.
Table 3 shows the results of Model II, the OR of the long-term prescription for benzodiazepines in the elderly (≥ 71 years old). Internists were more likely to prescribe benzodiazepines than surgeons, whereas no such tendency was observed in psychiatrists and physicians in the “other” group.

**Table 2.** Unadjusted and adjusted odds ratios (OR) of the age effect on long-term prescription of benzodiazepines (n = 4,239; Model I).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Long-term group (n = 3,240)</th>
<th>Short-term group (n = 999)</th>
<th>Univariate analyses 95% CI</th>
<th>Multivariate analyses (n = 3,183) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y/o)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-40</td>
<td>598</td>
<td>387</td>
<td>2.03</td>
<td>2.67</td>
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<tr>
<td>41-59</td>
<td>877</td>
<td>280</td>
<td>2.88</td>
<td>4.23</td>
</tr>
<tr>
<td>60-70</td>
<td>810</td>
<td>182</td>
<td>4.12</td>
<td>5.82</td>
</tr>
<tr>
<td>71-</td>
<td>955</td>
<td>150</td>
<td>2.88</td>
<td>5.82</td>
</tr>
</tbody>
</table>

*a Long-term = 1 vs short-term = 0.

*b Adjusting for patient gender, department group and pharmacological half-life; 1,056 patients who were prescribed more than one different pharmacological half-life benzodiazepines were excluded.

*c The Cochrane-Amitage trend test was used for age.

**Table 3.** Unadjusted and adjusted odds ratios (OR) of long-term prescription of benzodiazepines in the elderly aged 71 and older (n = 1,105; Model II).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Long-term group (n = 955, 86%)</th>
<th>Short-term group (n = 150)</th>
<th>Univariate analyses 95% CI</th>
<th>Multivariate analyses (n = 922) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n = 427)</td>
<td>369</td>
<td>58</td>
<td>1.00</td>
<td>0.89</td>
</tr>
<tr>
<td>Female (n = 678)</td>
<td>586</td>
<td>92</td>
<td>1.79</td>
<td>1.50</td>
</tr>
<tr>
<td>Department group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery (n = 139)</td>
<td>222</td>
<td>63</td>
<td>2.70</td>
<td>2.91</td>
</tr>
<tr>
<td>Internal medicine (n = 663)</td>
<td>600</td>
<td>10</td>
<td>1.97</td>
<td>2.01</td>
</tr>
<tr>
<td>Psychiatry (n = 285)</td>
<td>120</td>
<td>14</td>
<td>1.79</td>
<td>1.50</td>
</tr>
<tr>
<td>Others (n = 18)</td>
<td>13</td>
<td>28</td>
<td>0.74</td>
<td>0.62</td>
</tr>
<tr>
<td>Pharmacological half-life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long (n = 162)</td>
<td>140</td>
<td>22</td>
<td>1.12</td>
<td>1.00</td>
</tr>
<tr>
<td>Intermediate (n = 277)</td>
<td>243</td>
<td>88</td>
<td>0.79</td>
<td>0.68</td>
</tr>
<tr>
<td>Short (n = 483)</td>
<td>403</td>
<td>83</td>
<td>2.00</td>
<td>1.97</td>
</tr>
</tbody>
</table>

*a Long-term = 1 vs short-term = 0.

*b Adjusting for patient gender, department group and pharmacological half-life.

*c P values based on the Wald chi-squared test.

*d 183 patients who were prescribed more than one different pharmacological half-life benzodiazepines were excluded.
DISCUSSION

In contrast to their use and safety in younger populations, benzodiazepines should be limited in the elderly because long-term use can have serious health consequences, such as a fall, hip fracture, cognitive impairment, sedation, and impaired activity (Pierfitte et al. 2001; de Rekeneire et al. 2003; Fick et al. 2003; Wagner et al. 2004). Despite the recommendation that intervention with benzodiazepines be short based on several guidelines (Committee on Safety of Medicine 1988; Royal College of Psychiatrists 1988; Fick et al. 2003; Ashton 2005), previous studies repeatedly showed that the long-term use of these drugs was very common among the elderly (Magrini et al. 1996; Simon et al. 1996; Egan et al. 2000a, b; Gray et al. 2003; Fialova et al. 2005; Voyer et al. 2006). The majority of these previous studies were conducted overseas, and there are very few reports on elderly users in Japan (Miyamoto et al. 2002). This study demonstrated that, in Japan, benzodiazepines were more likely to be prescribed for a longer term as patient age increased. We discuss the results of this study below.

In this study, among patient gender, department group, and pharmacological half-life, department group was found to be a significant determinant of long-term prescriptions; internists were more likely to write long-term prescriptions as patient age increased (Model I), and internists were more likely to write the long-term prescriptions in the elderly compared to surgeons (Model II). However, the results require careful interpretation. Referring to the annual report of the hospital, it was found that the underlying disease of patients differed, according to the department. Thus, the prescription period might differ according to the characteristics of the patients’ underlying condition in each department clinic. Taking this into account, we performed sub-analyses that included all of the prescribed patients and confirmed that approximately 80% of those visiting the surgery group received drug prescriptions written for 2 months or less (short-term in this study). Hence, it was suggested that patients in the surgery group were less likely to receive a long-term prescription, regardless of whether it was benzodiazepine, compared with the internal medicine group.

Nevertheless, the characteristics of patients who were prescribed benzodiazepines over the long-term were similar in relation to patients in the internal medicine and surgery groups in terms of patient age (66 ± 14 years in the internal medicine group and 63 ± 14 years in the surgery group). The patients’ underlying health conditions in both groups differed from those in the psychiatry group. However, our additional analyses, which included all prescribed patients, regardless of benzodiazepine prescription, showed that the prescription period in the internal medicine group was longer than that in the surgery group, which led us to speculate that patients in the internal medicine group were more likely to have chronic illnesses than those in the surgery group. Nevertheless, a chronic health condition does not justify the long-term use of benzodiazepine. Moreover, our result showed that internists were more likely to prescribe benzodiazepines for the long-term, especially in the oldest age group. Since the long-term use of benzodiazepine leads to serious adverse effect in the elderly, any physician who might prescribe benzodiazepines requires special attention. At our university hospital, hundreds of physicians prescribe benzodiazepines, and the finding concerning physician specialty might better reflect the educational impact of conferences and the advice of supervisors, rather than individual prescribing preferences. Therefore, we suggest that increased education be provided to those working in department clinics concerning the rational prescription of these drugs to the elderly.

Regarding to pharmacological half-life of benzodiazepines, a guideline (Nelson and Chouinard 1999) denoted that short- and intermediate-beta half-life compounds carry a greater risk of rebound and withdrawal reactions, and drug dependence than long-acting agents, which resulted in long-term use of benzodiazepines. However, we did not find an association between the pharmacological half-life of benzodiazepines and long-term prescription, and the result was not
altered even in the analyses that included patients who had received long-term prescription in more than two different clinics, and after adjusting for gender and age. Hence, our findings do not support the idea that the difference in the pharmacological half-life determines the long-term use of benzodiazepines.

There are a few study limitations that need to be discussed. First, because this study is a cross-sectional study, our result does not immediately indicate a causal relationship between long-term prescription and patients’ age. Second, the dataset excluded 1,720 patients who were prescribed benzodiazepines at two or more different clinical departments. If the characteristics of the excluded population differed from those of our analyzed sample, our results would be biased. To address this issue, we also analyzed the entire dataset and still found that long-term prescription increased with patient age after adjusting for patient gender, age, and pharmacological half life of benzodiazepines. Third, although short-term intervention is recommended with benzodiazepine use, the long-term use of benzodiazepines is sometimes required in patients who need benzodiazepines for treatment reasons (e.g., augmentation therapy with other drugs such as lithium in mania [Gouliaev et al. 1996], antipsychotics in psychotic agitation, and selective serotonin reuptake inhibitors in panic disorder). Given that psychiatrists usually treat such patients, our additional analyses, which excluded patients who received benzodiazepines in the psychiatry group, showed that the long-term benzodiazepine prescription still increased with age. Fourth, rational prescription on demand such as PRN (pro re nata, “as needed”) was tolerated with long-term use of benzodiazepines, even in the elderly (Perry and Wu 1984). However, as our dataset did not include information about the dose of benzodiazepines prescribed, the result of our study requires careful interpretation. Also of importance, the relationship between benzodiazepine use and the incidence of hip fracture among older people has been the focus of many studies, with conflicting results. For example, Wagner et al. (2007) reported that policies that lead to substantial reductions in the use of benzodiazepines among older people do not necessarily lead to decreased incidence of hip fracture. Therefore, the adverse outcome of benzodiazepine use remains controversial and further evidence must be accumulated.

With the limited evidence described above, our findings indicate that long-term benzodiazepine prescriptions increase with patient age, and suggest that educational intervention at department clinics is useful to promote the rational prescription of benzodiazepines. A discussion of the rational prescribing of benzodiazepines in the elderly should be mandated in the education programs for physicians in university teaching hospitals, and the actual prescribing needs to be monitored carefully and continuously.

Acknowledgments
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