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水上勝義	特集アンチエイジング医学の進歩.認知症	臨床と研究	87	470-472	2010
水上勝義	脳画像検査の方法. １）脳画像理解のための脳解剖	神経内科	72(suppl.6)	112-117	2010
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水上勝義	アルツハイマー病におけるBPSDの治療と対応	老年精神医学雑誌	21	872-878	2010
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今村徹	慢性硬膜下血腫における認知機能障害	Cognition and Dementia	9	221-224	2010
三瓶麻衣，山崎惠莉奈，佐藤卓也，佐藤厚，今村徹	アルツハイマー病とレビー小体を伴う痴呆（Dementia with Lewy bodies; DLB）におけるclosing-in現象：疾患別およびタイプ別の検討	神経心理学	26	231-241	2010

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木藤友実子、数井裕光、吉田哲彦、久保嘉彦、高屋雅彦、徳永博正、武田雅俊	経時的に詳細な言語機能評価をした運動ニューロン疾患を伴う意味性認知症の1例	Brain and Nerve	62	625-630	2010
数井裕光、武田雅俊	認知症をどう診るか？認知症診療の実際　誌上ディベート　認知症の予防介入はいつ始めるべきか MCIの段階から介入するべきとの立場から	Cognition and Dementia	9	66-70	2010
木藤友実子、数井裕光、武田雅俊	意味性認知症（sematic dementia）	Cognition and Dementia	9	32-36	2010
和田民樹、数井裕光、武田雅俊	軽度認知症スクリーニングテストとしてのリバーミード行動記憶検査	老年精神医学雑誌	21	177-182	2010
野村慶子、数井裕光、武田雅俊	脳の老化と認知機能の変化	分子精神医学	10	126-129	2010
橋本 衛	知っておきたい認知症の臨床と画像、前頭側頭葉変性症	臨床放射線	55	1463-1474	2010
橋本 衛	認知症の治療と認知症疾患別のケア～レビー小体型認知症を通して考える	九州神経精神医学	56	11-14	2010
橋本 衛	BPSDの治療	日本老年医学会雑誌	47	294-297	2010
橋本 衛	症例からみたDLBの症候学	老年精神医学雑誌	21	98-104	2010
橋本 衛	意味性認知症	神経心理学	26	283-293	2010
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上村直人，下寺信次	Brain Science 認知症と自動車運転―医学的研究の最近の動向	精神科	17	295-301	2010

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井関美咲，上村直人	認知症と運転免許に関するかかりつけ医の役割	クリニシャン	57	469-473	2010
井関美咲，上村直人	認知症患者の運転免許	神経内科	72(supple.6)	225-228	2010
品川俊一郎.	前頭側頭型認知症におけるBPSDの治療と対応	老年精神医学雑誌	21	885-890	2010
品川俊一郎	ピック病	月刊神経内科特別増刊号 認知症診療マニュアル	72(Suppl.6)	380-384	2010
永田智行，品川俊一郎，笠原洋勇，中山和彦	アルツハイマー病におけるFrontal Asessment Battery(FAB)スコア低下と妄想的観念の関連性	精神神経学雑誌	112	199－205	2010
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渡邊友弥，品川俊一郎，三宮正久，小野和哉，忽滑谷和孝，中山和彦.	Donepezilとsulpirideの投与により急激な錐体外路症状とせん妄を呈した1例	精神医学	52	405-408	2010
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福原竜治	基礎から学ぶ麻酔科学ノート　せん妄	Anesthesia Network	14	17-21	2010
荒井由美子，新井明日奈，水野洋子	認知症高齢者と運転：社会支援のあり方	老年期認知症研究会誌	17	76 - 81	2010
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IV. 研究成果の刊行物・別刷

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ORIGINAL ARTICLE

Impact of donepezil hydrochloride on the care burden of family caregivers of patients with Alzheimer's disease

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Abstract

Background: To evaluate the impact of donepezil hydrochloride on the care burden on family members of patients with Alzheimer's disease (AD). At present, donepezil is the only drug approved for the treatment of AD in Japan. Although the care burden on primary caregivers of AD patients comprises both physical and psychological burdens and donepezil is recognized to improve cognitive dysfunction and associated symptoms, there are few data on the effects of the drug on the care burden.

Methods: Of the uninstitutionalized AD patients who visited a dementia clinic between June 2008 and May 2009 with their primary family caregivers, 416 subjects who satisfied the enrollment criteria were registered for the study. All participants provided informed consent. Assessment included changes in scores on the Japanese version of the Zarit Caregiver Burden Interview (J-ZBI) and the Mini-Mental State Examination (MMSE), as well as the presence of behavioral and psychological symptoms of dementia (BPSD). Caregivers answered the questionnaires at baseline and after 12 weeks treatment with donepezil (starting dose 3 mg, p.o., once daily, followed by 5 mg after 1 or 2 weeks).

Results: There were significant changes in mean scores on the J-ZBI (-1.9 ± 9.5; $P < 0.01$) and MMSE ($+0.9 \pm 2.9$; $P < 0.01$) from baseline to Week 12, without significant correlation between these two scores. In patients with BPSD, there was a significant decrease in J-ZBI scores over the 12 weeks ($P = 0.013$); in contrast, in patients without BPSD, the decrease in the J-ZBI score did not reach statistical significance ($P = 0.418$).

Conclusions: The results indicate that donepezil improves cognitive function and some of the BPSD. As a possible consequence of improvements in BPSD, donepezil may also reduce caregivers' burden.

Key words: *Alzheimer's disease, behavioral and psychological symptoms of dementia (BPSD), burden, caregiver, donepezil.*

INTRODUCTION

Alzheimer's disease (AD) is a progressive dementia characterized by cognitive dysfunction and associated symptoms including behavioral and psychological symptoms of dementia (BPSD). Even though the pathogenesis of BPSD is not yet fully understood,[1] clinicians are often expected to reduce the frequency and severity of BPSD by whatever means available; however, this is sometimes quite difficult.[2–5] Therefore, BPSD may increase the burden on patients' family and caregivers, and may be the main reason for visits to the hospital and/or clinic by patients and their families.[6]

Alzheimer's disease not only affects the quality of life (QOL) of patients, but is also considered a considerable burden by caregivers. Zarit *et al.*[7] reported that caregivers of AD patients are called hidden victims of AD and that the impact of AD on the caregivers socially is a significant issue.

Donepezil, an acetylcholinesterase inhibitor, was approved for manufactur in Japan in October 1999 as

the first AD drug with an indication for the suppression of progressive dementia symptoms in mild to moderate AD. In August 2007, the indication for donepezil was expanded to the treatment of symptoms in severe AD. It has been recently reported that 10 mg/day donepezil is effective for the treatment of advanced Alzheimer's disease after prolonged treatment at 5 mg/day.[8] There are several papers reporting the clinical efficacy of denepezil in Japanese patients.[9,10]

Nonetheless, because premarketing clinical studies conducted in Japan were focused only on the cognitive effects of donepezil, they did not address the QOL of patients and their caregivers. To our knowledge, only one post-marketing trial has been conducted to investigate the effects of donepezil on BPSD and caregivers' burden.[11] However, that study focused on only a few BPSD and did not use a formal assessment scale to establish the caregivers' burden. Thus, we conducted the present post-marketing survey in a general clinical practice setting to investigate the impact of donepezil on the care burden with a focus on the QOL of caregivers.

METHODS

Subjects

Outpatients diagnosed with AD and their primary family caregivers who could answer questionnaires throughout the assessment period were evaluated in the present study. The severity of AD was based on the Functional Assessment Staging of Alzheimer's disease (FAST) and the onset of AD (length of illness) was determined. Patients who had received donepezil before or were hypersensitive to any of its ingredients or piperidine derivatives were excluded from the study.

This prospective study was conducted by central registration and investigators filled out registration forms to enroll eligible patients prior to the initiation of donepezil treatment. Fifty-five medical institutions participated in the study over the period 30 June 2008–31 May 2009 and 44 institutions (12 departments of psychiatry, 17 departments of neurology, five departments of neurosurgery, five departments of internal medicine and five other departments) enrolled a total of 416 patients.

Methods

The treatment period was 12 weeks per patient. As listed in the dosage and administration information, 3 mg donepezil was administered orally once daily, followed by 5 mg after 1 or 2 weeks. Investigators were asked to record any changes in the donepezil treatment regimen made during the study period, including upward and downward titrations and discontinuations, start/stop date, dose, and reasons for the change.

Patients were excluded from analysis if the patient's treatment had been suspended for 3 weeks or longer, patients were hospitalized or institutionalized, primary caregivers changed, or questionnaires were not answered. When registering patients for the study, no restrictions were placed on concomitant medication, treatment and home help because the present study was a post-marketing survey in the setting of usual clinical practice.

Assessments

In the present study, we used the Japanese version of the Zarit Caregiver Burden Interview (J-ZBI)[12,13] to measure the care burden of primary family caregivers. The original ZBI, designed by Zarit *et al.* in 1980,[7] is a good tool with which to compare care burdens objectively in different countries. The J-ZBI was arranged by Arai *et al.* in 1997 for use in Japan.[12,13] There are some reports on the impact of donepezil on care burden based on data collected in studies conducted in Japan and abroad that were not clinical trials,[11,14–18] yet there are no reports on the effects of donepezil in AD patients as determined with the ZBI, except for one regarding dementia with Lewy Bodies (DLB).[18]

The J-ZBI scores were determined by asking caregivers to answer questionnaires. The J-ZBI consists of 22 questions and the maximum score is 88 points. The questionnaire is structured to ask about a caregiver's mental and health status, economic burden, social restrictions and relationship to the patient in Questions 1–21 and to quantify the overall care burden or 'single global burden' in Question 22. Caregivers choose answers that most closely match their feelings from options of 'never', 'rarely', 'sometimes', 'quite frequently' and 'nearly always', which correspond to scores of 0, 1, 2, 3 and 4 points, respectively. The points for each question are added together to obtain a final score. Scores were also calculated on the subscales of personal strain, which indicate a burden that arises purely from the caring task, and role strain, which represents the burden that occurred

when the caring task disrupts established daily activities.[19] The severity of the burden was defined on the basis of the total score[20] as follows: major burden = 61–88; moderate burden = 41–60; mild burden = 21–40; and minor burden ≦ 20. Assessments were conducted for each level of burden.

In addition, supervision time (time spent providing care for and keeping an eye on AD patients per day) and free time (time spent away from and the length of time it was possible to stay away from AD patients) were determined. The association between care burden and the time spent supervising AD patients is rarely reported and there is no consensus on the relationship between the two. However, referring to the report of Arai *et al.*,[12,21] who suggested that there was significant relationship between care burden and free time, we did determine the amount of free time caregivers had in the present survey.

Cognitive function was assessed using the Mini-Mental State Examination (MMSE). To evaluate changes in BPSD that may have considerable impact on the care burden, symptoms were examined at baseline with respect to abulia/apathy, depression, delusion, hallucination, anxiety, dependency, wandering, aggressive behavior, resistance to care and irritability. These behavioral disturbances were derived from previous studies[11,14] and are mostly included in the Neuropsychiatric Inventory (NPI).[22] These symptoms were examined again at Week 12 and the findings were compared with those at baseline and classified as: 1, improved; 2 ,unchanged; or 3, aggravated. Any symptoms that could not be evaluated were noted as such.

In addition, concomitant drug therapy and other treatment, as well as the use of home care services, were investigated as part of routine clinical practice to evaluate factors other than donepezil that may impact on the evaluation of efficacy and care burden. The data collected included demographics, utilization of home health services, medical and family history of dementia, and comobidities. Adverse reactions were assessed along with efficacy.

Analysis

Data from patients receiving donepezil treatment but who violated the predetermined rules were excluded from safety analysis. Then, data without efficacy parameters was further excluded from the safety analysis set for efficacy analysis.

Efficacy analysis

Changes in care burden (overall J-ZBI scores, personal strain, role strain, supervision time and free time) and MMSE from baseline were assessed at Week 12 using paired *t*-test. Changes in BPSD were assessed based on the ratio between improvement, no change, and aggravation using 95% confidence intervals. Changes in MMSE and care burden were then applied to calculate Pearson's correlation coefficient to evaluate the direct effect of donepezil on care burden. In addition, changes in care burden were analyzed for each stratum of BPSD (improvement, no change, and aggravation). The significance level of the paired *t*-test was two-sided 5%, whereas that of stepwise selection was 20%.

Safety analysis

Adverse reactions were calculated according to the Japanese version of the Medical Dictionary for Regulatory Activities (MedDRA/J, v12.0; http://www.sjp.jp/~jmo_new2006/php/indexj.php). The incidence, subject, and frequency were calculated for each System Organ Class (SOC) and preferred term (PT).

RESULTS

Subjects

As shown in Figure 1, safety analysis was performed on data from 398 patients after excluding three patients who were later found to be ineligible and 15 patients who did not return to the site after their first visit. Efficacy analysis was performed on data from 169 patients after removing more data from the safety analysis. The main reasons for the elimination of patients from analysis were discontinuation of treatment in 69 patients, unapproved dose and administration in 43 patients, missing or duplicate data on the J-ZBI for 40 patients and signing up of home help after enrollment for 30 patients. Other patients were excluded from analysis because the MMSE was not performed during the designated time frame or was completely missed: 11 patients were excluded because their baseline J-ZBI was not completed in the specified period or lost and two patients were excluded because their J-ZBI was not collected during the specified period at Week 12. One patient was excluded from analysis because the diagnosis was revised as mild cognitive impairment based on FAST.

Patient and caregiver characteristics

Of the 169 patients, 115 were women (68.0%). Mean patient age was 77.7 ± 6.8 years and the mean disease duration was 2.0 ± 1.7 years. The severity of dementia was minor (FAST 4) in 67.5% of patients, moderate (FAST 5) in 20.1% and severe (FAST 6) in 12.4%. The mean MMSE score at baseline was 18.6 ± 4.6 and 8.9% of patients had received medication for BPSD and had taken antidementia drugs other than donepezil (agents with possible antidementia properties, such as non-steroidal anti-inflammatory drugs, vitamin E, and ginkgo biloba) within the 3 months prior to the study.

Most caregivers were women (60.9%) and the mean age of caregivers was 63.8 ± 14.3 years. The relationship of the caregiver to the patient was spouse in 53.3% of cases, child in 32.0% of cases, daughter-in-law in 14.2% of cases, and another relative in 0.6% of cases. Of the caregivers, 38.5% were employed; 38.5% of carers had been looking after the patient before participating in the study for a mean period of 1.0 ± 1.5 years. Of the carers, 17.8% reported having looked after other patients, whereas 79.9% had not.

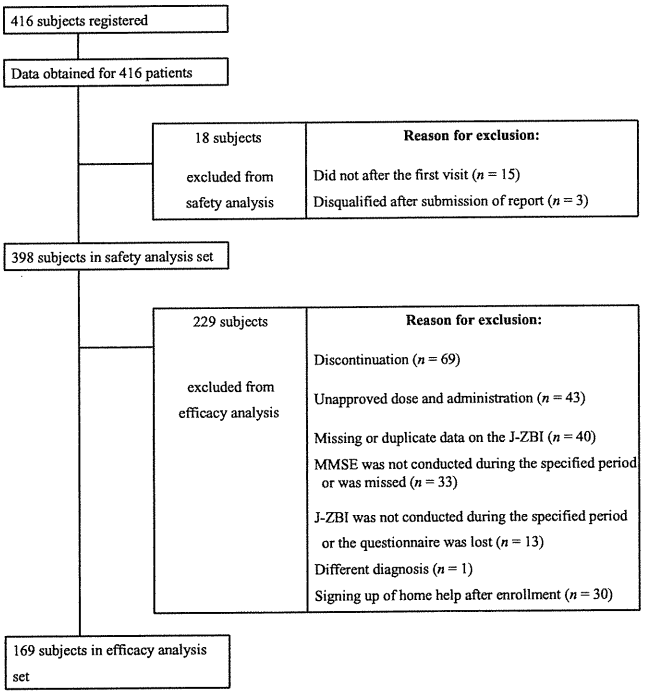

Figure 1 Distribution of subjects throughout the study. MMSE, Mini-Mental State Examination; J-ZBI, Japanese version of the Zarit Caregiver Burden Interview.

Change in care burden

Overall, J-ZBI scores decreased significantly by 1.9 ± 9.5 from a mean (± SD) score of 24.0 ± 15.0 at baseline to a score of 22.1 ± 15.4 at Week 12 ($P = 0.009$). In particular, there was a significant decrease in the personal strain score of 1.5 ± 5.9 from 14.4 ± 8.7 at baseline to 12.9 ± 9.7 at Week 12 ($P = 0.002$). Although no significant improvement was observed in role strain, the scores for role strain changed by 0.1 ± 3.0 from 4.6 ± 4.8 to 4.7 ± 4.7 (Table 1).

There was no significant decrease in the time spent supervising AD patients. Supervision time decreased by 17.2 ± 211.9 min from 307.8 ± 297.4 min at baseline to 291.9 ± 301.9 min at Week 12. In addition, although free time (i.e. the time caregivers spent away from patients) tended to increase by 4.8 ± 155.8 min from 343.0 ± 330.1 min at baseline to 345.3 ± 323.6 min at Week 12, the improvement did not reach statistical significance.

Overall MMSE scores were significantly increased by 0.9 ± 2.9 from a score of 18.6 ± 4.6 at baseline to a score of 19.5 ± 5.0 at Week 12 ($P < 0.001$). There was no significant correlation between J-ZBI and MMSE scores (Fig. 2).

The rates of improvement according to BPSD are given in Table 2. At baseline, 134 of the 169 patients evaluated in the efficacy analysis (79.2%) reported having BPSD, whereas 35 patients (20.7%) did not. Baseline J-ZBI scores were significantly higher in the group of patients with BPSD ($P = 0.019$) than in those

Table 1 Change in scores on the Japanese version of the Zarit Caregiver Burden Interview

	No. patients	J-ZBI score		Change from baseline	*P* (paired *t*-test)
		Baseline	Week 12		
J-ZBI (sum)	169	24.0 ± 15.0	22.1 ± 15.4	−1.9 ± 9.5	0.009
J-ZBI (personal strain)	169	14.4 ± 8.7	12.9 ± 9.0	−1.5 ± 5.9	0.002
J-ZBI (role strain)	169	4.6 ± 4.8	4.7 ± 4.7	0.1 ± 3.0	0.796

Data show the mean ± SD.
J-ZBI, Japanese version of the Zarit Caregiver Burden Interview.

without. In those who had BPSD at baseline, J-ZBI scores were significantly decreased by 2.1 ± 8.8 from a score of 25.4 ± 15.2 at baseline to a score of 23.3 ± 15.6 at Week 12 ($P = 0.013$). In patients without BPSD, J-ZBI scores tended to decreased by 1.1 ± 8.2 from a score of 18.7 ± 13.5 at baseline to a score of 17.6 ± 13.6 at Week 12, but this differnce did not reach statistical significance ($P = 0.418$). As indicated in Table 3, for the BPSD that improved by 50% or more after treatment, improvement rates were 63.0% for depression (17/27 patients), 60.0% for delusion (18/30 patients), 83.3% for hallucination (10/12 patients), and 50.0% for anxiety (25/50 patients). The J-ZBI scores tended to decrease more with improvements in each of the BPSD symptoms, except wandering and aggressive behavior (Table 4). In particular, a significant reduction in J-ZBI scores was observed in the group of patients whose delusion improved by 5.6 ± 9.4 ($P = 0.022$) and in the group whose anxiety improved by 4.8 ± 8.5 ($P = 0.009$). The J-ZBI scores were also significantly decreased by 4.7 ± 8.1 in patients who reported an improvement in dependency ($P = 0.014$), but were increased significantly by 15.0 ± 6.9 in patients whose dependency worsened ($P = 0.022$; Table 4).

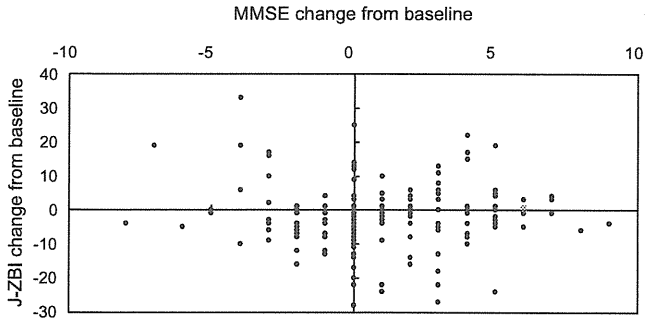

Figure 2 Relationship between the Japanese version of the Zarit Caregiver Burden Interview (J-ZBI) and the Mini-Mental State Examination (MMSE). There was no significant correlation found between the two ($r = -0.015$; $P < 0.844$).

Adverse reactions

Table 5 indicates that of the 398 patients included in the safety analysis, 46 adverse reactions were observed in 36 patients. Adverse reactions occurred at a rate of 9.0% (36/398 patients). This rate is comparable to that reported in a previous post-marketing survey conducted in patients with mild to moderate AD conducted by Eisai co., Ltd. in 2005 (10.7%; 346/3240 patients). These data were provided us from the

Table 2 Scores of Japanese version of Zarit Caregiver Burden Interview depending on the presence of behavioral and psychological symptoms of dementia

	No. patients	J-ZBI (total score) Baseline	Week 12	Change from baseline	*P* (paired *t*-test)
Baseline BPSD					
Yes	134	25.4 ± 15.2	23.3 ± 15.6	−2.1 ± 9.8	0.013
No	35	18.7 ± 13.5	17.6 ± 13.6	−1.1 ± 8.2	0.418

Data show the mean ± SD.
J-ZBI, Japanese version of the Zarit Caregiver Burden Interview; BPSD, behavioral and psychological symptoms of dementia.

Table 3 Improvements in behavioral and psychological symptoms of dementia

	Improved			Unchanged			Worsened			
BPSD	*n*	%	95% CI	*n*	%	95% CI	*n*	%	95% CI	Total
Abulia/apathy	22	31.0	(20.5–43.1)	46	64.8	(52.5–75.8)	3	4.2	(0.9–11.9)	71
Depression	17	63.0	(42.4–80.6)	7	25.9	(11.1–46.3)	3	11.1	(2.4–29.2)	27
Delusion	18	60.0	(40.6–77.3)	11	36.7	(19.9–56.1)	1	3.3	(0.1–17.2)	30
Hallucination	10	83.3	(51.6–97.9)	2	16.7	(2.1–48.4)	0	0.0		12
Anxiety	25	50.0	(35.5–64.5)	21	42.0	(28.2–56.8)	4	8.0	(2.2–19.2)	50
Dependency	22	32.4	(21.5–44.8)	42	61.8	(49.2–73.3)	4	5.9	(1.6–14.4)	68
Wandering	5	41.7	(15.2–72.3)	4	33.3	(9.9–65.1)	3	25.0	(5.5–57.2)	12
Aggression	16	37.2	(23.0–53.3)	23	53.5	(37.7–68.8)	4	9.3	(2.6–22.1)	43
Resistance	3	9.7	(2.0–25.8)	25	80.6	(62.5–92.5)	3	9.7	(2.0–25.8)	31
Irritation	20	43.5	(28.9–58.9)	22	47.8	(32.9–63.1)	4	8.7	(2.4–20.8)	46

BPSD, behavioral and psychological symptoms of dementia; CI, confidence interval.