

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

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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 (± 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).

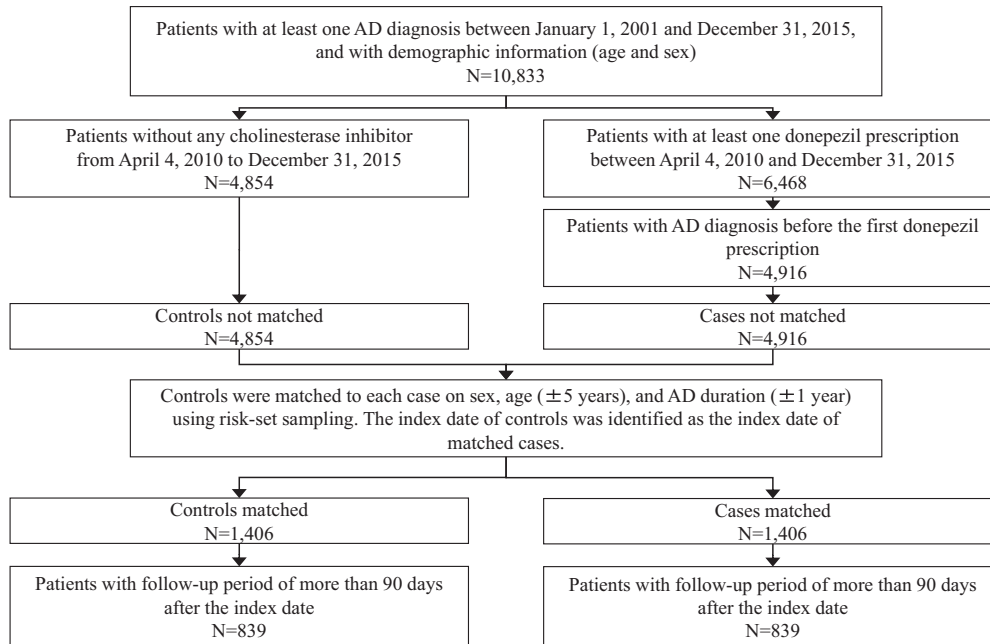


Fig. 1. Patient identification. Abbreviation: AD, Alzheimer's disease.

The matched cohort based on age, sex, and CCI score at the index date consisted of 1406 cases and an equal number of controls. Of this cohort, subjects were excluded if they could not be followed for more than 90 days after the index date, leaving 839 cases and the same number of matched controls (Fig. 1).

In overall sample (N = 9749), all comorbid conditions apart from delirium were significantly fewer in the user group than in the nonuser group (Table 2). From the multivariate logistic regression analysis adjusted for age, sex, CCI, duration of illness, use of hypnotics, osteoporosis drugs, laxative drugs, antiepileptic drugs, and antipsychotics, less occurrence of osteoporosis, aspiration pneumonia, decubitus, constipation, and overactive bladder was significantly associated with donepezil initiation in the matched cohort (N = 1678) (Table 3).

4. Discussion

The present study showed that donepezil utilization was associated with fewer physical comorbidities, some of which

are related to daily functioning or activities. This finding indicates that cognitive function in patients with dementia may have a close relationship with physical ability and that ChEIs such as donepezil may have positive effects on both cognition and physical status, either directly or indirectly. Underlying these associations, we propose the following hypotheses.

4.1. Cognitive decline

The link between cognitive decline and physical comorbidities in AD has been substantially reported so far [11–14]. People with more comorbidities had more rapid deterioration in cognition and also showed significantly faster decline in daily functioning [15–17]. It has been shown that the effect of physical activity and exercise might be effective on cognitive function [18] and thus the decline in daily functioning due to cognitive deterioration could raise physical comorbidities in older subjects. Moreover, people with decline in cognition such as attention and executive function have some difficulties in

Table 1 Characteristics of the study cohort according to donepezil use

	Total cohort			Matched cohort		
	Users	Nonusers	P value	Users	Nonusers	P value
N	4916	4833		839	839	
Female, N (%)	2881 (58.6)	2893 (59.9)	.209	502 (58.9)	502 (58.9)	1.000
Age, years (MAD)	81 (5.9)	81 (7.4)	.079	81 (7.4)	81 (7.4)	.621
CCI, score (MAD)	3 (3.0)	5 (4.5)	<.001	3 (3.0)	3 (3.0)	1.000

Abbreviations: CCI, Charlson Comorbidity Index; MAD, median absolute deviation.

Table 2

Associations between donepezil use at baseline and the occurrence risk of physical comorbidities in the total study cohort

Comorbid condition	Nonuser (N = 4833); n (%)	User (N = 4916); n (%)	Unadjusted odds ratio	95% CI		Adjusted odds ratio	95% CI		P value
				Lower	Upper		Lower	Upper	
Femur fracture	151 (3.1)	137 (2.8)	0.89	0.79	1.26	0.45	0.30	0.68	<.01
Osteoporosis	401 (8.3)	217 (4.4)	0.51	0.84	1.19	0.36	0.27	0.47	<.01
Trauma	492 (10.2)	403 (8.2)	0.79	0.87	1.15	0.58	0.47	0.71	<.01
Head injury	242 (5.0)	192 (3.9)	0.77	0.82	1.21	0.55	0.41	0.73	<.01
Delirium	66 (1.4)	68 (1.4)	1.01	0.71	1.41	0.57	0.32	1.02	.06
Sleep disturbance	663 (13.7)	466 (9.5)	0.66	0.88	1.13	0.44	0.36	0.54	<.01
Aspiration pneumonia	220 (4.6)	210 (4.3)	0.94	0.82	1.21	0.69	0.54	0.88	<.01
Disuse atrophy	319 (6.6)	272 (5.5)	0.83	0.85	1.18	0.45	0.33	0.60	<.01
Decubitus	279 (5.8)	188 (3.8)	0.65	0.83	1.21	0.32	0.22	0.45	<.01
Anemia	662 (13.7)	425 (8.6)	0.60	0.88	1.14	0.41	0.34	0.51	<.01
Constipation	893 (18.5)	627 (12.8)	0.65	0.90	1.12	0.27	0.22	0.34	<.01
Overactive bladder	95 (2.0)	109 (2.2)	1.13	0.76	1.32	0.42	0.27	0.68	<.01

Abbreviation: CI, confidence interval.

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

seeking necessary help and support in a timely manner [19,20]. Taken these robust associations among cognitive decline, daily functioning, and physical comorbidities into consideration, the effect of donepezil on delaying cognitive decline might prevent future physical comorbidities in AD patients.

4.2. Apathy and depression

As some studies previously revealed, donepezil has an effect on apathy or subjective depressive symptoms in AD patients. Waldemar et al. [21] suggested from the pooled analyses of two randomized, double-blind, placebo-controlled studies that donepezil treatment appears to have resulted in a significant reduction over 6 months of the emergence of apathy in patients with AD. Rockwood et al. [22] showed that both clinicians and caregivers recognized improvement in cognitive activation and apathy for the patients with AD treated with donepezil and indicated that improvements in executive function may underpin these specific symptomatic changes. In addition, the results of some trials suggested that donepezil may improve cognitive impairment in depressed subjects with amnesic mild cognitive impairment and delay conversion to a diagnosis of AD in mild cognitive impairment patients with mild depressive symptoms [23,24]. Taken together, although the effect of donepezil on apathy and depressive symptoms in patients with AD is still controversial, we speculated that improvements in these symptoms may have a better impact on the physical activation among AD patients.

4.3. Gait and balance

The effect of donepezil in delaying the progression of dementia may also have a direct impact on patients' daily activities [8]. In general, cognitive function is a key component in maintaining the physical functioning in the elderly, such as

gait and balance [25,26]. Both the control of gait and balance and cognitive function share a neuronal network and neurotransmitters such as acetylcholine [27]. Donepezil stabilizes the cholinergic system in the brain and may thereby improve attention and physical functioning, and subsequently gait and balance performance [28]. We therefore suggest that the improvements in gait and balance performance based on cognitive enhancement due to donepezil are likely to prevent the worsening of daily activities, and consequently reduce the risk of physical comorbidities.

4.4. Frailty

The onset of osteoporosis, aspiration pneumonia, decubitus, and constipation was delayed following donepezil prescription in this study, and these comorbidities appeared to be associated with a worsening of physical function in daily life, resulting in frailty. Frailty is a state of increased physical and cognitive vulnerability, which is strongly associated with the progression of dementia [29], and has been regarded as a predictor of hospitalization among community-dwelling elderly [30,31].

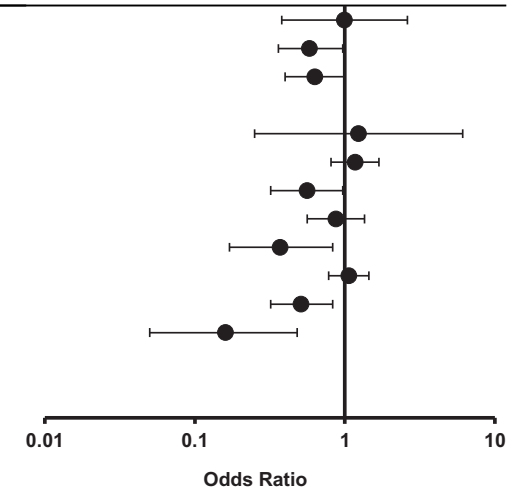
As previously mentioned, donepezil can demonstrate a positive effect on the progression of frailty, including gait performance [4] as well as daily activities [32,33]. In addition, donepezil treatment may result in an improvement in social behavior or interaction [8,34], which can avoid patients from becoming bedridden and help them maintain their physical functioning. Based on these observations, we can assume that donepezil would prevent the emergence of physical comorbidities partly due to its effect on the development of frailty.

4.5. Limitations and strengths

This study has some limitations. The study design was retrospective, observational, and naturalistic, which might

Table 3
Associations between donepezil use at baseline and the occurrence risk of physical comorbidities in the matched cohort

Comorbid condition	Nonuser (N = 839); n (%)	User (N = 839); n (%)	Unadjusted odds ratio	95% CI		Adjusted odds ratio	95% CI		P value
				Lower	Upper		Upper	Lower	
Femur fracture	25 (3.0)	32 (3.8)	1.29	0.59	1.70	0.99	0.38	2.61	.99
Osteoporosis	64 (7.6)	42 (5.0)	0.64	0.67	1.49	0.58	0.36	0.97	.02
Trauma	86 (10.3)	83 (9.9)	0.96	0.73	1.37	0.63	0.40	1.00	.05
Head injury	44 (5.2)	40 (4.8)	0.90	0.64	1.55	-	-	-	-
Delirium	6 (0.7)	12 (1.4)	2.01	0.37	2.68	1.23	0.25	6.12	.80
Sleep disturbance	74 (8.8)	93 (11.1)	1.29	0.73	1.38	1.17	0.81	1.69	.40
Aspiration pneumonia	43 (5.1)	49 (5.8)	1.15	0.66	1.52	0.56	0.32	0.97	.04
Disuse atrophy	54 (6.4)	54 (6.4)	1.00	0.68	1.48	0.87	0.56	1.35	.52
Decubitus	50 (6.0)	59 (7.0)	1.19	0.68	1.48	0.37	0.17	0.83	.02
Anemia	98 (11.7)	108 (12.9)	1.12	0.75	1.34	1.06	0.78	1.45	.72
Constipation	134 (16.0)	151 (18.0)	1.15	0.77	1.29	0.51	0.32	0.83	<.01
Overactive bladder	22 (2.6)	21 (2.5)	0.95	0.55	1.83	0.16	0.05	0.48	<.01



Abbreviation: CI, confidence interval.

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

impact the interpretation. Information on the severity of AD, socioeconomic status, and lifestyle-related risk factors was not available, such that the association of these characteristics with the occurrence of comorbid conditions could not be examined or adjusted.

Our study shows that in the total cohort, the users had lower CCI scores, which means that the users could have less comorbidities than nonusers due to contraindications for prescribing donepezil. For mitigating these confounding effects between comorbidities at baseline as the CCI scores and donepezil prescription, we used a risk set matching method so that the effect of donepezil prescription on the outcomes could be independently evaluated regardless of patient vulnerability at baseline.

Donepezil prescription also depended on physician's choice and preference without clear scientific criteria, and other interventional approaches for possible comorbidities among AD patients were not controlled. Moreover, the reasons for drug discontinuation were unavailable so that it would be unclear in the strict sense whether donepezil prescription could be correlated to subsequent occurrence of comorbidities. Furthermore, the record of drug prescription in the database did not ensure the actual uptake of drugs by patients, and poor compliance can result in estimation errors in models. Under these uncontrolled conditions, the relationship between donepezil use and physical comorbidities should be interpreted with caution, and nonpharmacological factors should be taken into account (e.g., rehabilitation, occupational therapy, and physical exercise).

Finally, there may be some censoring because the majority of electronic medical records databases in Japan are operated independently by hospitals, and patients transferred to other hospitals are not followed up. However, the present study only included patients with AD who were required to visit to same hospital regularly, such that the impact of this limitation is likely to be small. Regardless of these methodological limitations, the findings are likely to be robust because this study utilized a large sample size from more than 60 hospitals across Japan, which reflects the real clinical setting in Japan and real-time characteristics of patients with AD, unlike those included in clinical trials.

5. Conclusion

In summary, this study showed that donepezil treatment may be associated with fewer physical comorbidities in patients with AD. Although the mechanisms underlying these results remained unclear, donepezil may have positive effects on both cognition and physical status, either directly or indirectly. For clarifying these associations, further prospective study should be needed.

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Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.trci.2018.03.002>.

RESEARCH IN CONTEXT

1. Systematic review: Using PubMed for English language articles, we identified and reviewed all publications reporting on the association between donepezil prescription and the occurrences of physical comorbidities in patients with Alzheimer's disease, focusing on health records databases.
2. Interpretation: The association between donepezil and comorbidities in patients with Alzheimer's disease has been poorly reported, but some clinical findings showed that donepezil might have a positive influence on physical aspects. Our data are consistent with those previous findings and suggest that it would be necessary to consider risk-benefit balance more cautiously from both cognitive and physical perspectives when utilizing donepezil.
3. Future directions: Future studies should investigate those risk factors of occurring comorbid conditions with Alzheimer's disease in a real-world setting. Given that cognitive and physical frailty would be a key factor in this context, clinical or nonclinical studies on identifying the influence of donepezil on frailty should be needed.

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