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Original article

Concomitant use of psychotropics and donepezil in Japanese patients with dementia: Pooled postmarketing surveillance data analysis

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ABSTRACT

Background/Purpose: Psychotropics are administered to control behavioral and psychological symptoms of dementia. In 2005, the Food and Drug Administration (FDA) issued alerts regarding their use as antipsychotics in elderly patients with dementia-related psychosis. Guidelines on psychotropic use were also recently established in Japan; however, few studies have reported on the actual usage of psychotropics among patients with dementia in clinical settings. The aim of this study was to estimate the frequency of psychotropic use in patients with Alzheimer's disease receiving donepezil.

Methods: Data from six prospective, postmarketing studies of donepezil in patients with Alzheimer's disease conducted between 1999 and 2011 were pooled for analysis. Patient and clinical characteristics at baseline were analyzed descriptively. The proportion of psychotropics used concomitantly with donepezil was calculated for all patients and for patients divided into types of psychotropics used, sex, age, and study time period. As for the study time period, studies were divided into two groups: the period before the FDA alert was issued (1994–2004) and the period after (2005–2011).

Results: A total of 14,726 patients were analyzed (67.0% women, aged 79.3 ± 7.2 years). The overall proportion of psychotropic use was 24.2%. The number of psychotropics used was one in 8.2% of patients, two in 8.1%, and ≥ 3 in 5.5%. The types of psychotropics used were as follows: typical antipsychotics, 7.8%; atypical antipsychotics, 4.4%; antidepressants, 5.7%; anxiolytics, 6.4%; and hypnotics, 11.0% (% does not sum up to 24.2% due to multiple use). With regards to the time periods, in studies conducted between 1999 and 2004 versus those between 2005 and 2011, the proportions were 31.7% and 21.3%, respectively.

Conclusion: Psychotropic use was seen in a quarter of patients with dementia receiving donepezil in Japan. Additionally, the overall proportion decreased after the alert issued by the FDA in 2005.

1. Introduction

Dementia is a disease with core symptoms of cognitive deficits that are usually accompanied by noncognitive symptoms such as behavioral abnormalities and psychological symptoms. These noncognitive symptoms, referred to as Behavioral and Psychological Symptoms of Dementia (BPSD), include psychotic symptoms, such as verbal aggression, physical aggression, anxiety, hallucination, and delusion; sleep disorders; wandering; and defiant behavior.[1] It is reported that BPSD is observed in ~60–90% of patients with dementia.[2–7]

BPSD deteriorates the quality of life of patients more than the cognitive impairment, the hallmark of dementia, does. Consequently, caregiver burden increases due to increased levels of patient behavior disturbance.[8] When patients' BPSD becomes burdensome to caregivers, treatment of BPSD is required. If BPSD is relatively mild, nonpharmacological treatment can alleviate the symptoms. However, if BPSD is moderate to severe, or the symptoms impair the caregivers' quality of life, pharmacological treatment is necessary in many cases. Although psychotropic agents are currently used to treat BPSD, no specific pharmaceutical products

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are indicated for the treatment of BPSD. In 2005, the Food and Drug Administration (FDA) warned that atypical antipsychotics, a type of psychotropic, are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis.[9] Similarly, in 2008, the FDA warned that typical antipsychotics are also associated with an increased risk of mortality.[10]

Following the 2005 FDA alert, the package inserts of atypical antipsychotics were revised in 2005,[11] and following the 2008 FDA alert, the package inserts of all antipsychotics were revised in 2009.[12] In 2013, the Ministry of Health, Labor, and Welfare issued a guideline for the use of psychotropics for BPSD.[13] The guideline states that, since treatment of BPSD with antipsychotics is an off-label use, it is necessary to consider that psychotropics should basically not be used and that the first-line treatment should be nonpharmacological intervention, in principle.

In Japan, it is estimated that there are > 4 million elderly people with dementia;[14] the number is expected to increase with the future aging of the population. Among dementia, Alzheimer's disease (AD) is the most common form of dementia. Donepezil hydrochloride (Aricept®; Eisai Co., Ltd., Tokyo, Japan), the first drug for AD in Japan, was approved in 1999 with the indication of preventing the progression of symptoms of dementia in patients with mild or moderate AD. In 2007, the administration of 10 mg/d for severe AD was also approved. Postmarketing, real-world data on the use of donepezil hydrochloride in patients with any stage of AD are available to date.

A recent study investigating the antipsychotic use among > 13,000 elderly AD outpatients who were newly administered with donepezil hydrochloride between 2007 and 2009 in Japan using a prescription database reported that 8.9% were prescribed with antipsychotics, predominantly atypical agents.[15] Of these patients treated with antipsychotics, in round numbers, 11% received combinations of antipsychotics, and 44% continued the treatment for > 3 months after the alerts issued by FDA and Ministry of Health, Labor, and Welfare since 2005. To date, reports on the actual usage of psychotropics in AD in clinical settings are few compared with other countries. Thus, the objective of the present study was to estimate the frequency of psychotropic use in Japanese AD patients receiving donepezil hydrochloride, using pooled large real-world data from Postmarketing Surveillance (PMS) conducted since 1999.

2. Methods

2.1. Data source

In the present study, data collected from six prospective, PMS studies of donepezil hydrochloride in patients with AD were pooled and used for analysis. The Japanese regulatory authority obliges applicants for new drug approval to conduct PMS after approval. Evidence from clinical trials is obtained in a limited environment. Therefore, PMS aims to continuously build evidence of the safety and efficacy of a drug in clinical settings after it has been marketed. PMS was also mandatory for the approval of donepezil hydrochloride. The safety and efficacy of the drug was evaluated by PMS and it was re-examined.

The pooled PMS data were collected from the following six studies: ART01S, ART01T, ART02T, ART03T, ART04T, and ART05T (Table 1). Of the six studies, three studies that had started earlier than 2005 (ART01S, 01T, and 02T) were conducted in compliance with the Good Postmarketing Surveillance Practice, a ministerial ordinance as a guideline for postmarketing pharmacovigilance in Japan. The other three studies which had started after April 2005 were conducted in compliance with the Good Postmarketing Study Practice, a ministerial ordinance, due to the replacement of Good Postmarketing Surveillance Practice with Good Postmarketing Study Practice in April 2005.

2.2. Patients

The pooled data for this analysis compromised of patients derived from the safety analysis set in each study. The safety analysis set was used because it can be assumed that the patients had received at least one dose of donepezil hydrochloride and had had at least one postdose safety assessment. A total of 14,729 patients with AD were identified in the pooled data. Of them, three of the patients who had been enrolled in the study before a diagnosis of AD or who had been suspected of having AD were excluded, resulting in 14,726 patients included in the analysis.

2.3. Classification of psychotropic drugs

In the present study, psychotropics were classified into the following five categories: (1) typical antipsychotics; (2) atypical antipsychotics; (3) antidepressants; (4) anxiolytics; and (5) hypnotics. Typical antipsychotics included chlorpromazine hibenzate, chlorpromazine hydrochloride, sultopride hydrochloride, sulpiride, nemonapride, haloperidol, pipamperone hydrochloride, fluphenazine, propericiazine, bromperidol, levomepromazine hydrochloride, and thioridazine hydrochloride (12 drugs). Atypical antipsychotics included mosapramine hydrochloride, oxypertine, clocapramine hydrochloride hydrate, zotepine, nortriptyline hydrochloride, and quetiapine fumarate (6 drugs). Antidepressants included amitriptyline hydrochloride, clomipramine hydrochloride, lofepramine hydrochloride, and lithium carbonate (4 drugs). Anxiolytics included alprazolam, etizolam, clotiazepam, chlordiazepoxide, diazepam, bromazepam, ethyl loflazepate, and lorazepam (8 drugs). Hypnotics included amobarbital, zopiclone, nimetazepam, passiflora extract, flunitrazepam, brotizolam, bromvalerylurea, and lormetazepam (8 drugs).

2.4. Clinical assessments

To evaluate the severity of dementia, Functional Assessment Staging was used. Clinical features were evaluated in Stages 1–7.[16] Stage 1 indicates normal, and a higher stage indicates a higher decline in cognitive function.

Cognitive function was evaluated using the Mini-Mental State Examination, a 30-point questionnaire with 11 questions.[17] A lower score indicates worse cognitive function. The cognitive impairment is interpreted according to the following scores: ≥ 27 points, none; < 20 points, moderate; < 10 points, severe.

Language ability was evaluated with The Revised Hasegawa's Dementia Scale.[18] The Revised Hasegawa's Dementia Scale is a 30-point simple language impairment test consisting of nine questions. Patients with 20 points or lower are suspected of having dementia.

2.5. Statistical analysis

Descriptive statistics were calculated for baseline patient and clinical characteristics. Categorical variables were expressed as numbers and percentages, while continuous variables were expressed as mean ± standard deviation (SD), unless otherwise stated.

The proportion of patients who used psychotropics at least once during the study period was calculated as the user of psychotropics. The use of psychotropics was analyzed by dividing patients into types of psychotropics used, sex, age, and study time period.

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