



Prescription of triazolam for the elderly in Japan: A sub-analysis of the drug event monitoring project by the Japan Pharmaceutical Association

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ABSTRACT

Japan has the highest rate of triazolam use per capita in the world. A questionnaire-based survey of 820 triazolam users was conducted in order to assess the safety of triazolam therapy in a real-world clinical setting in Japan. The patients who used more than the recommended dose of triazolam (3.8%) were all elderly (65 years of age or older), and were more likely to be dissatisfied with their treatment and to increase the dose by themselves compared with those using an appropriate dose. Adverse symptoms were reported by 4.5% of subjects. The most common symptoms were morning drowsiness (1.7%) and impaired balance and/or falls (1.2%). None of the patients discontinued the use of hypnotics, and 99% of subjects continued triazolam treatment in spite of the unsatisfactory efficacy and/or adverse symptoms. This preliminary study suggests that prescription of triazolam may be associated with addictive behaviors in the elderly.

Keywords: triazolam, drug dependence, adverse drug effects, elderly population, benzodiazepines

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INTRODUCTION

Recently, a large cohort study including more than 22,000 benzodiazepine users (64% of the total number of subjects) demonstrated that anxiolytic and hypnotic drugs were associated with a significant risk of mortality, which doubled over a seven-year period [1]. The use of prescription benzodiazepines is widespread in developed countries [1-3]. Many people take them for many years, regardless of good practice guidelines suggesting that the duration of use should be limited to a few weeks [3]. Long-term use of benzodiazepines is associated with paradoxical anxiety and sleep

difficulties, falls and fractures, domestic and traffic accidents and dementia [3]. These risks increase with age, and the development of dependence to prescribed benzodiazepines is also a problem in elderly patients [4, 5].

Triazolam, a short-acting benzodiazepine, was removed from the market in the United Kingdom and other European countries 20 years ago due to safety concerns (<http://www.nap.edu/read/5940/chapter/1>). The United States of America modified the labeling to reduce the recommended dose and duration of prescription and to heighten awareness regarding possible side effects affecting behavior and cognition

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(<http://www.nap.edu/read/5940/chapter/1>). In contrast, Japan is the largest importer of triazolam, accounting for almost 60% of all global imports in 2012, and is the country with the highest calculated per capita use of triazolam (https://www.incb.org/documents/Psychotropics/technical-publications/2013/en/English_2013_Tech_pub.pdf).

Therefore, we aimed to assess the safety and efficacy of current triazolam therapy in a real-world clinical setting in Japan, with particular attention to the risks in elderly users.

SUBJECTS AND METHODS

We conducted a sub-analysis of an annual nationwide surveillance study, the Drug Event Monitoring (DEM) project of the Japan Pharmaceutical Association (JPA) [6]. Three short-acting hypnotics (triazolam, zolpidem and zopiclone) were investigated in 2009 [7]. We restricted the present analysis to triazolam because the sample size for zopiclone was small ($n = 121$) and there were large differences in the patient characteristics, including accuracy of prescription and/or patient satisfaction, between triazolam and zolpidem users, as could be seen based the detailed characteristics of zolpidem users that have been reported previously [8].

Every patient who presented a prescription for and received a target drug from a pharmacy affiliated with the JPA DEM project during the surveillance period from February 16 through 22, 2009 was asked to participate in the project. Patients who received one of the target drugs but did not receive other hypnotics, sedatives, antidepressants or psychotropic agents were included in the survey. The participants were interviewed by pharmacists using structured questionnaires to assess the participants' self-perception of adverse symptoms after the last prescription of the target drug. The questionnaires included open questions about demographic information, satisfaction and adverse symptoms and a check list of symptoms that can be caused by the target drugs (Table 1). The pharmacists also questioned the participants about their symptoms as needed and completed the checklist. Six hundred and twenty-four (86.4%) pharmacies in Kumamoto prefecture, Japan participated in the survey. The survey results were collected via a web-based system as described previously [6]. This protocol was approved by the institutional ethics committees of the Faculty of Life Sciences, Kumamoto University (approval number: 589). The study was performed in accordance with the Declaration of Helsinki.

Table 1. Questionnaire and checklist items for the Japan Pharmaceutical Association Drug Event Monitoring project, 2008

Age (years)	Satisfaction
Sex	Satisfied/neither satisfied nor dissatisfied/dissatisfied †
Male/female	†Reasons: difficulty in falling asleep/middle of the night wakening/adverse drug symptoms/other ‡
Hypnotic currently being used	Prescription on the surveillance day
Triazolam/Zolpidem/Zopiclone	Same as previous prescription/ dose changed (reduced/ increased)/changed to other hypnotic/ discontinued §
Previous day of prescription of hypnotic	§Reasons : unnecessary/ unused/adverse drug symptoms/other
Previous prescription of hypnotic	Adverse drug symptoms ¶
Dose (mg) for _ days	Agitation, confusion, somnambulism/ amnesia/ dizziness/dysgeusia/headache/ impaired balance, fall/ malaise/morning drowsiness/nightmare/ twilight state/weakness/other ‡
Adherence	
Used as prescribed/self-dosing (reduced/increased)/never used	
Use of hypnotic after consumption of alcohol	
Used without care/used at a lower dose/used after an intervening time/never used/non drinker	

‡ Multiple answers allowed.

¶ The question was phrased "Have there been any changes since the previous prescription?" with the questioner cautioned against leading the patient to any particular response.

We investigated the satisfaction and the prevalence of adverse symptoms with triazolam treatment, focusing on doses exceeding the recommended dose: i.e., doses exceeding 0.25 mg in elderly (65 years of age or older) subjects or 0.5 mg in non-elderly subjects.

Categorical and continuous variables were compared using Fisher's exact test and Student's *t*-test, respectively. To determine the risk factors associated with adverse symptoms when using triazolam, bi-variable and multivariable logistic regression

analyses were performed with calculation of the odds ratios (ORs) and 95% confidence intervals (95% CIs). A *P* value of < 0.05 was considered to be statistically significant. All statistical analyses were performed using the SPSS software package for Windows (Version 17.0, IBM Japan Ltd., Tokyo, Japan).

RESULTS

A total of 127,731 patients visited the pharmacies during the surveillance period, and 820 triazolam users (311 males and 509 females) were eligible for the analysis. The median period from the last prescription to the surveillance was 16 (range: 4-102)

days. The patient characteristics are shown in Table 2. The mean age of the subjects was 72.9 ± 11.8 (range: 21-101) years old, and elderly subjects accounted for 80.5% of all participants. The mean dose was 0.226 ± 0.085 (range: 0.0625–0.5000) mg. Elderly subjects were prescribed lower doses of triazolam than non-elderly subjects (0.221 ± 0.080 mg vs. 0.248 ± 0.099 mg, *P* < 0.001). Females were older (74.0 ± 11.9 y.o. vs. 71.0 ± 11.5 y.o., *P* < 0.001), had a lower dose (0.221 ± 0.085 mg vs. 0.234 ± 0.083 mg, *P* = 0.030) and exhibited a lower rate of concomitant alcohol consumption (12.2% vs. 42.8%, *P* < 0.001) than males.

Table 2. Patient characteristics and demographics by sex and age[†]

	Total <i>n</i> = 820	Sex		<i>P</i> -value	Age		<i>P</i> -value
		Male <i>n</i> = 311	Female <i>n</i> = 509		< 65 y.o. <i>n</i> = 160	≥ 65 y.o. <i>n</i> = 660	
Age (years)	72.9 ± 11.8	71.0 ± 11.5	74.0 ± 11.9	<0.001	54.2 ± 9.6	77.4 ± 6.8	<0.001
Dose (mg)	0.226 ± 0.085	0.234 ± 0.083	0.221 ± 0.085	0.030	0.248 ± 0.099	0.221 ± 0.080	<0.001
Overdose				1.000			0.003
Appropriate dose	792 (96.6)	300 (96.5)	492 (96.7)		160 (100.0)	632 (95.8)	
Overdose	28 (3.4)	11 (3.5)	17 (3.3)		0 (0.0)	28 (4.2)	
Concomitant alcohol use				<0.001			0.216
Never used triazolam after drinking	625 (76.2)	178 (57.2)	447 (87.8)		116 (72.5)	509 (77.1)	
Used triazolam after drinking	195 (23.8)	133 (42.8)	62 (12.2)		44 (27.5)	151 (22.9)	
Adherence [‡]				0.669			0.586
Used as prescribed	608 (74.8)	237 (76.5)	371 (73.8)		117 (74.1)	491 (75.0)	
Self-decreased	192 (23.6)	69 (22.3)	123 (24.5)		40 (25.3)	152 (23.2)	
Self-increased	13 (1.6)	4 (1.3)	9 (1.8)		1 (0.6)	12 (1.8)	
Satisfaction [‡]				0.939			0.403
Satisfied	704 (86.3)	270 (86.8)	434 (85.9)		136 (85.0)	568 (86.6)	
Neither satisfied nor dissatisfied	23 (2.8)	8 (2.6)	15 (3.0)		7 (4.4)	16 (2.4)	
Dissatisfied	89 (10.9)	33 (10.6)	56 (11.1)		17 (10.6)	72 (11.0)	
Continuation				1.000			1.000
Continued to use triazolam	711 (98.9)	308 (99.0)	503 (98.8)		159 (99.4)	652 (98.8)	
Changed to other hypnotic	9 (1.1)	3 (1.0)	6 (1.2)		1 (0.6)	8 (1.2)	

The values are presented as the number (percentage) of subjects or the mean \pm standard deviation.

[‡] Some data were missing

Eighty-nine subjects (10.9%) were dissatisfied with their triazolam treatment; the reasons were difficulty in falling asleep (50.6%), middle of the night wakening (47.1%) or adverse drug symptoms (2.3%). The patients using a dose exceeding the recommended dose of triazolam (3.8%) were all elderly, and were more likely to be dissatisfied with their treatment (25.0% vs. 10.4%, *P* = 0.016) and to have increased the dose by themselves (11.5% vs. 1.3%, *P* = 0.009) than those using an appropriate dose. Adverse

symptoms after the last prescription were reported by 37 subjects (4.5%). The most common symptoms were morning drowsiness (1.7%) and impaired balance and/or falls (1.2%), as shown in Table 3. The mean age of the subjects with adverse symptoms was lower than that of subject without adverse symptoms, but the difference was not significant (68.1 ± 15.0 y.o. vs. 73.1 ± 11.6 y.o., *P* = 0.054). No significant association was observed between the prevalence of adverse symptoms and an older age, female sex,

overdose and/or concomitant alcohol consumption during the use of triazolam (Table 4). Surprisingly, none of the patients discontinued the use of hypnotics, and 99% of subjects continued triazolam treatment

despite unsatisfactory efficacy and/or adverse symptoms, although the adherence rates of satisfied and unsatisfied subjects could not be compared due to a lack of information.

Table 3. Reported adverse symptoms[†]

Adverse symptoms	Total <i>n</i> = 820	Sex		Age	
		Male <i>n</i> = 311	Female <i>n</i> = 509	< 65 y.o. <i>n</i> = 160	≥ 65 y.o. <i>n</i> = 660
All symptoms	37	13	24	11	26
Morning drowsiness	14	4	10	5	9
Impaired balance/ fall	10	4	6	4	6
Headache	4	1	3	0	4
Nightmare	3	1	2	1	2
Malaise	3	2	1	1	2
Amnesia	2	1	1	0	2
Twilight state	2	1	1	0	2
Dysgeusia	2	1	1	1	1
Dizziness	1	1	0	0	1
Dependence	1	0	1	1	0
Weakness	1	1	0	0	1
Others	2	1	1	0	2

[†]More than one symptom was reported in some cases.

Table 4. Distribution of the characteristics of the patients with or without adverse symptoms during triazolam use

Variable	Without symptoms N = 783	With symptoms N = 37	Crude OR [95% CI]	Adjusted OR [‡] [95% CI]
Age				
< 65 y.o. (%)	149 (19.0)	11 (29.7)	1	1
≥ 65 y.o. (%)	634 (81.0)	26 (70.3)	0.56 [0.27-1.15]	0.55 [0.26-1.14]
Sex				
Male (%)	298 (38.1)	13 (35.1)	1	1
Female (%)	485 (61.9)	24 (64.9)	1.13 [0.57-2.26]	1.22 [0.59-2.56]
Dose				
Appropriate dose	756 (96.6)	36 (97.3)	1	1
Overdose	27 (3.4)	1 (2.7)	0.78 [0.10-5.89]	1.11 [0.14-8.47]
Concomitant alcohol use				
Never used triazolam after drinking	597 (76.2)	28 (75.7)	1	1
Used triazolam after drinking	186 (23.8)	9 (24.3)	1.03 [0.48-2.23]	1.08 [0.48-2.46]

[‡]Adjusted for other factors listed in this table.

DISCUSSION

The main findings of the present study are that the prescription use of triazolam as the primary hypnotic for home-dwelling elderly patients is common in Japan, and that triazolam continued being prescribed to 99% of triazolam users, including those who complained of unsatisfactory efficacy and/or adverse symptoms. Mild and tolerable adverse symptoms were reported by 4.5% of the subjects after the last prescription of triazolam. An older age, female sex,

overdose or concomitant alcohol consumption were not significant risk factors for the adverse symptoms. In the original JPA DEM study, which included 38,581 Japanese subjects (mean age 71.3 years old, 64.0% females) prescribed triazolam (36.7%), zolpidem (46.2%) or zopiclone (17.0%), adverse symptoms were reported by 4.9%, 6.6% and 8.8% of triazolam, zolpidem or zopiclone users, respectively. In that study, 98.0% of triazolam users and 97% of zolpidem or zopiclone users continued to receive the same therapy. The subjects in the JPA DEM study,

including this sub-analysis, may be a low-risk group for adverse symptoms, because patients receiving any hypnotics, sedatives, antidepressants or psychotropic agents other than the target drug were excluded from the study. Even so, these results do not mean that the long-term use of triazolam is effective and tolerable.

The patients using doses exceeding the recommended dose of triazolam were all elderly, one-fourth of them were dissatisfied with triazolam treatment, and one-tenth of them had increased their dose themselves. Despite such dissatisfaction, all continued to use triazolam. These facts suggest the patients may have developed tolerance and/or dependence, as reported previously [4, 5]. By contrast, benzodiazepine dependency in older adults may not be associated with abuse [5]. A previous study showed that 47% of patients using a benzodiazepine for more than one month developed psychological dependence on these compounds, and patients using short half-life benzodiazepines exhibited higher rates of dependence [4]. Elderly people are particularly vulnerable to the development of dependence, as well as adverse reactions, due to several factors associated with aging, including increased frailty, changes in body composition and drug metabolism, increased morbidity and increased use of prescription medications with addiction potential [5]. Therefore, the American Geriatrics Society has recommended avoidance of benzodiazepines for insomnia in elderly people. Why, then, are benzodiazepines prescribed to elderly people for long-term use? Some studies have indicated that general practitioners feel overwhelmed by the psychosocial problems of their patients and show sympathy by writing such prescriptions [9]. In fact, 90% of patients who consult their physicians about their sleeping problems receive a drug prescription in Japan, while 50% of those in western Europe or the United States of America receive a prescription [10].

Several limitations associated with the present study warrant mention. First, the sample size was small, and the cross-sectional study design was not optimum. Additionally, the present study analyzed patient-reported symptoms, which may not be adequate for assessing impairment, as people to whom triazolam is prescribed frequently do not recognize their impaired state. These facts may be associated with the finding that older subjects were less likely to report adverse symptoms than younger subjects, although a significant association between older age and the risk of adverse symptoms was not found (Table 4). Furthermore, we restricted the present analysis to triazolam because the number of zopiclone users was

small and there were large differences in the patient characteristics, including accuracy of prescription and/or patient satisfaction, between triazolam and zolpidem users in the JPA DEM project. An appropriate dose was prescribed for almost all zolpidem users (except for one case), dose adjustments were made for elderly patients, and most of the subjects appeared to be satisfied with the zolpidem treatment [8]. Lastly, this study also lacks information on the duration of triazolam use, the adherence rate, the fields of specialty of the physicians who prescribed the hypnotics, co-medications, complications and health status, all of which may affect the results of the present study.

Although the results we present here are preliminary and further larger studies are needed to verify our findings, this study suggests that long-term triazolam prescription may be a critical issue in general practice in Japan.

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