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The influence and changes in the dosages of concomitantly used psychotropic drugs associated with the discontinuation of donepezil in severe Alzheimer's disease with behavioral and psychological symptoms on dementia: a preliminary open-label trial

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Abstract

Objective: We investigated the influence on behavioral and psychological symptoms on dementia (BPSD) and the changes in the dosages of concomitant psychotropic drugs associated with the discontinuation of donepezil in patients with severe Alzheimer's disease (AD) who developed BPSD during donepezil therapy.

Methods: The subjects were 44 inpatients who had been diagnosed with AD according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV). The outcome measures assessed were BPSD and cognitive function. BPSD was assessed using the Neuropsychiatric Inventory (NPI) and cognitive function was assessed using the Mini Mental Examination (MMSE). The changes in the dosages of concomitant psychotropic drugs were also assessed.

Results: Significant decreases were found in the donepezil treatment discontinuation group in the following NPI total score and two NPI subscales (agitation and irritability), but no significant differences were seen between the donepezil treatment discontinuation group and the control group. Furthermore, the mean changes from baseline in the risperidone equivalent dose and the diazepam equivalent dose were hardly changed in the donepezil treatment discontinuation group.

Conclusion: The results of this study suggest that the discontinuation of donepezil treatment in patients with AD with BPSD may afford superior efficacy and may make it possible to not increase the dosage of other psychotropic drugs.

Keywords: Alzheimer's disease, behavioral and psychological symptoms on dementia, donepezil, psychotropic drugs

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Introduction

Alzheimer's disease (AD) starts with a marked memory and/or orientation impairment, and progresses to generalized cognitive dysfunction. During the course of the disease, behavioral and psychological symptoms of dementia (BPSD) are observed [Finkel *et al.* 1996]. BPSD are often a caregiving burden in patients with dementia; however, as opposed to cognitive dysfunction, which progresses irreversibly and from which there is little chance of recovery, BPSD can be prevented or alleviated with appropriate interventions such as changes in the environment or drug therapy.

Patients being treated with donepezil, one of the cholinesterase inhibitors used to treat AD, sometimes experience psychiatric symptoms such as irritability and agitation. Furthermore, donepezil cannot be expected to be particularly efficacious

in severe AD and this increases the cost of therapy. However, in Japan, there have been almost no reports about donepezil's influence on BPSD, or the changes in the dosages of concomitantly administered psychotropic drugs associated with the discontinuation of donepezil in patients with severe AD (who developed BPSD) during donepezil therapy. In this study, therefore, patients with severe AD who developed BPSD during donepezil therapy were withdrawn from donepezil, and the influence on BPSD and the changes in the dosages of concomitant psychotropic drugs, both before discontinuation and 16 weeks after discontinuation, were confirmed.

Methods

Subjects

The subjects were 44 patients who were being treated on an inpatient basis at the psychiatry departments of Tanzawa Hospital, or the Adachi Shinseien or Hadano Shojuen homes for the elderly, and had been diagnosed with AD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. Patients were also diagnosed with probable AD according to the diagnostic criteria of the National Institute of Neurological and Communicative Disorders and Stroke and (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) [McKhann *et al.* 1984]. Only patients with AD with BPSD who had been using a stable dose of donepezil, a cholinesterase inhibitor, for at least 3 years were included. In addition, a group of patients with AD (22 subjects) was established as a control group who were not concomitantly receiving cholinesterase inhibitors and whose background characteristics were consistent with those of the patients in the group that discontinued their donepezil treatment (22 subjects). The donepezil treatment discontinuation group and the control group were recruited separately.

Furthermore, all the subjects who participated in this study were inpatients whose treatment compliance had been confirmed each time by a nurse or caregiver, and whose treatment compliance was thus assured. They were required to be symptomatically stable, as judged by the treating psychiatrist, and to be able to complete all the clinical measures.

The study was an open-label, flexible-dose, naturalistic observational trial of patients with AD undergoing the usual care and in whom it was necessary to discontinue donepezil treatment because of persistent symptoms or financial considerations. The control group had persistent symptoms or side effects. Patients had high scores in the Neuropsychiatric Inventory (NPI), even though they were considered stable. However, these patients could not be considered refractory to psychotropic drugs.

Only patients or family (caregivers) who had provided voluntary informed consent in writing to participate in this study, upon receiving a full explanation of the purpose and method of the study, were enrolled. Patient confidentiality was strictly adhered to, as were ethical considerations.

Donepezil treatment was discontinued as follows: patients receiving 5 mg were discontinued immediately at 0 week, whilst patients receiving 10 mg had their dosages reduced to 5 mg at 0 week, and were then withdrawn from donepezil at 2 weeks.

The psychotropic equivalents calculation table of Inagaki and Inada was used as a guideline for psychotropic equivalents [Inagaki and Inada, 2006, 2012] when calculating the baseline to postdose changes in the dosages of the concomitant psychotropic drugs. The subjects' daily dosages were calculated in terms of risperidone or diazepam equivalents.

Assessment methods

The following clinical assessments were performed at baseline and 16 weeks by the psychiatrist who was providing the actual therapy. The outcome measures assessed were BPSD and cognitive function. BPSD was assessed using the NPI [Cummings *et al.* 1994] and cognitive function was assessed using the Mini Mental Examination (MMSE) [Folstein *et al.* 1975] because our facilities did not have the Severe Impairment Battery (SIB), which is one of the best evaluation tools for cognition.

Statistical analysis

1) Comparison of baseline demographics – Fisher's exact tests.
2) Changes in symptoms and dosages of concomitantly used psychotropic drugs over time (within groups): paired *t*-tests. If the data did not show a normal distribution,

Table 1. Subject characteristics.

Characteristics	Control group (n = 22)	Donepezil treatment discontinuation group (n = 22)	p value
Age (years) (mean ± SD)	85.9 ± 5.4	84.2 ± 6.0	0.34
Gender (M : F)	1 : 21	6 : 16	
Duration of illness (years) (mean ± SD)	7.7 ± 4.0	7.3 ± 4.6	0.75
Risperidone equivalents dose (mg/day) (baseline) (mean ± SD)	0.18 ± 0.20	0.08 ± 0.24	0.13
Diazepam equivalents dose (mg/day) (baseline) (mean ± SD)	1.6 ± 2.7	1.5 ± 3.1	0.97
MMSE score (baseline) (mean ± SD)	1.6 ± 3.3	0.9 ± 1.6	0.39
NPI total score (baseline) (mean ± SD)	31.3 ± 14.3	28.6 ± 5.7	0.42

MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; SD, standard deviation.

then the Wilcoxon rank-sum test was used instead.

3) Changes in symptoms and dosages of concomitantly used psychotropic drugs over time (between groups): Mann-Whitney U test.

The significance level was $p < 0.05$ in all analysis.

Results

No significant differences were observed between the donepezil treatment discontinuation group and the control group in the baseline NPI total score, baseline MMSE score, mean daily dose of the previous treatment drug, mean duration of illness or the mean age of the patients (Table 1). The mean duration of donepezil treatment before the trial started was 64.9 ± 31.0 months.

Because all patients had a baseline score of ≤5 on the MMSE, they were all inpatients or in 24-hour care, with advanced or severe AD. Therefore, they also had difficulty communicating with the staff.

Significant decreases were found in the donepezil treatment discontinuation group in the NPI total score and two NPI subscales, agitation and irritability. No significant differences were seen between the donepezil treatment discontinuation group and the control group (Table 2). Moreover, no changes in the MMSE score were found either in the donepezil treatment discontinuation group or in the control group (Table 2).

Both groups in this study received the following psychotropic drugs. In the donepezil treatment discontinuation group, 13.6% (3/22) received antipsychotics, 13.6% (3/22) received benzodiazepine, and 27.3% (6/22) received trazodone. However, in the control group, 59.0% (13/22) received antipsychotics and 45.5% (10/22) received benzodiazepine. The mean changes from baseline in the risperidone equivalent dose and the diazepam equivalent dose were hardly different in the donepezil treatment discontinuation group, but a significant difference was seen between the donepezil treatment discontinuation group and the control group in the risperidone equivalent dose (Table 3). Although the mean change from baseline in the dosage of trazodone increased in the donepezil treatment discontinuation group, the difference was not significant (Table 3).

Discussion

The long-term use of donepezil may cause bradycardia and parkinsonism, which are the main reasons to discontinue donepezil. In this study, because the period of use of donepezil was relatively short, no serious adverse events such as bradycardia or parkinsonism were noted.

In the donepezil treatment discontinuation group, significant decreases were found in the agitation and irritability NPI subscales. Although there have been reports of the concomitant use of memantine monotherapy or memantine and cholinesterase inhibitors being effective against BPSD [Clerici *et al.* 2011; Cummings *et al.* 2006; Suzuki *et al.* 2013], there are also reports that donepezil worsens BPSD [Kimura *et al.* 2010; Kimura and Takamatsu, 2013a, 2013b]. Therefore, donepezil, a cholinesterase inhibitor, may worsen BPSD.

In the UK, when the MMSE score is ≤10, guidelines from the National Institute for Health and Care Excellence (NICE) recommend stopping the administration of cholinesterase inhibitors.

Table 2. Clinical efficacy.

	Control group (n = 22)				Donepezil treatment discontinuation group (n = 22)				p value
	Baseline		Change from baseline to 16 weeks		Baseline		Change from baseline to 16 weeks		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
NPI									
Total	31.3	14.3	−6.9	7.2*	28.6	5.7	−7.4	4.7*	0.48
Delusions	2.5	3.2	−0.6	1.0**	0.5	0.9			0.13
Hallucinations	4.1	3.0	−1.4	1.4*	0.9	2.0	−0.3	0.8	0.008
Agitation	6.1	4.2	−1.9	2.4*	8.0	2.9	−3.0	2.3*	0.14
Depression	0.1	0.2			0.4	1.8	−0.3	1.1	0.78
Anxiety	2.7	3.2	−0.7	1.2	2.7	3.5	−0.5	1.1	0.72
Euphoria	0.0	0.0			0.4	1.8	−0.1	0.5	0.78
Apathy	6.8	2.1			4.5	3.5	−0.4	1.2	0.58
Disinhibition	0.0	0.0			0.4	1.8	−0.1	0.5	0.78
Irritability	5.9	4.2	−3.6	3.8*	8.0	2.9	−2.8	2.4*	0.27
Aberrant motor behavior	2.9	3.2	−0.6	1.1**	3.3	2.8	0.3	2.2	0.46
MMSE score	1.6	3.3			0.9	1.6			

*$p < 0.005$ *versus* baseline, **$p < 0.05$ *versus* baseline.
MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; SD, standard deviation.

Table 3. Change over time in the risperidone equivalent dose, the diazepam equivalent dose and trazodone daily dose.

	Control group (n = 22)				Donepezil treatment discontinuation group (n = 22)				p value
	Baseline		Change from baseline to 16 weeks		Baseline		Change from baseline to 16 weeks		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Risperidone equivalent dose (mg/day)	0.18	0.20	0.08	0.12	0.08	0.24	-0.02	0.11	0.04
Diazepam equivalent dose (mg/day)	1.55	2.65			1.52	3.10	-0.61	1.65*	0.19
Trazodone daily dose (mg/day)					6.88	13.13	3.13	11.38	0.41

*Significant difference was found by Wilcoxon rank sum test ($p < 0.05$).
SD, standard deviation.

Conversely, in Japan, cholinesterase inhibitors are not stopped unless there are serious adverse events. In this study, we felt that in the case of patients with severe AD who had a baseline MMSE score of ≤5, it would not be possible to expect therapeutic medications for dementia to provide much efficacy and that this would result in an increased financial burden for the patients. In the clinical setting, therefore, it is always necessary to keep in mind the financial costs of therapeutic medications for dementia. The results of this study suggest that discontinuing donepezil treatment may at least not worsen BPSD. Furthermore, the control group had a significantly lower score on the NPI delusions and hallucinations subscale than the donepezil discontinuation group.

The reason for this was believed to be that the control group had a significantly higher

risperidone equivalent dose than the donepezil discontinuation group did. As far as the effects on cognitive function (a secondary outcome measure in this study) were concerned, no changes were found in the MMSE score, as observed in the control group. When BPSD accompanies severe AD, this frequently results in a considerable caregiving burden, appreciably complicates treatment and care, and leads to drug therapy with, for example, antipsychotic medications.

Since elderly patients generally have reduced liver and kidney function and are thus more susceptible to adverse drug reactions, every effort must be made to reduce the dosing levels that are used in the elderly. In 2005, the US Food and Drug Administration (FDA) reported effects such as increased death rate caused by the use of new antipsychotic medications in elderly patients and also reported similar results with conventional antipsychotic medications. In elderly patients, therefore, caution must be exercised when initiating drug therapy [Kudo, 2012]. The results of this study suggest that discontinuing donepezil treatment might not result in an increase in the risperidone equivalent dose, which would result in at least a certain degree of improvement in safety. In particular, in elderly patients, benzodiazepine is known to impair cognitive function, and elderly patients being given benzodiazepine must be watched carefully for signs of delirium [Inoue *et al.* 2011].

The results of this study suggest that discontinuing donepezil treatment might help reduce the equivalent dose of diazepam, even if only a little, which results in cognitive impairment. Moreover, serotonin plays an important role in the emergence of behavioral symptoms in dementia [Lawlor, 1990]. Previous research has shown that trazodone is effective against agitation in patients presenting with BPSD [Pinner and Rich, 1988; Aisen *et al.* 1993; Lawlor *et al.* 1994; Sultzer *et al.* 1997]. Therefore, trazodone is sometimes used. Although discontinuing donepezil treatment increased the trazodone dosage, the mean dose was 10.0 mg, suggesting that an appropriate level of safety was maintained.

As defined by the International Psychogeriatric Association (IPA), BPSD are symptoms of dementia. Therefore, BPSD should be controlled using therapeutic medications for dementia, rather than off-label drugs. The findings of this study are consistent with this position.

Limitations

In this study, the subjects had quite advanced (severe) dementia and, similarly, the different NPI subscale scores were very low, and we chose clinical assessments that could be investigated practically in a common clinical practice. Therefore, there were not many behavioral problems in the patients with AD with advanced stages of dementia and there was very little information about their clinical presentation.

The greatest limitation of this study was that it was a short-term study (16 weeks) with a relatively small sample size, and that it was an open-label, not a double-blind, study; therefore, the possibility that bias was introduced to the results cannot be ruled out. Consequently, there are limits to the conclusions that can be drawn from this study. A double-blind, randomized, controlled study in patients with AD with BPSD may be necessary in the future to clarify the efficacy and the changes in the dosages of concomitant psychotropic drugs, of memantine monotherapy, memantine and cholinesterase inhibitors, or placebo.

Conclusion

The results of this study suggest that the discontinuation of donepezil treatment in patients with AD with BPSD may afford superior efficacy and may make it possible to not increase the dosage of other psychotropic drugs.

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Conflict of interest statement

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