Featured Article

Donepezil may reduce the risk of comorbidities in patients with Alzheimer's disease: A large-scale matched case-control analysis in Japan

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Abstract

Introduction: Few studies have focused on the association between donepezil and physical comorbid conditions in Alzheimer's disease patients.

Methods: We investigated the association between donepezil prescription and the occurrences of comorbidities in Alzheimer's disease patients, by using an electronic medical records database which contains case-based information on approximately three million patients from more than 60 hospitals across Japan.

Results: Nine thousand seven hundred forty-nine patients had at least one diagnosis of Alzheimer's disease between 2001 and 2015. To test the robustness of the results, we used a risk set sampling method, and the matched cohorts based on age, sex, comorbidity level, and duration of illness consisted of 1406 cases and an equal number of controls. From the multivariate logistic regression analysis adjusted for covariance, less occurrence of physical comorbidities was associated with donepezil prescription in the matched cohort.

Discussion: Although the mechanisms are unknown, donepezil may have positive effects on both cognition and physical status.

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Keywords: Alzheimer's disease; Physical comorbidity; Donepezil; Database research; Frailty; Apathy

1. Introduction

To date, most studies or investigations, or even models of care, for patients with Alzheimer's disease (AD) have tended to consider dementia as a single disease and, consequently, have focused on brain dysfunction relevant to cognitive decline rather than physical disturbances. However, recent studies have shown that AD often reveals a more complex clinical picture, with many comorbidities that can lead to longer hospital stays and increased health-care costs or caregiver burden and mortality risks [1–3]. The mechanisms underlying these comorbidities in patients with AD are multifactorial, and it is therefore crucial to consider both physical comorbid conditions and cognitive impairment as one complex phenotype.

Donepezil, cholinesterase inhibitors (ChEIs), have consistently been shown to not only delay the progression of cognitive decline in AD patients but also have a positive

influence on physical aspects such as gait performance [4], the risk of myocardial infarction [5], and life expectancy [6]. It is suggested that donepezil could improve voluntary attention [7] and physical functioning [8], which impact the elderly patient's activities of daily living, physical complaints, and comorbidities. However, few studies have focused on the association between donepezil and physical comorbid conditions in patients with AD.

Thus, the objective of this retrospective, observational study was to investigate the association between donepezil prescription and comorbidities in around 10,000 patients with AD in Japan. Our hypothesis was that patients who were prescribed donepezil had fewer comorbid conditions than those who were not.

2. Methods

2.1. Data source

Data were obtained from a Japanese electronic medical records database which contains case-based information on approximately three million patients across all age ranges from more than 60 hospitals including six university hospitals and 14 public hospitals nationwide, which is considered to appropriately reflect real-world clinical settings in Japan. The database also includes patient demographics, drug prescriptions, diagnosis of AD, medical comorbid conditions, and laboratory results in both inpatient and outpatient care settings. Patients' identities were masked throughout the study as researchers received only a limited data set from which identifiable personal information had been excluded.

2.2. Patient selection and identification

Data were extracted for patients with at least one diagnosis of AD, according to the International Classification of Disease, 10th version codes (Supplementary Table 1) between January 1, 2001 and December 31, 2015. We examined AD diagnoses across the whole observation period because, in most cases, only the first diagnosis is recorded in Japanese electronic medical records databases. Patients without demographic information (e.g., age or sex) were excluded.

Patients prescribed donepezil between April 1, 2010 and December 31, 2015 after the AD diagnosis were considered "users", and those not prescribed any ChEI in this period were considered "nonusers". The index date was defined as the date of donepezil initiation for users (cases), and controls (nonusers) were assigned the same index date as the cases to which they were matched. The calendar time distributions of index date were thus the same for both cases (users) and controls (nonusers). In this study, we focused on donepezil alone and excluded the data of patients having two or more ChEIs because of avoiding the confounding effect of combination of ChEIs on the outcomes. All patients were followed up from the index date until the occurrence of any comorbid condition, or the date of the last record of medical examination, whichever came first.

2.3. Assessment of diagnosis and medication

Diagnoses of AD and comorbidity at baseline and during the follow-up period were identified according to International Classification of Disease, 10th version codes and corresponding local Japanese codes (Supplementary Tables 1 and 2). For comorbidities, we reviewed literature on medical conditions that are commonly observed in AD patients and considered to affect their quality of life [1,3] and listed 97 comorbidities relevant to AD. Of these 97 medical conditions, we finally selected 12 comorbidities using the hierarchical clustering analyses for our database: femur fracture, osteoporosis, trauma, head injury, delirium, sleep disturbances, aspiration pneumonia, disuse atrophy, decubitus, anemia, constipation, and overactive bladder.

The date of the first diagnosis of each comorbidity during the follow-up period was defined as the date of onset, and days between the index date and the onset date were calculated. Psychotropics and other drugs for comorbid conditions used during the follow-up period were also identified using local Japanese drug codes (YJ codes) (Supplementary Table 3).

2.4. Statistical analyses

Patient demographic and clinical characteristics at the index date were compared using Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. Associations between donepezil use and the occurrence of physical comorbid conditions were examined using multivariate logistic regression models, with the baseline defined as the index date.

Models were adjusted for age, sex, Charlson Comorbidity Index (CCI) score [9], duration of illness, use of hypnotics (benzodiazepines and nonbenzodiazepines), antipsychotics, anticholinergic drugs, osteoporosis drugs, laxatives, and antiepileptics.

A risk set matching method was used to test the robustness of the results [10]. Each control (nonuser) was matched to one case (user) according to age ($\pm$5 years), sex, and CCI score at the index date of the matched case (the date of the donepezil initiation). When more than one control was matched, the patient with the smallest difference in age and CCI score was selected.

All statistical tests were two-sided and performed using R (http://www.r-project.org/), version 3.1.0. A P value < .01 was considered to be statistically significant.

3. Results

This study cohort consisted of 9749 patients who had at least one diagnosis of AD between 2001 and 2015. Of these patients, 5774 (59.2%) were female, and 4916 (50.4%) were "users" of donepezil (Fig. 1). Among this cohort, there were no significant differences in age between users and nonusers, but nonusers had a significantly higher CCI score at the index date (Table 1).