depression screening rates in elderly individuals, to reduce item non-response and not to exclude subjects with item non-response would be important.

### Conflict of interest

None of the authors has a conflict of interest to disclose.

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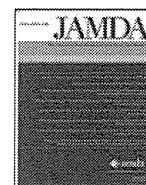
Original Study

# Patient-Related Factors Associated With Depressive State in Caregivers of Patients With Dementia at Home

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## ABSTRACT

Keywords:
Activities of daily living
caregiver
dementia
depression

Objectves: To identify patient-related factors associated with depressive state in caregivers of patients with dementia, we investigated the caregivers' and patients' characteristics in relation to the depressive state in their caregivers.
Design: Prospective hospital-based cohort study.
Setting: Two memory clinics in Japan.
Participants: Outpatients with dementia (n = 135) and their caregivers at home.
Measurements: The outpatients and their caregivers were divided into 2 groups according to the Center for Epidemiologic Studies Depression Scale for caregivers. To identify the patient-related factors that cause depressive state in caregivers, Mini-Mental State Examination (MMSE), the Physical Self-Maintenance Scale for fundamental activities of daily living (ADL), and the instrumental ADL scale (IADL) scores for instrumental ADL and the neuropsychiatric inventory (NPI) subscale score for behavioral and psychological symptoms of dementia were compared between the 2 groups. We used logistic regression to determine the independent predictors of caregiver depressive state.
Results: There was no significant difference in MMSE score between the 2 groups. Logistic regression analysis revealed that the depressive state in caregivers was related with IADL score and delusion in NPI subscale of patients.
Conclusions: Depressive state in caregivers was independent of the decline in cognitive function in patients with dementia but was associated with decline in instrumental ADL and severity of delusion.
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The caregiver burden in patients with dementia has been frequently investigated because of its adverse effect on the mental health of caregivers and on the quality of care provided to the patients. Previous studies demonstrated that the cognitive abilities of patients with dementia do not have a strong influence on caregiver burden,[1] whereas behavioral disturbances in patients contributes the most to family caregiver burden.[2] In addition, low activities of daily living (ADL) levels in patients with dementia are correlated with caregiver burden.[3]

Although caregiver burden and depressive symptoms in caregivers are both rooted in their emotional and psychological reaction to care demands, the relationship between these 2 parameters is unclear. Caregivers with higher levels of burden tend to have higher levels of depressive symptoms; however, caregivers with higher levels of depressive symptoms do not necessarily have higher levels of burden.[4]

Some comprehensive epidemiologic studies have focused on the presence of depressive state in caregivers. A cross-sectional analysis using the Medicare Alzheimer's Disease cohort revealed that 32% of caregivers had significant depressive symptoms.[5] Several dimensions of the caregiver's personality influences both burden and depressive symptoms in them.[6] Several studies suggest that caregivers with poor health condition, or fewer financial resources, are at a higher risk for depression. Some evidence also suggests that women and spousal caregivers are at a higher risk for depression.[7,8] Thus, previous studies on depression in caregivers mainly focused on caregiver

characteristics. However, we have hypothesized that not only factors associated with caregivers, but also patient-related factors, may induce caregiver depressive state.

In this study, we estimated the prevalence of depressive state among family caregivers of patients with dementia, and investigated the caregivers' and patients' characteristics in relation to the depressive state in caregivers.

## Methods

### Participants

All procedures followed the Clinical Study Guidelines of Ethics Committee of Kumamoto University Hospital and Kumamoto Mental Health Hospital and were approved by the internal review board. A complete description of all procedures was provided to the patients and their caregivers, and written informed consent was obtained from patients or their caregivers.

We studied 135 outpatients with dementia and their caregivers at the memory clinics of Kumamoto University and Kumamoto Mental Health Hospital. The participants were selected on the basis of inclusion/exclusion criteria from a consecutive series of 232 outpatients who had undergone their first medical examination at the memory clinics from June 2011 to March 2012. All individuals were examined by senior neuropsychiatrists (M.I. and M.H.) using routine laboratory tests, standard neuropsychological examinations, and brain magnetic resonance imaging (MRI) or brain computed tomography (CT). The diagnosis of dementia was based on the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition-revised (DSM-III-R). The following patients were excluded from the current study: (1) those without a reliable informant; (2) those with developmental abnormalities, serious psychiatric diseases, such as major depression, or substance abuse before the onset of dementia; (3) complication of other neurological diseases or unstable medical illnesses such as diabetes mellitus, thyroid disease, vitamin deficiencies, or malignant diseases; (4) those whose caregivers had hearing loss; and (5) inability to provide informed consent. The diagnosis of each dementia was established according to the international consensus criteria. Patients were divided into probable Alzheimer's disease (AD), which was defined according to the criteria of the National Institute for Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association,[9] probable vascular dementia (VaD), which was defined according to the criteria of the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences,[10] and probable dementia with Lewy bodies (DLB), which was defined according to the Consensus Criteria for the clinical diagnosis of DLB 2005.[11] The physical comorbidity (hypertension, diabetes, hyperlipidemia, etc) in patients was confirmed by routine laboratory tests and interviews of their caregivers.

### Assessments

Caregiver depressive symptoms were assessed using the Center for Epidemiologic Studies Depression (CES-D) scale.[12,13] The CES-D score was used as a total summed score, with 16 as a cutoff point for the risk of clinical depressive state. Patients and their caregivers were divided into 2 groups according to the CES-D score for caregivers. Patients and caregivers were classified into the depressive group if the caregiver's CES-D score was ≥16 points and into the nondepressive group if it was <16 points.[12]

The degree of perceived burden was measured using the Zarit Caregiver Burden Interview (ZBI)[14,15] We also evaluated caregiver burden using the Neuropsychiatric Inventory, Caregiver Distress

(NPI-D) subscale[16]; for each symptom domain of the Neuropsychiatric Inventory (NPI), caregivers were asked to rate their emotional or psychological distress on a scale of 0–5.

Mini-Mental State Examination (MMSE)[17] is one of the most widely used cognitive screening tests that quantitatively assess the severity of cognitive functions. The fundamental ADL of patients were evaluated using the Physical Self-Maintenance Scale (PSMS),[18,19] We also assessed instrumental ADL using the Instrumental Activities of Daily Living scale (IADL).[18,19]

We evaluated the comprehensive behavioral and psychological symptoms of dementia (BPSD) of patients semiquantitatively through their caregivers using the NPI.[20,21] Using this inventory, the following 10 BPSD were rated based on the patients' condition during the month that preceded the interviews: delusion, hallucination, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behavior.

### Statistical Analysis

Statistical differences between the depressive caregiver group and the nondepressive caregiver group were assessed using Student's 2-tailed t-test for age, education, duration of illness, and MMSE, ZBI, PSMS, IADL, and NPI scores. The $\chi^2$ test of independence was used to compare the parameters: sex, physical comorbidity, relationship of caregiver with the patient, living with patients, and diagnosis. Moreover the NPI and NPI-D subscale scores were compared between the 2 groups using Student's t-tests. Significance was set at 0.05 (2-tailed) for all analyses. To determine independent predictors of caregiver depressive state, we used multiple logistic regression analysis with forward selection method (likelihood ratio). We controlled all the factors that were included in the bivariate comparisons. Statistical analyses were performed using SPSS for Windows, v. 17.0.

### Results

A total of 135 patients consisted of 86 women and 49 men with mean age 79.5 years (standard deviation = 8.1), mean MMSE score of 16.8 points (standard deviation = 6.1). The level of severity of dementia was Clinical Dementia Rating (CDR) 0.5 in 41 cases, CDR1 in 59, CDR2 in 29, and CDR3 in 6. Among the 135 caregivers of patients with dementia, 44 caregivers (32.6%) presented depressive state. The diagnosis of patients was as follows: AD in 62.2% (84/135), VaD in 16.3% (22/135), DLB in 14.1% (19/135), and other conditions in 7.4% (10/135). The diagnosis of patients was AD in 50.0% (22/44), VaD in 36.4% (16/44), DLB in 9.1% (4/44) of patients in the depressive group, and AD in 68.1% (62/91), VaD in 6.6% (6/91), DLB in 16.5% (15/91) of patients in the nondepressive group. There was a significant difference in each diagnosis between the 2 groups (P = .001).

The characteristics of patients and caregivers in each group of depressive and nondepressive are presented in Table 1. The depressive group included 35 female caregivers (79.5%) and the nondepressive group included 57 female caregivers (62.6%); thus, caregivers with depressive state exhibited a significant female predominance compared with those with a nondepressive state (P = .048). In addition, the caregivers with depressive state exhibited a higher ZBI score than those without depressive state (P < .001).

PSMS and IADL scores were significantly lower in patients in the depressive caregiver group than in the nondepressive caregiver group (P < .001). However, there was no significant difference in either of the PSMS and IADL subscale scores between the 2 groups. The total NPI score was significantly higher in patients in the depressive caregiver group than in those in the nondepressive caregiver group (P = .003). There was no significant difference between the 2 groups with respect to other demographic variables of patients and caregivers.

**Table 1**
Characteristics of Patients and Caregivers in Each Group of Depressive and Nondepressive

| | Depressive Group (n = 44) | Nondepressive Group (n = 91) | P |
|---|---|---|---|
| **Caregivers** | | | |
| Age, mean (SD) | 62.8 (13.3) | 62.0 (12.9) | .726 |
| Male/female | 9/35 | 34/57 | .048* |
| Relations, spouse/children/others | 13/21/10 | 37/44/10 | .153 |
| Living with patients/separated | 34/10 | 71/20 | .922 |
| ZBI total score, mean (SD) | 33.0 (14.2) | 17.9 (13.5) | <.001* |
| **Patients with dementia** | | | |
| Age, mean (SD) | 80.9 (7.9) | 78.8 (8.1) | .165 |
| Male/female | 15/29 | 34/57 | .711 |
| Years of education, mean (SD) | 9.4 (2.4) | 10.0 (2.9) | .249 |
| Duration of illness, mean (SD) | 2.3 (2.1) | 2.2 (1.9) | .882 |
| Physical comorbidity, having / not having | 37/7 | 63/28 | .065 |
| MMSE score, mean (SD) (range 0–30) | 15.5 (6.8) | 17.5 (5.6) | .095 |
| PSMS, mean (SD) (range 0–6) | 2.8 (2.0) | 4.4 (1.8) | <.001* |
| IADL, mean (SD) (range 0–8) | 3.0 (2.3) | 5.1 (2.3) | <.001* |
| NPI total scores, mean (SD) (range 0–120) | 15.0 (11.5) | 9.0 (8.7) | .003* |

IADL, Instrumental Activities of Daily Living scale; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; PSMS, Physical Self-Maintenance Scale; ZBI, Zarit Caregiver Burden Interview.
*$P < .05$.

**Table 3**
Predictors of Caregiver Depressive State: Multivariate Analysis

| | B | Odds Ratio (95% CI) | P |
|---|---|---|---|
| **Caregiver factor** | | | |
| ZBI score | 0.054 | 1.055 (1.022–1.090) | .001* |
| **Patient-related factors** | | | |
| IADL score | −0.258 | 0.772 (0.639–0.934) | .008* |
| Delusion in NPI subscale | 0.241 | 1.273 (1.043–1.554) | .018* |

CI, confidence interval; IADL, Instrumental Activities of Daily Living scale; NPI, Neuropsychiatric Inventory; ZBI, Zarit Caregiver Burden Interview.
*$P < .05$, Model $\chi^2$ $P < .01$.

The results of the analysis of the relation between the NPI subscale score of patients and the presence of a depressive state in the caregivers are presented in Table 2. Apathy was found to be the most common symptom, whereas euphoria was the rarest symptom in both groups. Patients in the depressive caregiver group had significantly higher NPI and NPI-D scores in the delusion domain compared with those in the nondepressive caregiver group ($P = .006$ and $P = .005$, respectively). There was no significant difference between the 2 groups in other domains.

The result of multiple logistic regression analysis is presented in Table 3. Of caregiver factors, ZBI score was independently associated with depressive state [odds ratio (OR), 1.055; $P = .001$]. Of patient-related factors, IADL score and delusion in NPI subscale score were independently associated with caregiver depressive state (OR, 0.772; $P = .008$ and OR, 1.273; $P = .018$, respectively).

## Discussion

In this study, we analyzed the patient-related predictors of depressive state in caregivers of patients with dementia. While several factors have been pointed out as the predictors of caregiver

depression in previous studies,[8,22,23] simultaneous investigations of various patient-related factors was the strength of our study. We comprehensively assessed the association between depressive state in main family caregivers and patient-related factors using the MMSE, PSMS, IADL, and NPI scores. These results suggest that depressive state in caregivers is associated with a decline in ADL and the severity of BPSD rather than with a decline in cognitive function, in patients with dementia. In addition, we also found that instrumental ADL and delusion as patient-related factors were independently associated with caregiver depressive state.

Some studies reported that a lower level of ADL in patients with dementia was associated with higher caregiver burden,[2,3,8] whereas others reported that caregiver burden was not associated with the level of ADL in patients.[4,13] In the present study, patients' instrumental ADL independently associated with caregiver depressive state, whereas patients' fundamental ADL did not associate with caregiver depressive state. Therefore, we suggest that even if there is a small subjective care burden, the decline in instrumental ADL may directly induce depressive state in caregivers. In other words, even if caregivers were free from subjective burden, there might be objective burden that induced their depressive state on the caregivers of patients with impaired instrumental ADL. To confirm this hypothesis, it will be necessary to investigate the objective care burden, such as actual care time (the time required for caring for a patient at home). Compared with AD, VaD was generally associated with severe ADL limitations.[24] Thus, the caregivers of patients with VaD may have a higher risk of developing depressive state due to the decline in patient's ADL. To compare other types of dementia, patients with VaD were observed more frequently in the depressive caregiver group than the nondepressive caregiver group in this study.

A previous community-based study showed that irritability in patients resulted in the highest caregiver burden as well as the presence of strong associations between caregiver burden and agitation, depressive state, delusion, and hallucinations in patients.[16] Another study indicated that agitation was associated with the highest caregiver burden and that agitation, delusions, apathy,

**Table 2**
NPI and NPI-D Subscale Scores of Patients and Their Relation to the Depressive State in Caregivers

| Subscales | Depressive Group (n = 44) | | | Nondepressive Group (n = 91) | | | P | |
|---|---|---|---|---|---|---|---|---|
| | n (%) | Mean (SD) | | n (%) | Mean (SD) | | NPI | NPI-D |
| | | NPI | NPI-D | | NPI | NPI-D | | |
| Delusion | 19 (43.2%) | 1.95 (3.1) | 0.95 (1.4) | 18 (19.8%) | 0.54 (1.4) | 0.27 (0.7) | .006* | .005* |
| Hallucination | 20 (45.5%) | 1.36 (2.6) | 0.68 (1.2) | 18 (19.8%) | 0.65 (1.7) | 0.30 (0.8) | .056 | .060 |
| Agitation/aggression | 17 (38.6%) | 1.25 (2.0) | 1.02 (1.4) | 31 (34.1%) | 0.99 (1.9) | 0.60 (1.1) | .465 | .087 |
| Depression/dysphoria | 23 (52.3%) | 1.68 (2.5) | 0.93 (1.1) | 38 (41.8%) | 1.00 (1.7) | 0.54 (0.8) | .105 | .044* |
| Anxiety | 15 (34.1%) | 1.14 (2.1) | 0.61 (0.9) | 31 (34.1%) | 1.04 (2.2) | 0.47 (0.9) | .816 | .410 |
| Euphoria | 4 (9.1%) | 0.25 (1.0) | 0.07 (0.3) | 2 (2.2%) | 0.03 (0.2) | 0.01 (0.1) | .168 | .273 |
| Apathy | 33 (75.0%) | 4.14 (3.9) | 1.13 (1.0) | 62 (68.1%) | 2.98 (3.1) | 0.83 (0.9) | .063 | .091 |
| Disinhibition | 6 (13.6%) | 0.48 (1.4) | 0.34 (0.9) | 8 (8.8%) | 0.22 (0.9) | 0.13 (0.5) | .277 | .176 |
| Irritability/lability | 15 (34.1%) | 1.07 (1.8) | 0.75 (1.5) | 25 (27.4%) | 0.80 (1.7) | 0.45 (0.9) | .409 | .160 |
| Aberrant motor behavior | 14 (31.8%) | 1.70 (3.2) | 0.68 (1.2) | 16 (17.6%) | 0.78 (2.0) | 0.32 (0.8) | .082 | .066 |

NPI, Neuropsychiatric Inventory; NPI-D, Neuropsychiatric Inventory Caregiver Distress; SD, standard deviation.
*$P < .05$, Analysis by $t$-test.

irritability and aberrant motor behavior were significantly correlated with caregiver burden.[25] A clinic-based study revealed that delusions yielded the highest caregiver burden score, followed by agitation, anxiety, irritability, and depressive state.[3] Although the relationship between individual BPSD and the caregiver burden for patients with dementia has been investigated in detail, few comprehensive epidemiologic studies have focused on the relationship between individual BPSD and depressive state in caregivers. In the present hospital-based study, patients in the depressive caregiver group had significantly higher NPI and NPI-D scores in the delusion domain than those in the nondepressive caregiver group. Delusions of theft were the most common type of delusion among patients with AD.[26] Moreover, these patients complained to neighbors or other family members that principal caregivers were stealing their valuables. They directly criticized the principal caregivers and in some cases attacked them.[27] As indicated in previous studies,[3,16,25] delusions in AD are strongly related to the caregiver burden, which may induce depressive state in the caregivers of these patients.

This study had several limitations. First, the results may have been biased because all patients were recruited from the dementia outpatient clinics. BPSD varies depending on the patient's care settings. Second, we did not perform pathologic confirmation of the dementia subtype in our patients. Third, our sample size was relatively small for analyzing each dementia subtype, although the relatively large cohort used (compared with those of previous studies) was one of the advantages of the present study. A similar investigation should be performed in future using a larger sample size.

## Conclusions

In this prospective hospital-based cohort study of patients with dementia and their caregivers at home, depressive state in caregivers was independent of the decline in cognitive function in patients with dementia but was associated with decline in instrumental ADL and severity of delusion. These findings suggest that we should focus on support for instrumental ADL impairments and on the treatment of BPSD (particularly delusions) in the management of patients with dementia before their caregivers develop a depressive state. Focusing not only on caregiver characteristics but also assessing patient-related factors are essential for supporting long-term care of patients with dementia at home.

## Acknowledgments

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ORIGINAL ARTICLE

# Is sense of coherence helpful in coping with caregiver burden for dementia?

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## Abstract

**Background:** Sense of coherence (SOC) is associated with a reduced risk of various health problems and is thought to be a major factor related to the ability to cope with stress. In the present study, we examined the association between caregiver burden and SOC among caregivers to persons with dementia.

**Methods:** Participants included 274 caregivers or family members of community-dwelling elderly dementia patients. To assess the cognitive function of patients, neuropsychological tests (e.g. Mini-Mental State Examination, Clinical Dementia Rating) were conducted by a clinical psychologist who was well trained in interviewing participants; the tests used a semi-structured interview protocol. Senior neurologists and psychiatrists also independently evaluated the dementia status of patients. To assess the SOC and caregiver burden, a social welfare counsellor asked questions from a 13-item version of the SOC scale and the short, eight-item Japanese version of the Zarit Caregiver Burden Interview (ZBI).

**Results:** Among 78 caregivers of elderly subjects with cognitive impairment due to dementia, the ZBI score was significantly associated with SOC ($r = -0.38$, $P = 0.001$). Multiple regression analyses revealed that SOC scores ($\beta = -0.42$, $P < 0.001$) and Mini-Mental State Examination scores ($\beta = -0.28$, $P = 0.009$) were significantly associated with ZBI scores ($F_{(2, 76)} = 10.51$, $P < 0.001$). SOC was closely associated with personal strain in the ZBI ($\beta = -0.41$, $P < 0.001$; $F_{(3, 75)} = 8.53$, $P < 0.001$).

**Conclusion:** Caregivers with a strong SOC may be less prone to experiencing personal strain from their burden. These results suggest that reinforcement of SOC would contribute to reducing the personal strain.

## INTRODUCTION

In 2012, the Japanese population included an estimated 30.79 million people 65 years of age and older, accounting for 24.1% of the population.[1] It is therefore predicted that the incidence of age-related diseases will increase along with the growth of the elderly population. Among the diseases associated with ageing, dementia is often accompanied by behavioural and psychological symptoms of dementia (BPSD) and related cognitive impairment, and as a consequence, is associated with an enormous drain on caregivers.[2-4]

Today, Japan faces an unprecedented situation with respect to its rapidly growing elderly population; therefore, reducing the burden on caregivers for dementia patients is an urgent social objective.

In 1986, George and Gwyther defined caregiver burden as 'the physical, psychological or emotional, social and financial problems that can be experienced by family members caring for impaired older adults'.[5] Many subsequent studies have suggested that caregiver burden is closely associated with the health and well-being of caregivers.[6-10] Furthermore,

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whether a caregiver feels burdened in a particular situation depends on their ability to cope with stressful situations.[11,12]

With respect to the ability to cope with stress, Antonovsky proposed sense of coherence (SOC) as an important factor for health enhancement based on the results of research in highly motivated and healthy middle-aged and older people under stressful conditions.[13] According to Antonovsky's conceptualization, SOC has three components: comprehensibility, manageability and meaningfulness. Comprehensibility refers to people's ability to realize that their situation is understandable and/or predictable. Manageability refers to people's perception of their ability to cope with a difficult situation. Lastly, meaningfulness is the ability to find meaning in everyday events and/or in problems confronted.

Recently, it has been reported that the relationship between strong SOC and better health exists in various countries and ethnic/cultural groups.[14–16] Among caregivers for terminally ill cancer patients, but not for dementia patients, a strong SOC has been shown to mediate the effects of caregiving stressors, appraisals of caregiving confidence, and subjective caregiving burden on caregivers' depressive distress.[17] It is believed that those with a strong SOC are better able to cope with difficult situations as caregivers, which can have a positive impact on dementia patients.[18–20]

Hospital-based studies may provide a biased representation of caregiver's burden. Because extreme BPSD will motivate caregivers to take their charge to a hospital, the caretaker who visits the hospital would likely feel a greater burden and weakened self-esteem. Therefore, we aimed to explore in this epidemiological study whether a significant relationship exists between caregiver burden and SOC.

## METHODS

### Participants and procedures

We randomly selected 1000 community residents aged 65 years old and older who lived in Omuta City, Japan, from a nationwide dementia prevalence study. Participants were admitted to the survey between January 2012 and November 2012. Among the 1000 residents selected, 511 elderly participated. And of these 511 participants, 274 who participated in the study with a family member or caregiver were subjected to an investigation. A total of 229 subjects and

their family members/caregivers who did not have missing data values were included in the statistical analyses. The procedure for enrolment of the participants is shown in Figure 1. Caregivers for subjects with mild cognitive impairment and dementia ($n$ = 78) were included in the statistical analysis to assess the relationship between burden and SOC.

Participants were sent a study invitation that instructed them to visit a municipal facility to participate in the study and undergo neurocognitive and medical examinations. In cases where the examinee could not visit a study site, a physician and a healthcare professional visited the residence and conducted the interview. Interviews and neurocognitive testing were performed by well-trained clinical psychologists, social welfare counsellors, or nurses. A neurologist or psychiatrist then performed a physical examination and were responsible for diagnosing dementia. When it was difficult to reach a diagnosis, several doctors diagnosed the subjects using magnetic resonance imaging.

In order to assess cognitive function, we used the Japanese version of the Mini-Mental State
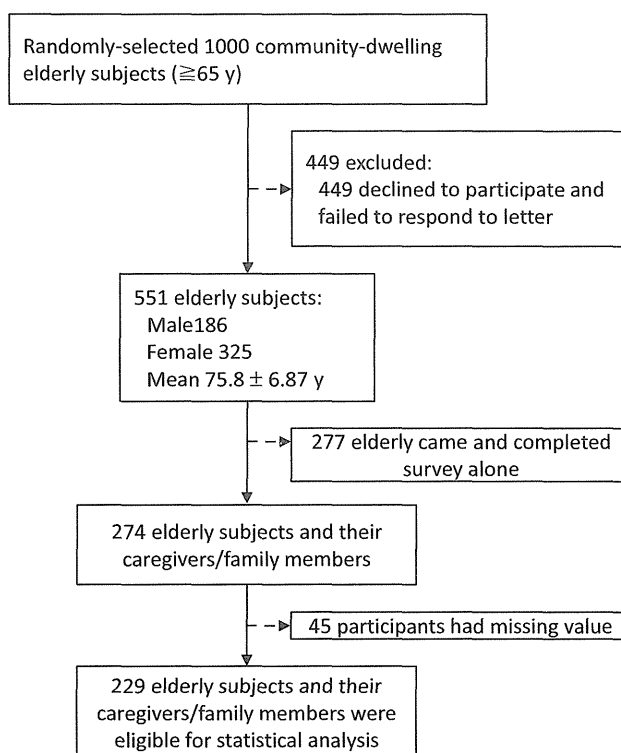


**Figure 1** Enrolment of participants. y, years.

Examination (MMSE) and the logical memory scale (I) of the Wechsler Memory Scale-Revised.[21-24] Among cases in which dementia was suspected based on the results of these two neuropsychological tests, the Geriatric Depression Scale was used to assess depression in the elderly,[25] and the Psychogeriatric Assessment Scale was used to assess cognitive impairment due to depression or stroke.[26] In cases where a more in-depth examination was necessary, cerebral magnetic resonance imaging was performed to determine the type of dementia.

Caregivers and family members who attended with the study participants were assessed using the Zarit Caregiver Burden Interview (ZBI),[27-29] the 13-item SOC scale,[30] and the Clinical Dementia Rating (CDR),[31] which is a standardized clinical dementia staging instrument. This study was approved by the Human Ethics Review Committee of Kumamoto University (Number 491) (Kumamoto, Japan). All participants and caregivers provided written informed consent before participating in this study.

## Measurements

The MMSE is a one of the most frequently used assessment methods for the estimation of cognitive function, and it has been shown to have adequate reliability and validity.[22] The Japanese version of the MMSE, which has a maximum score of 30 points, consists of 10 cognitive function domains. A higher score on the MMSE reflects better cognitive function.

The CDR is a widely used observational method for the assessment of dementia severity. The CDR consists of six domains for cognitive and functional performance in relation to dementia; global severity scoring is classified as non-dementia (CDR 0), mild cognitive impairment or questionable dementia (CDR 0.5), mild dementia (CDR 1), moderate dementia (CDR 2), and severe dementia (CDR 3).

Caregiver burden was assessed using the short, eight-item Japanese version of the ZBI developed by Arai et al.[27] The eight items were assessed on a 5-point Likert scale, ranging from 0 (never) to 4 (nearly always). The total score for this scale ranged from 0 to 32 points, with higher scores indicating increased caregiver burden. The validity and reliability of this test have been well established in previous studies.[28,29]

The ability to cope with stress was evaluated using the 13-item SOC scale. For each of the 13 questions, a family member or caregiver was asked to provide an answer on a 7-point scale with two anchoring phrases, 'very often' (1) and 'very seldom or never' (7). The total SOC score ranged from 13 to 91, with a higher score reflecting a stronger SOC. The 13-item version of the SOC scale has been shown to have adequate reliability and validity.[30,32]

## Statistical analyses

Pearson's correlation and multiple linear regression were used for data analysis. We applied the stepwise procedure to identify related variables for inclusion in regression models ($P < 0.05$). All statistical analyses were performed using SPSS Statistics 20.0.0.1 statistical software (IBM Corporation, Armonk, NY, USA). A two-tailed $P$-value of less than 0.05 was considered significant.

## RESULTS

The characteristics of participants and information regarding dementia are summarized in Table 1. The mean age of the 229 impaired elderly subjects was $74.0 \pm 7.0$ years, and 94 of the participants were men (41.0%). Of the 229 subjects, 53 (23.1%) were diagnosed with mild cognitive impairment, 16 (7.0%) with Alzheimer's disease, 4 (1.7%) with vascular dementia, 2 (0.9%) with dementia with Lewy bodies, 1 (0.4%) with Parkinson's disease with dementia, and 1 (0.4%) with frontotemporal dementia. The rate of CDR equal to or greater than 0.5 in the sample was 34.1%; the CDR informant was typically the subject's spouse (65.9%).

Table 2 shows Pearson's correlation coefficients for relationships between background information, cognitive function, stress-coping ability, and caregiver burden among the 78 caregivers and/or family members. The ZBI score was significantly associated with the SOC score ($r = -0.38$, $P < 0.001$). Multiple linear regression analysis revealed that the SOC score ($\beta = -0.42$, $P < 0.001$) and MMSE score ($\beta = -0.28$, $P = 0.009$) were significantly associated with the ZBI score ($F_{(2, 76)} = 10.51$, $P < 0.001$) (Table 3).

To more closely examine the association between stress coping ability and caregiver burden, we performed multiple linear regression analysis with the SOC score as the dependent variable and with sex, age, years of education, MMSE score, and ZBI score as independent variables (stepwise method). As shown in Table 4, decreased personal strain in the ZBI was significantly associated with a high SOC score

**Table 1** Characteristics of participants

| | |
|---|---|
| Age, mean ± SD (years) | 74.0 ± 7.0 |
| Sex (n) | |
|   Men | 94 (41.0%) |
|   Women | 135 (59.0%) |
| Condition and diagnosis (n) | |
|   Normal control | 154 (67.2%) |
|   Mild cognitive impairment | 53 (23.1%) |
|   Alzheimer's disease | 16 (7.0%) |
|   Vascular dementia | 4 (1.7%) |
|   Dementia with Lewy bodies | 2 (0.9%) |
|   Frontotemporal dementia | 1 (0.4%) |
|   Parkinson's disease with dementia | 1 (0.4%) |
|   Difficulty in diagnosis | 1 (0.4%) |
| Clinical Dementia Rating (n) | |
|   CDR 0 | 151 (66.0%) |
|   CDR 0.5 | 54 (23.6%) |
|   CDR 1 | 9 (3.9%) |
|   CDR 2 | 7 (3.1%) |
|   CDR 3 | 8 (3.5%) |
| Geriatric Depression Scale, mean ± SD | 3.6 ± 2.9 |
| Mini-Mental State Examination, mean ± SD | 25.9 ± 5.6 |
| Zarit Caregiver Burden Interview, mean ± SD[†] | 2.3 ± 4.7 |
|   Personal strain | 1.7 ± 3.3 |
|   Role strain | 0.7 ± 1.9 |
| Score of sense of coherence, mean ± SD | 72.4 ± 12.7 |
| Informant about CDR, burden, and SOC (n) | |
|   Spouse | 151 (65.9%) |
|   Child (living together) | 31 (13.5%) |
|   Child (living separately) | 27 (11.8%) |
|   Child's partner (living together) | 6 (2.6%) |
|   Child's partner (living separately) | 3 (1.3%) |
|   Other | 11 (4.8%) |

†Eight-item version of the test.
CDR, Clinical Dementia Rating; SOC, sense of coherence.

($F_{(3,\ 75)} = 8.53$, $P < 0.001$) among elderly subjects after controlling for sex and cognitive function.

## DISCUSSION

In this study, we aimed to examine the factors that determine caregiver burden and to identify the association between caregiver burden and stress-coping ability. We found that for elderly subjects, caregiver burden was significantly associated with a lower MMSE score of participants and a weakened SOC. Furthermore, SOC was particularly closely related to personal strain in the ZBI after confounding factors such as sex and cognitive function were controlled.

The ZBI score is based on two subscores: personal strain and role strain. Stress-coping ability is related to personal strain, which is 'how personally stressful the experience is'.[29] Reinforcement of SOC might therefore decrease the personal strain of a caregiver's burden. In contrast, role strain, which is 'stress due to

role conflict or overload',[29] was not associated with SOC. Therefore, the introduction of formal instrumental support such as respite care would help reduce the role strain of a caregiver's burden rather than enhance stress-coping ability.

To our knowledge, four studies have examined SOC among caregivers for individuals with dementia.[18–20,33] In 2008, Andrén and Elmståhl revealed that caregivers with a lower caregiver burden had significantly higher SOC scores than those with a higher burden. They proposed that a low SOC might be a hallmark characteristic of a high-risk group of caregivers for whom early interventions to reduce the burden would be warranted.[20] Furthermore, Orgeta and Sterzo reported that caregivers with a low SOC are more likely to report high levels of depression and anxiety. They emphasized the need to for psychotherapeutic interventions that target the enhancement of SOC for familial caregivers of people with dementia.[18] In a randomized controlled trial, Langeland *et al.* reported that group talk therapy for community residents with mental health problems enhanced the SOC and life satisfaction of participants.[32] It is therefore expected that employing interventions to enhance SOC, such as the nursing care activities for community residents reported by Langeland *et al.*, might be effective in reducing caregiver burden for dementia. The results of that study, however, pertain to European nations, and there is a paucity of data from research involving Japanese caregivers. The similar association regarding Japanese subjects in the present study lends support to these previous findings.

Our study has several notable limitations. First, cause-and-effect relationships could not be determined because of the cross-sectional study design. Second, only a limited amount of caregiver information was collected, and some potentially confounding factors cannot be ruled out. SOC is believed to be nurtured in the process of maturation. Because it is thought that factors such as familial background, life experience, and individual economic conditions can potentially influence SOC, these caregiver factors should be controlled for in future studies. Third, our analysis did not assess or control for the severity of BPSD. Regarding psychosocial factors of caregivers and the BPSD of participants, these should ideally have been, but were not, controlled for statistically by multivariate data analysis in large samples. Fourth, the paucity of data regarding caregivers for dementia

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**Table 2** Correlations between age, years of education, cognitive function, sense of coherence, and ZBI

| | Age | | Years of education | | MMSE score | | SOC score | |
|---|---|---|---|---|---|---|---|---|
| | r | P-value | r | P-value | r | P-value | r | P-value |
| ZBI score | 0.21 | 0.066 | −0.05 | 0.650 | −0.21 | 0.067 | −0.38 | <0.001*** |
| Age | – | – | −0.24 | 0.033* | −0.34 | 0.002** | −0.14 | 0.233 |
| Years of education | −0.24 | 0.033* | – | – | 0.17 | 0.145 | 0.20 | 0.076 |
| MMSE score | −0.34 | 0.002** | 0.17 | 0.145 | – | – | −0.16 | 0.154 |
| SOC score | −0.14 | 0.233 | 0.20 | 0.076 | −0.16 | 0.154 | – | – |

***$P < 0.001$, **$P < 0.01$, *$P < 0.05$. MMSE, Mini-Mental State Examination; SOC, sense of coherence; ZBI, Zarit Caregivers Burden Interview.

**Table 3** Association between caregivers' burden and related factors

| | β | t | P-value |
|---|---|---|---|
| Sex (male = 0, female = 1) | | n.s | |
| Age | | n.s | |
| Years of education | | n.s | |
| MMSE score | −0.28 | −2.68 | 0.009** |
| SOC score | −0.42 | −4.10 | <0.001*** |

***$P < 0.001$, **$P < 0.01$. MMSE, Mini-Mental State Examination; n.s means not significance; SOC, sense of coherence.

**Table 4** Association between sense of coherence and two subscores of Zarit Burden Interviw

| | β | t | P-value |
|---|---|---|---|
| Sex (male = 0, female = 1) | −0.25 | −2.36 | 0.021* |
| Age | | n.s | |
| Years of education | | n.s | |
| MMSE score | −0.29 | −2.75 | 0.007** |
| Zarit Burden Interview | | | |
| Personal strain | −0.41 | −4.04 | <0.001*** |
| Role strain | | n.s | |

***$P < 0.001$, **$P < 0.01$, *$P < 0.05$. MMSE, Mini-Mental State Examination; n.s means not significance.

patients with clinically moderate or severe symptoms may limit the generalizability of results in this study.

In summary, this study yielded new evidence regarding the association between caregiver burden and stress-coping ability. The study's limitations notwithstanding, our findings contribute to a better understanding of the concept of SOC in dementia care. Caregiver burden related to the care of dementia patients is a very common problem in Japan. Therefore, further longitudinal or interventional studies would be worthwhile.

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RESEARCH

# Long-term donepezil use for dementia with Lewy bodies: results from an open-label extension of Phase III trial

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## Abstract

**Introduction:** The long-term efficacy and safety of donepezil 10 mg in patients with dementia with Lewy bodies (DLB) were investigated in a 52-week Phase 3 trial.

**Methods:** This 52-week study consisted of 16-week randomized placebo-controlled (RCT) and 36-week open-label extension phases. Of 142 DLB patients enrolled in the RCT phase (three arms: placebo, 5 mg, and 10 mg), 110 entered the extension phase. The placebo group of the RCT phase initiated active treatment at week 16, and the active groups maintained allocated treatment and dosages until week 24. After week 24, all patients received 10 mg. Dose reduction to 5 mg for safety concerns was allowed. Efficacy measures included Mini-Mental State Examination (MMSE) for cognitive function and Neuropsychiatric Inventory (NPI) for behavioral symptoms. Safety evaluations included adverse events (AEs) and the unified Parkinson disease rating scale.

**Results:** In total, 100 subjects completed the study. Cognitive function improvement was sustained for 52 weeks (MMSE at week 52 in 10 mg: $2.8 \pm 3.5$ (mean ± standard deviation); $P < 0.001$, Student paired $t$ test)). Those who received placebo in the RCT phase showed an improvement after starting active treatment. NPI improved in all the groups throughout the study, including the placebo period. In the subgroup of the 5 mg group without remarkable cognitive or behavioral improvement at week 24, further improvement was observed after a dose increase to 10 mg. After week 24, 21 patients experienced dose reduction. The incidence of any AEs did not increase over time.

**Conclusions:** The long-term administration of donepezil at 10 mg/day improved cognitive function for up to 52 weeks in patients with DLB without increasing the risk of clinically significant safety events.

**Trial registration:** NCT01278407. Trial registration date: January 14, 2011.

## Introduction

Dementia with Lewy bodies (DLB) is a common form of dementia in the elderly, and constitutes the second largest group of patients with dementia, following Alzheimer disease (AD) [1]. The core clinical features of DLB include neuropsychiatric symptoms and parkinsonism, as well as cognitive impairment characterized by deficits of attention, executive function, and visual perception [2]. The progression of cognitive impairment is faster than or similar to that in AD [3-6]. Patients with DLB have a higher risk for falls [7,8], higher risk of admission [9],

lower activities of daily living, lower quality of life, and a heavier caregiver burden [10-13], compared with those with AD.

Cholinergic neurotransmission is more defective in patients with DLB than in those with AD [14]. Although cholinergic losses in DLB affect both brainstem and basal forebrain presynaptic nuclei, postsynaptic cortical muscarinic and nicotinic receptors are preserved [15]. For these reasons, cholinesterase inhibitors (ChEIs) may be effective for treating DLB, and several clinical trials have demonstrated favorable potential of ChEIs such as galantamine, rivastigmine, and donepezil for DLB [16-22].

The previous Phase 2, 12-week, randomized double-blind placebo-controlled trial of three different doses of donepezil in patients with DLB [22] demonstrated that

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donepezil significantly improved all of the efficacy end-points of cognitive impairment, behavioral and psychiatric symptoms, global clinical symptoms, and caregiver burden, compared with placebo, and the open-label 1-year extension study of donepezil at 5 mg/day [23] showed that the major concerns about the safety of long-term administration of 5 mg donepezil, including parkinsonism and cardiovascular events, were minimal, and that the mild improvement of cognitive impairment and psychiatric symptoms was sustained for up to 52 weeks.

Based on these results, a Phase 3 study, which integrated a randomized placebo-controlled, double-blind comparative study (RCT phase) and an open-label extension study (extension phase), was conducted in patients with DLB to confirm the superiority of donepezil at 5 and 10 mg/day for 12 weeks over placebo and to evaluate the safety and efficacy of long-term administration of 10 mg/day. The RCT phase yielded the efficacy of donepezil on cognitive impairment with significant improvement in MMSE compared with placebo in the 10 mg group (mean ± standard deviation (SD): 0.6 ± 3.0 and 2.2 ± 2.9 in the placebo and 10 mg group, respectively; $P = 0.016$, analysis of covariance (ANCOVA)), although a significant difference was not detected on the behavioral and neuropsychiatric measures (change in Neuropsychiatric Inventory-2 (NPI-2) (mean ± SD): −2.0 ± 4.2 and −2.9 ± 4.7 in the placebo and 10 mg group, respectively; $P = 0.391$, ANCOVA), falling short of confirming the pre-defined superiority of donepezil compared with placebo at either dose (5 or 10 mg/day). With detailed information of the results reported elsewhere [24], this report describes the results obtained through long-term administration of the higher dose of donepezil in DLB.

## Methods
### Patients
Patients diagnosed as probable DLB, according to the consensus diagnostic criteria [2], were recruited from 72 psychiatric or neurologic specialty centers throughout Japan from February 2011 to March 2012. Eligible patients were outpatients aged ≥50 years with mild to moderately severe dementia (10 to 26 on the MMSE and Clinical Dementia Rating ≥0.5) and behavioral and psychiatric symptoms NPI-plus ≥8 and NPI-2 ≥ 1). NPI-plus consisted of 12 items: original 10 items [25,26], sleep, and cognitive fluctuation, which was reported as Cognitive Fluctuation Inventory [27]. NPI-2 consisted of hallucinations and cognitive fluctuation [22]. Caregivers of the eligible patients had to stay with them routinely at least 3 days per week and 4 hours per day, provide information for this study, assist with the compliance with treatment, and escort them to required visits. The evidence or rationale for the presence of the core features, on which

each diagnosis of DLB was based, was provided and examined by the review board (Mori, Ikeda, and Kosaka) to assure the validity of the diagnosis.

Exclusion criteria included Parkinson disease diagnosed at least 1 year prior to the onset of dementia; focal vascular lesions on MRI or CT that might cause cognitive impairment (for example, infarcts/hemorrhages affecting the thalamus, caudate nucleus, or globus pallidus, single infarct of diameter ≥1.5 cm or multiple infarcts in any other regions, and moderate or severe white matter changes); other neurologic or psychiatric diseases; clinically significant systemic disease; complications or history of severe gastrointestinal ulcer, severe asthma or obstructive pulmonary disease; systolic hypotension (<90 mm Hg); bradycardia (<50 m$^{-1}$); sick sinus syndrome; atrial or atrio-ventricular conduction block; QT-interval prolongation (≥450 ms); hypersensitivity to donepezil or piperidine derivatives; severe parkinsonism (Hoehn and Yahr score ≥ IV) [28]; and treatment with ChEIs or any investigational drug within 3 months before screening. ChEIs, antipsychotics, and anti-Parkinson drugs other than L-dopa or dopamine agonists were not allowed during the study.

### Procedures
This was a 52-week, multicenter, Phase 3 study consisting of a 16-week, randomized, double-blind, placebo-controlled phase (referred as RCT phase) and the subsequent 36-week, open-label extension phase (referred as extension phase) (Figure 1).

After a 2-week prerandomization period with placebo administration, the patients were randomly assigned in a 1:1:1 ratio to placebo or 5 mg or 10 mg of donepezil in the RTC phase. Treatment began with 3 mg and was then titrated. After the RCT phase (ended before Week 16), the dose was maintained until Week 52 in the 10 mg group of the RCT phase (referred to as DON10-DON10). In the 5 mg group of the RCT phase, the dose was increased to 10 mg/day at Week 24 (referred to as DON5-DON10). The placebo group started active treatment with 3 mg at the beginning of the extension phase (at Week 16), and the dose was then increased to 5 mg at Week 18 and to 10 mg at Week 24 (referred to as PLA-DON10). After Week 24, dose reduction to 5 mg was allowed if continuation at 10 mg caused any safety concerns.

The randomization code was broken in August 2012 after all data of the RCT phase were fixed before the end of the extension phase (March 2013). The physicians and patients were kept blinded to the treatment allocation until the extension phase completion by blinded titration by using a similar placebo.

Written informed consent was obtained from the patient (if at all possible) and his/her primary caregiving family member before initiating the study procedures. The study was conducted in accordance with the principles of

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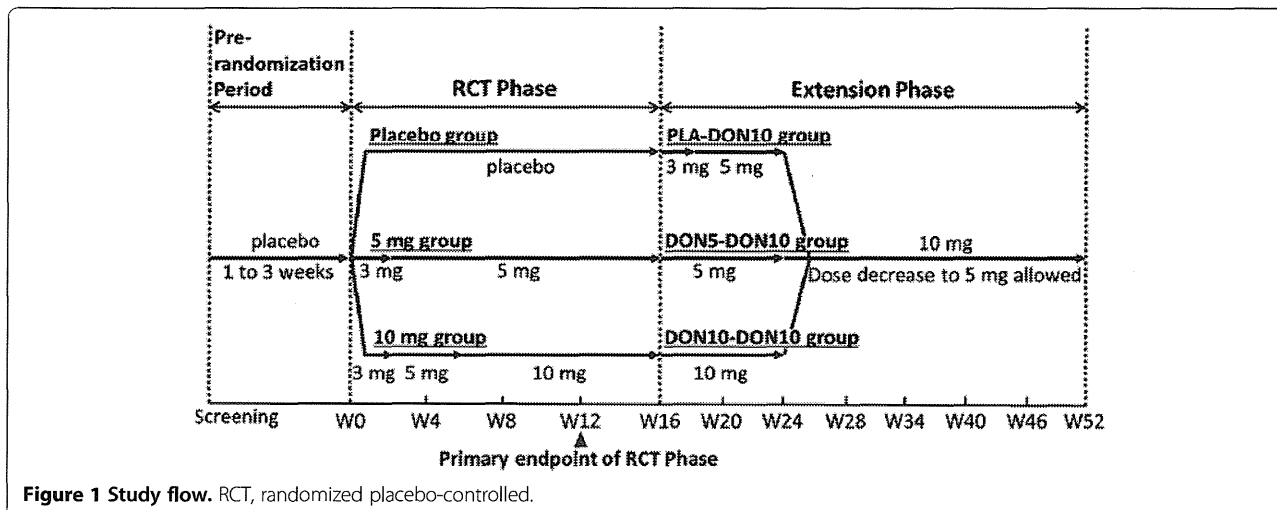


**Figure 1 Study flow.** RCT, randomized placebo-controlled.

the Declaration of Helsinki. The protocol was approved by the institutional review board at each center (see Additional file 1).

## Outcome measures

Cognitive function was assessed by using the MMSE [29]. Behavioral and psychiatric symptoms were assessed by using the NPI-2 [22] and NPI-10 [25,27]. NPI-2 was calculated as the sum of the scores for hallucinations and cognitive fluctuation [26], which correspond to the core features of DLB in the consensus criteria. These measures were assessed at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 34, 40, 46, and 52. Caregiver burden was assessed by using the Zarit Caregiver Burden Interview (ZBI) [30], which evaluates the physical, psychological, and social consequences of caring activities. The ZBI contains 22 items scored from 0 (best) to 4 (worst), from which a total score of 0 to 88 is calculated. The ZBI was assessed at 0, 12, 24, 40, and 52 weeks.

Safety was assessed based on the adverse events (AEs), vital signs, electrocardiogram, and laboratory tests. All AEs were classified and coded according to Medical Dictionary for Regulatory Activities (MedDRA) terms. Gastrointestinal symptoms, parkinsonian symptoms, psychiatric symptoms, and arrhythmia were assessed as AEs of interest. Motor function was assessed as a safety measure by using the Unified Parkinson's Disease Rating Scale (UPDRS) part III [31].

## Statistical analyses

Sample-size calculation is reported elsewhere [24]. The safety analysis set (SAS) comprised all patients who received at least one dose of donepezil and had safety-assessment data. The incidence of AEs was summarized based on the treatment period with the active drug; safety analysis in the DON5-DON10, DON10-DON10 groups, and the combined group of them (referred to

as DON-DON10) encompasses the entire study period, including the RCT phase (52 weeks), and that in the PLA-DON10 group covers the extension phase alone (36 weeks). Laboratory parameters and vital signs were summarized by descriptive statistics. Scores or their changes in UPDRS part III from the baseline in each of the DON5-DON10 and DON10-DON10 groups or in the DON-DON10 group were analyzed by using Student paired $t$ test.

Efficacy was analyzed in the full analysis set (FAS), including the randomized patients who received the study drug at least once and had valid efficacy assessment data at more than one point. Exploratory analyses were performed as appropriate to compare scores at every evaluation point in each of the three groups with the baseline (Week 0) by paired $t$ tests, and in the DON5-DON10 group, also to compare scores at every evaluation point with Week 24 to evaluate the effect of dose increment by paired $t$ tests and mixed-effect model for repeated measures (MMRMs). The parameters included in the model were the Observed value at week 24 as a covariate, and Subgroup stratified according to the degree of improvement, Visit, and Interaction as factors. Values at the final evaluation were imputed by using a last observation carried forward (LOCF) method.

$P$ values were not adjusted for multiplicity. All statistical tests were two-tailed, and $P < 0.05$ was considered to indicate statistical significance. All analyses were made on SAS versions 9.1 and 9.2 (SAS Institute, Cary, NC, USA).

## Results

### Baseline characteristics

Of 161 patients enrolled in the pre-randomization period, 142 were enrolled in the RCT phase and randomized to the placebo, 5 mg, and 10 mg groups (46, 47, and 49 patients, respectively). During the RCT phase (by Week 16), 32 patients were discontinued (9, 17, and 6 patients in the

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placebo, 5 mg, and 10 mg groups, respectively). The reasons for the discontinuations were AEs (17 patients), patient's request (11 patients), and other reasons (4 patients). In the placebo group, 37 patients started active treatment at Week 16. During the extension phase, 10 patients were discontinued (3, 4, and 3 patients in the PLA-DON10, DON5-DON10, and DON10-DON10 groups, respectively) because of AEs (6 patients) and patient's request (4 patients) (Figure 2).

Demographic and baseline characteristics of the FAS are summarized in Table 1. No characteristic differences occurred between the three groups. Females accounted for 58.0%. The mean age was 77.9 (range, 57 to 95) years; all but 2 patients were 65 years or older. Dementia medication had previously been used by only 5.8% of the patients. The mean score of the MMSE at baseline was 20.4 points.

### Cognitive function

Changes in MMSE are shown in Figure 3. Significant improvement compared with baseline was observed from Weeks 8 to 52 in the DON5-DON10 group, and from Week 4 to 52 in the DON10-DON10 group. The mean changes (mean ± SD, Student paired $t$ test) at Week 52 and at the final evaluation (LOCF) from baseline were 2.5 ± 3.1 ($P < 0.001$) and 1.3 ± 3.6 ($P = 0.018$) in the

DON5-DON10 group, 2.8 ± 3.5 and 2.4 ± 3.7 ($P < 0.001$ each) in the DON10-DON10 group, respectively.

In the DON5-DON10 group, MMSE increased by 0.4 to 1.1 points at Week 28 to 52 compared with that before the dose increase at Week 24, although it was not significant (Student paired $t$ test). For further exploration of this result, changes in MMSE by the subgroups with and without MMSE improvement of 3 points or more from baseline at Week 24 (cognitively improved and less improved by 5 mg) were calculated (Figure 4). Using MMRM for the observed value at or after Week 24, the effect of dose increment was found significant (subgroup, visit, and interaction were $P = 0.018$, $P = 0.328$, and $P = 0.047$, respectively). In the subgroup of less-improved, MMSE significantly increased after dose increment (mean changes from Week 24 with SD (Student paired $t$ test) at Weeks 28, 34, 46, and 52: 2.2 ± 3.1 ($P = 0.019$), 2.6 ± 3.2 ($P = 0.011$), 2.0 ± 2.4 ($P = 0.013$), and 1.8 ± 2.2 ($P = 0.019$), respectively).

The PLA-DON10 group showed significant improvement from the baseline (Week 0) through the period after starting active drug at Week 16; the mean changes at Week 28 or later were similar to those in the DON5-DON10 and DON10-DON10 groups, in which treatment with active drugs was started earlier.

In 18 patients whose dose was reduced from 10 mg to 5 mg because of adverse events (9, 4, and 5 patients in
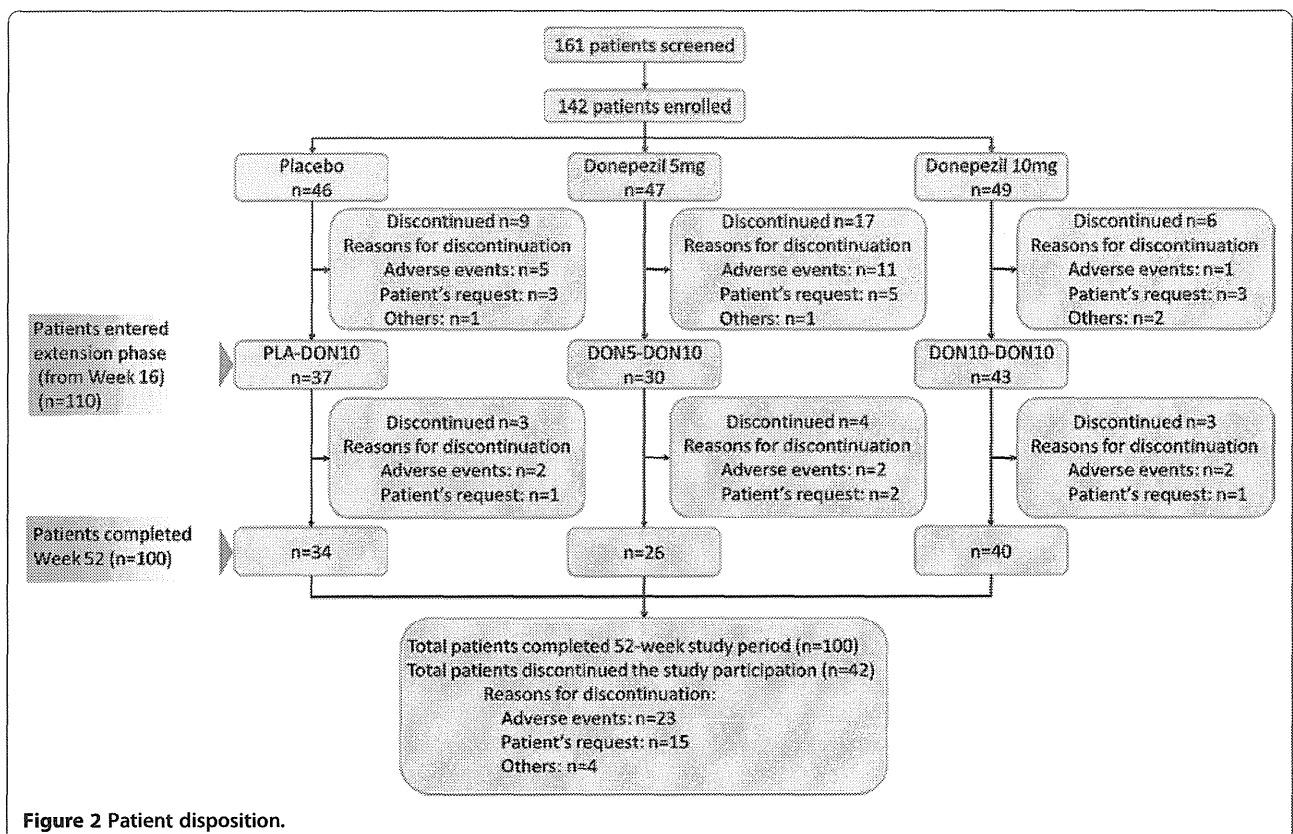


**Figure 2 Patient disposition.**

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## Table 1 Patient demographics and baseline characteristics (FAS)

| | PLA-DON10 (n = 37) | DON5-DON10 (n = 45) | DON10-DON10 (n = 49) | DON-DON10 (n = 94) |
|---|---|---|---|---|
| Sex, number (%) | | | | |
|    Male | 14 (37.8) | 20 (44.4) | 21 (42.9) | 41 (43.6) |
|    Female | 23 (62.2) | 25 (55.6) | 28 (57.1) | 53 (56.4) |
| Age, years | 76.7 ± 6.0 | 78.8 ± 5.1 | 77.7 ± 6.8 | 78.2 ± 6.1 |
| Weight, kg | 51.52 ± 10.68 | 50.68 ± 9.24 | 51.72 ± 9.89 | 51.22 ± 9.55 |
| Duration of dementia, years | 2.1 ± 2.4 | 2.7 ± 1.8 | 2.3 ± 1.9 | 2.5 ± 1.9 |
| History of antidementia medication, number (%) | | | | |
|    Yes | 1 (2.7) | 3 (6.7) | 4 (8.2) | 7 (7.4) |
|    No | 36 (97.3) | 42 (93.3) | 45 (91.8) | 87 (92.6) |
| Visual hallucinations, number (%) | | | | |
|    Yes | 37 (100.0) | 39 (86.7) | 39 (79.6) | 78 (83.0) |
|    No | 0 | 6 (13.3) | 10 (20.4) | 16 (17.0) |
| Cognitive fluctuation, number (%) | | | | |
|    Yes | 34 (91.9) | 41 (91.1) | 46 (93.9) | 87 (92.6) |
|    No | 3 (8.1) | 4 (8.9) | 3 (6.1) | 7 (7.4) |
| Parkinsonism, number (%) | | | | |
|    Yes | 32 (86.5) | 39 (86.7) | 44 (89.8) | 83 (88.3) |
|    No | 5 (13.5) | 6 (13.3) | 5 (10.2) | 11 (11.7) |
| Hoehn & Yahr, number (%) | | | | |
|    I | 4 (10.8) | 8 (17.8) | 7 (14.3) | 15 (16.0) |
|    II | 15 (40.5) | 17 (37.8) | 19 (38.8) | 36 (38.3) |
|    III | 13 (35.1) | 14 (31.1) | 18 (36.7) | 32 (34.0) |
| MMSE | 20.2 ± 4.3 | 20.6 ± 4.1 | 20.3 ± 4.8 | 20.4 ± 4.4 |
| NPI-2 | 6.9 ± 3.9 | 6.9 ± 4.5 | 7.3 ± 4.7 | 7.1 ± 4.6 |
| NPI-10 | 19.1 ± 13.5 | 18.9 ± 15.3 | 16.6 ± 11.7 | 17.7 ± 13.5 |
| ZBI | 26.0 ± 15.4 | 28.3 ± 18.5 | 31.4 ± 17.8 | 29.9 ± 18.1 |

FAS, full analysis set, MMSE, Mini-Mental State Examination, NPI: Neuropsychiatric Inventory, ZBI: Zarit Caregiver Burden Interview. Values are expressed as mean ± SD, unless otherwise specified.
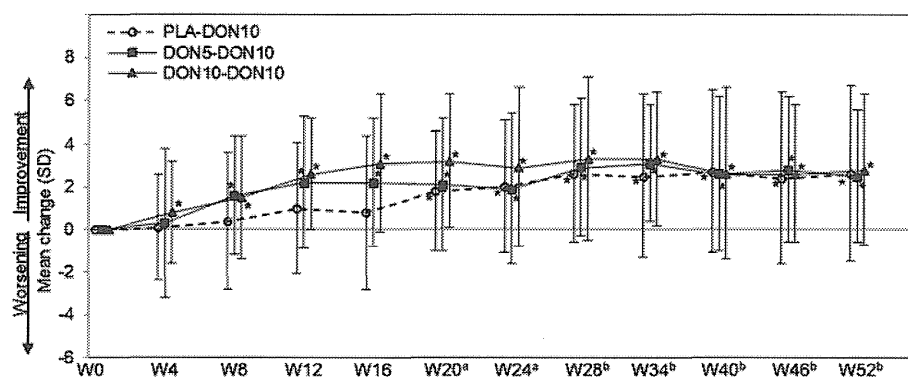


**Figure 3 Mean change in MMSE from baseline (FAS).** MMSE, Mini-Mental State Examination; FAS, full-analysis set. [a] PLA-DON10 group started treatment with 3 mg at Week 16, and the dose was increased to 5 mg at Week 18. [b] PLA-DON10 and DON5-DON10 groups started treatment with 10 mg at Week 24 (dose decrease to 5 mg was allowed). $*P < 0.05$ (paired $t$ test versus Week 0).

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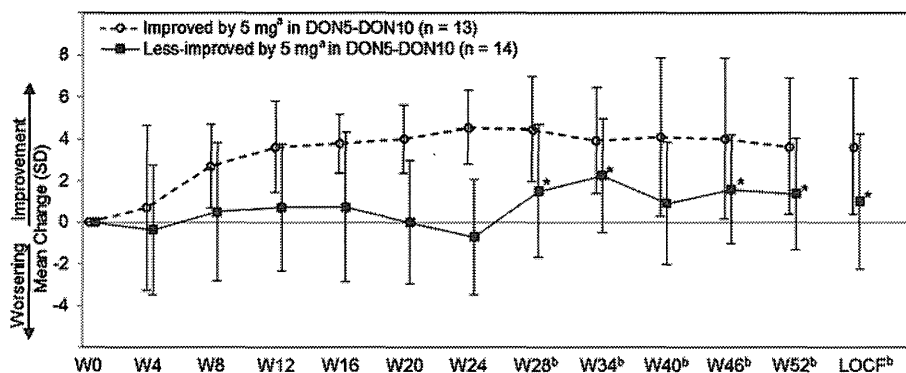


**Figure 4 Mean MMSE change in subgroups of improved and less-improved by 5 mg (FAS, DON5-DON10 group).** MMSE, Mini-Mental State Examination; FAS, full analysis set; LOCF, last observation carried forward. [a]The cognitively improved by 5 mg is defined as a patient with 3 points or more improvement in the MMSE score at Week 24, and the less-improved as a patient with fewer than 3 points improvement. [b]Treatment with 10 mg started at Week 24 (dose decrease to 5 mg was allowed). *$P < 0.05$ (paired $t$ test versus Week 24).
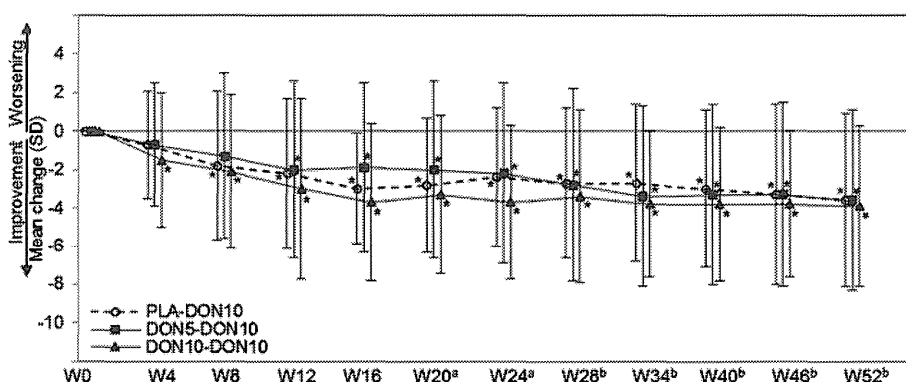
the PLA-DON10, DON5-DON10, and DON10-DON10 groups), the change in MMSE from the last administration of the 10 mg was calculated. The changes (mean ± SD) at 6, 12, 18, and 24 weeks after the dose reduction were 0.7 ± 3.0, 0.5 ± 3.5, −0.5 ± 3.6, and −0.7 ± 3.9, respectively; the score was still above the baseline at 24 weeks after the dose reduction (mean change from the baseline, 1.0 ± 3.8).

### Behavioral and neuropsychiatric symptoms

NPI-2 significantly improved compared with baseline from Weeks 12 to 52 in the DON5-DON10, and from Weeks 4 to 52 in the DON10-DON10 groups (Figure 5). The mean changes (mean ± SD, Student paired $t$ test) at Week 52 and at the final evaluation (LOCF) from baseline were −3.6 ± 4.7 ($P < 0.001$) and −2.1 ± 4.8 ($P = 0.005$) in the DON5-DON10 group, and −3.9 ± 4.2 and −3.4 ± 4.4 ($P < 0.001$ each) in the DON10-DON10 group, respectively. The PLA-DON10 group also showed a

sustained reduction in the score from the RCT phase under placebo administration through the extension phase.

In the DON5-DON10 group, NPI-2 decreased by 0.6 to 1.0 points at Weeks 28 to 52 compared with that before the dose increase at Week 24, although it was not significant (Student paired $t$ test). Changes in NPI-2 by the subgroups with and without NPI-2 improvement of 30% or more from baseline at Week 24 (behaviorally improved and less improved by 5 mg) are shown in Figure 6. As the result of an MMRM for observed value at or after Week 24 with observed value at week 24 as a covariate, and with subgroup, visit and interaction as factors, the factor of interaction were significant ($P < 0.001$) and the factors of subgroup and visit were not significant ($P = 0.282$, $P = 0.199$). In the subgroups of less-improved, NPI-2 significantly decreased after dose increment (mean changes from Week 24 with SD (Student paired $t$ test) at Weeks 40, 46, and 52: −3.2 ± 4.0 ($P = 0.033$), −3.8 ± 4.9 ($P = 0.035$), and −3.7 ± 4.9 ($P = 0.042$), respectively).



**Figure 5 Mean change in NPI-2 from baseline (FAS).** NPI, Neuropsychiatric Inventory; FAS, full analysis set. [a]PLA-DON10 group started treatment with 3 mg at Week 16, and the dose was increased to 5 mg at Week 18. [b]PLA-DON10 and DON5-DON10 groups started treatment with 10 mg at Week 24 (dose decrease to 5 mg was allowed). *$P < 0.05$ (paired $t$ test).

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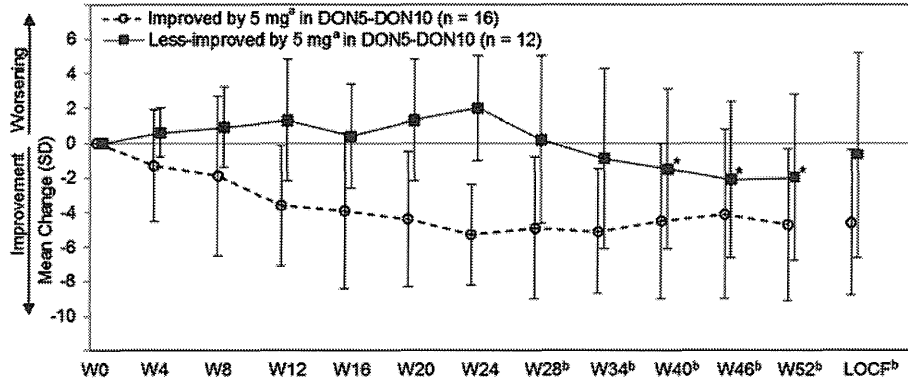


**Figure 6 Mean NPI-2 change in subgroups of improved and less improved by 5 mg (FAS, DON5-DON10 group).** NPI, Neuropsychiatric Inventory; FAS, full analysis set; LOCF, last observation carried forward. [a]The behaviorally improved by 5 mg is defined as a patient with 30% or more improvement in NPI-2 score at Week 24, and the less-improved as a patient with less than 30% improvement. [b]Treatment with 10 mg started at Week 24 (dose decrease to 5 mg was allowed). *$P < 0.05$ (paired $t$ test versus Week 24).

Significant improvement in NPI-10 compared with baseline was observed from Weeks 34 to 52 in the DON5-DON10 group, and from Weeks 4 to 52 in the DON10-DON10 group, with the largest changes (mean ± SD) at Week 40 (−8.8 ± 14.9) in the DON5-DON10 group, and Week 16 (−7.3 ± 7.2) in the DON10-DON10 group. The PLA-DON10 group also showed a sustained score decrease from baseline for 52 weeks.

### Caregiver burden

Changes in ZBI scores from baseline in each of the PLA-DON10, DON5-DON10, and DON10-DON10 groups are shown in Figure 7. The improvement was significant at Week 40 in the DON5-DON10 group, but not at any points in the PLA-DON10 and DON10-DON10 groups.

### Safety

AEs were reported by 93.8% (90 of 96) in the DON-DON10 group throughout the 52-week study period and by 89.2% (33 of 37) in the PLA-DON10 group during 36

weeks of the extension phase. Sixteen patients reported 23 serious AEs. Of these, 2 patients died because of asphyxia (PLA-DON10) or pneumonia (DON5-DON10) while receiving 10 mg, but a causal relation with the study drug was ruled out.

The incidence of AEs reported by more than 5% of the DON-DON10 group is shown in Table 2 (by 12-week intervals and total period). Major AEs with high incidence were nasopharyngitis (17.7% (17 of 96)) and parkinsonism (12.5% (12 of 96)). Treatment-related AE reported by more than 5% was only parkinsonism (10.4% (10 of 96)). All the treatment-related AEs were mild or moderate, except for 5 events (insomnia, visual hallucinations, irritability, agitation, and paranoia) reported by 2 patients in the DON5-DON10 group. The incidence of no AEs increased over time. AEs reported by the PLA-DON10 group showed a similar trend as the DON-DON10 group (Table 3).

Gastrointestinal events were reported by 31.3% (30 of 96) in the DON-DON10 group. The events reported by more
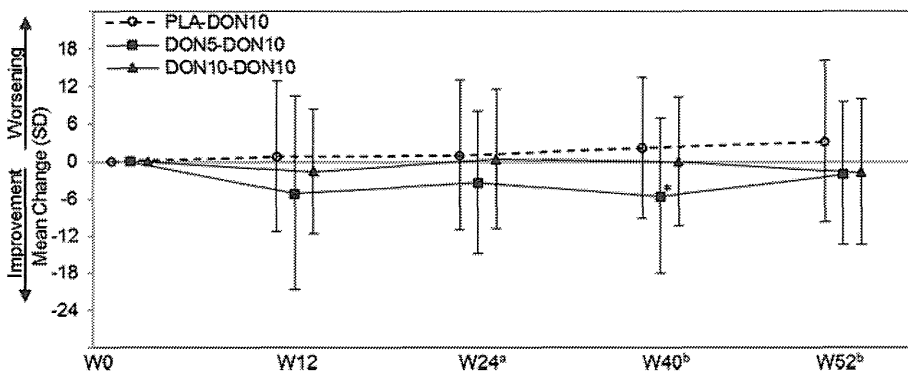


**Figure 7 Mean change in ZBI from baseline (FAS).** ZBI, Zarit Caregiver Burden Interview; FAS, full analysis set. [a]PLA-DON10 group started treatment with 3 mg at Week 16, and the dose was increased to 5 mg at Week 18. [b]PLA-DON10 and DON5-DON10 groups started treatment at 10 mg from Week 24 (dose decrease to 5 mg was allowed). *$P < 0.05$ (paired $t$ test).

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**Table 2 Incidence of adverse events reported by more than 5% in the DON-DON10 group over time (SAS)**

| AE | DON-DON10 group (DON5-DON10[a] and DON10-DON10) | | | | | Treatment-related AE[b] |
|---|---|---|---|---|---|---|
| | AE | | | | | |
| | Week 1–12 | >Week 12–24 | >Week 24–36 | >Week 36 | 52 weeks | 52 weeks |
| | ($n = 96$) | ($n = 75$) | ($n = 72$) | ($n = 69$) | ($n = 96$) | ($n = 96$) |
| | | | | | n (%) | n (%) |
| Total number of incidents | 65 | 15 | 7 | 3 | 90 (93.8) | 46 (47.9) |
| Constipation | 0 | 2 | 0 | 3 | 5 (5.2) | 2 (2.1) |
| Diarrhea | 2 | 1 | 1 | 2 | 6 (6.3) | 1 (1.0) |
| Nausea | 4 | 1 | 0 | 0 | 5 (5.2) | 3 (3.1) |
| Nasopharyngitis | 6 | 4 | 4 | 3 | 17 (17.7) | 0 |
| Contusion | 1 | 2 | 1 | 3 | 7 (7.3) | 0 |
| Blood creatine phosphokinase increased | 2 | 1 | 0 | 2 | 5 (5.2) | 0 |
| Glucose urine present | 2 | 2 | 1 | 0 | 5 (5.2) | 0 |
| Decreased appetite | 5 | 1 | 0 | 0 | 6 (6.3) | 4 (4.2) |
| Muscle spasms | 3 | 2 | 0 | 0 | 5 (5.2) | 1 (1.0) |
| Parkinsonism | 6 | 1 | 3 | 2 | 12 (12.5) | 10 (10.4) |
| Insomnia | 2 | 2 | 2 | 0 | 6 (6.3) | 4 (4.2) |

SAS, safety analysis set; AE, adverse event.
[a]Treatment with 10 mg started from Week 24.
[b]AEs for which a causal relation with the study drug was considered possible or probable.

than 5% were diarrhea, decreased appetite (6.3% (6 of 96) each), constipation, and nausea (5.2% (5 of 96) each). All the gastrointestinal events but ileus in 1 patient (DON5-DON10, while receiving 10 mg) were mild or moderate (Table 4). In the PLA-DON10, the incidence rate was 32.4% (12 of 37). Constipation, diarrhea (8.1% (3 of 37) each), abdominal pain upper, dyspepsia, gastritis, nausea, and decreased appetite (all 5.4% (2 of 37) each) were reported by more than 5%. All these events were mild or moderate. Analyzed by 2-week intervals, the incidence rate was the highest (22.2% (8 of 36)) in the interval from Weeks 24 to 26 subsequent to the dose increase to 10 mg.

Parkinsonian symptoms were reported by 12.5% (12 of 96) in the DON-DON10 group; parkinsonism (12.5% (12 of 96)) and camptocormia (1.0% (1 of 96)) were reported (Table 5). In the PLA-DON10 group (13.5% (5 of 37)), parkinsonism (8.1% (3 of 37)), akinesia, and tremor (2.7% (1 of 37) each) were reported. None of the reported parkinsonian symptoms were severe or serious. Six events led to discontinuation or dose reduction in these patients, but all of them were recovered or relieved. UPDRS part III did not significantly increase from the baseline in any groups (Table 6). In the DON5-DON10 group, the score significantly improved throughout the study.

**Table 3 Incidence of adverse events reported by more than 3 patients in the PLA-DON10 group over time (SAS)**

| AE | PLA-DON10 group[a] | | | | Treatment-related AE[b] |
|---|---|---|---|---|---|
| | AE | | | | |
| | Week 16–28 | Week 28-40 | Week >40 | 36 weeks | 36 weeks |
| | ($n$ =37) | ($n$ =36) | ($n$ =34) | ($n$ =37) | ($n$ =37) |
| | | | | *n* (%) | *n* (%) |
| Total number of incidents | 26 | 7 | 0 | 33 (89.2) | 22 (59.5) |
| Constipation | 3 | 0 | 0 | 3 (8.1) | 1 (2.7) |
| Diarrhea | 3 | 0 | 0 | 3 (8.1) | 2 (5.4) |
| Nasopharyngitis | 6 | 3 | 4 | 13 (35.1) | 0 |
| Dizziness | 3 | 0 | 0 | 3 (8.1) | 2 (5.4) |
| Parkinsonism | 2 | 1 | 0 | 3 (8.1) | 3 (8.1) |

SAS, safety analysis set; AE, adverse event.
[a]Treatment with 3 mg started at Week 16, and the dose was increased to 5 mg at Week 18 and to 10 mg at Week 24.
[b]AEs for which a causal relation with the study drug was considered possible or probable.

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**Table 4 Incidence of gastrointestinal events[a] (SAS)**

| AE[a] | PLA-DON10 (n =37) | DON5-DON10 (n =47) | DON10-DON10 (n =49) | DON-DON10[b] (n =96) |
|---|---|---|---|---|
| Subjects with any gastrointestinal events, number (%) | 12 (32.4) | 15 (31.9) | 15 (30.6) | 30 (31.3) |
| Abdominal discomfort | 0 | 1 (2.1) | 1 (2.0) | 2 (2.1) |
| Abdominal pain | 0 | 2 (4.3) | 0 | 2 (2.1) |
| Abdominal pain upper | 2 (5.4) | 0 | 0 | 0 |
| Constipation | 3 (8.1) | 1 (2.1) | 4 (8.2) | 5 (5.2) |
| Diarrhea | 3 (8.1) | 2 (4.3) | 4 (8.2) | 6 (6.3) |
| Dyspepsia | 2 (5.4) | 0 | 0 | 0 |
| Epigastric discomfort | 1 (2.7) | 0 | 0 | 0 |
| Fecal incontinence | 0 | 1 (2.1) | 0 | 1 (1.0) |
| Functional gastrointestinal disorder | 0 | 0 | 1 (2.0) | 1 (1.0) |
| Gastric ulcer | 0 | 0 | 1 (2.0) | 1 (1.0) |
| Gastritis | 2 (5.4) | 1 (2.1) | 0 | 1 (1.0) |
| Gastrointestinal disorder | 0 | 0 | 1 (2.0) | 1 (1.0) |
| Gastroesophageal reflux disease | 0 | 2 (4.3) | 1 (2.0) | 3 (3.1) |
| Intestinal obstruction | 0 | 1 (2.1) | 0 | 1 (1.0) |
| Nausea | 2 (5.4) | 3 (6.4) | 2 (4.1) | 5 (5.2) |
| Proctalgia | 0 | 1 (2.1) | 0 | 1 (1.0) |
| Vomiting | 1 (2.7) | 1 (2.1) | 1 (2.0) | 2 (2.1) |
| Gastroenteritis | 0 | 1 (2.1) | 0 | 1 (1.0) |
| Decreased appetite | 2 (5.4) | 3 (6.4) | 3 (6.1) | 6 (6.3) |

SAS, safety analysis set; AE, adverse events. [a]"Gastrointestinal events" included Preferred Terms (PTs) classified by the SOCs of "gastrointestinal disorders" (except for "dry mouth," "inguinal hernia," "dysphagia," "toothache," "food poisoning," "dental caries," "periodontal disease," "salivary hypersecretion," and "oral ulceration") as well as "decreased appetite" and "gastroenteritis.
[b]DON5-DON10 and DON10-DON10 groups.

Psychiatric events were reported by 18.8% (18 of 96) in the DON-DON10 group. Only insomnia was reported by more than 5% (6.3% (6 of 96)) (Table 7). Ten severe psychiatric events (visual hallucinations, 3; insomnia, 2; paranoia, 2; agitation, irritability, and hallucinations, 1 each) were reported by 5 patients. In the PLA-DON10 group, these events were also reported by 16.2% (6 of 37); all events were mild or moderate.

Arrhythmic events were reported by 9.4% (9 of 96) in the DON-DON10 group, each of which was reported by less than 5% (Table 8). All the events were mild or moderate, except for loss of consciousness in 1 patient (DON10-DON10, while receiving 5 mg). In the PLA-DON10 group, 8.1% (3 of 37) of the patients reported arrhythmic events. Only loss of consciousness was reported by more than 5% (5.4% (2 of 37)). All events were mild or moderate. Four events led to discontinuation or dose reduction in these patients, but 3 of them recovered or were relieved.

Excessive decrease of systolic and diastolic blood pressure was reported by 8.4% (11 of 131) and 10.7% (14 of 131) of all the subjects, respectively. Excessive increase of

**Table 5 Incidence of parkinsonian events (SAS)**

| AE | PLA-DON10 (n =37) | DON5-DON10 (n =47) | DON10-DON10 (n =49) | DON-DON10[a] (n =96) |
|---|---|---|---|---|
| Subjects with any parkinsonian events, n (%) | 5 (13.5) | 3 (6.4) | 9 (18.4) | 12 (12.5) |
| Camptocormia | 0 | 0 | 1 (2.0) | 1 (1.0) |
| Akinesia | 1 (2.7) | 0 | 0 | 0 |
| Parkinsonism | 3 (8.1) | 3 (6.4) | 9 (18.4) | 12 (12.5) |
| Tremor | 1 (2.7) | 0 | 0 | 0 |

SAS, safety analysis set; AE, adverse event.
[a]DON5-DON10 and DON10-DON10 groups.