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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	Vol. 14 No.1	17-21	2010

Ⅳ. 研究成果の刊行物・別刷

■シンポジウム：臨床の技（スキル）

認知症

池田　学*

要旨：本稿では，比較的初期（CDRの0.5ないし1のレベル）認知症の診断に必要な症候学を論じた。原因疾患では，頻度の高いアルツハイマー病（AD）と脳血管性認知症（VaD），ADとVaDに次ぐ認知症の原因疾患として注目されているレビー小体型認知症，ならびに若年性認知症の原因疾患として重要である前頭側頭葉変性症を対象とした。各疾患に特徴的な認知機能障害のパターン，精神症状と行動特徴を，診察ならびに検査場面から把握することの重要性を強調した。また，特定の認知症性疾患の診断には，認知症類似の症状を呈する，せん妄やうつ病などの精神障害，他の認知症性疾患が正確に診断できることが条件であることを述べた。

（高次脳機能研究29（2）：222～228，2009）

Key Words：症候学，アルツハイマー病，脳血管性認知症，レビー小体型認知症，前頭側頭葉変性症
symptomatology, Alzheimer's disease, vascular dementia, dementia with Lewy bodies, frontotemporal lobar degeneration

はじめに

認知症の原因疾患は多様であるが，疾患別の治療法やケアが開発されつつあり，根治療法の基礎的研究も進んでいる。したがって，これまで以上に正確な早期診断が求められようになってきた。補助診断法としての画像診断やバイオマーカーの進歩は著しく，診断にもこれらを偏重する傾向がある。しかし，基本は臨床症候学である。認知症の場合は，診断のみならずケアを含む非薬物療法や治療評価尺度の開発においても症候学の知識が必要となる。認知症の症候学は，精神医学的，神経学的，神経心理学的な総合的アプローチを意味する。

本稿では，比較的初期（CDRの0.5ないし1のレベル）認知症の診断に必要な症候学を論じてみたい。原因疾患では，頻度の高いアルツハイマー病（AD）と脳血管性認知症（VaD），ADとVaDに次ぐ認知症の原因疾患として注目されているレビー小体型認知症（DLB），ならびに若年性認知症の原因疾患として重要である前頭側頭葉変性症（FTLD）を対象とした。

Ⅰ．認知症と類似の状態像の鑑別

初期の認知症の場合，とくに正常老化による物忘れやうつ病など，認知症と類似の状態像の除外診断がきわめて重要である。認知症であれば，深刻味を伴う病識を有する例は若年性ADの一部を除いてほとんどないが，記憶障害や喚語困難など部分的な症状に対して病識を有する場合はある。VaDやDLBの場合，病感を有していることは多い。FTDの場合は，初期から病識が欠如していることが診断上も重要な要件である。したがって，単独で認知症を心配して受診することはまずない。病識の評価は，介護者の認識と患者の自覚のズレが重要な手がかりとなるので，可能な限り患者と介護者を別々に診察・面接できる時間を短時間でも確保することが望ましい。

うつ病患者は，客観的な評価に比べてむしろ大げさに自分の物忘れを訴えることが多い。既往歴として，うつ状態，躁状態の有無を確認する。老年期のうつ病の場合は，全身倦怠，肩こり，便秘

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などの身体愁訴が前景に立ち，抑うつ気分が目立たない場合もあるので注意が必要である。注意・集中力低下により見かけ上の物忘れが出現し，MMSEなどの認知症のスクリーニングテストを実施すると，初期の認知症と同程度の成績を示すことも多いので，テストの成績だけに診断を頼ると誤診につながる。若年性ADやDLBでは抑うつの合併はしばしば認められるが，認知症患者の多くが呈するアパシーとうつ状態を混同しないことが重要である。

意識レベルと認知機能の変動，幻視があれば，まずせん妄を考える。しかし，せん妄はしばしば認知症に合併するので，慎重に診断する必要がある。DLBとの鑑別が困難な場合もあるが，DLB患者は幻視の内容をある程度覚えていることに特徴がある。とくに外来診療では，薬剤性せん妄の可能性を常に念頭におく必要がある。

Ⅱ．発症・進行過程の重要性

比較的最近発症し，急速に症状が悪化している場合には，慢性硬膜下血腫や脳炎による認知症など，根本的治療の可能性がある認知症（treatable dementia）の存在を疑う。潜在性に発症し緩徐に進行するADなどの変性疾患による認知症や，たとえ急性に発症したとしても基本的には急速に進行することのないVaDとは，発症や進行過程が異なる（**図1**）。根本的治療の可能性がある認知症は，早急な対応が必要な疾患が多いので見逃すことは許されない。

Ⅲ．アルツハイマー病

潜在性に発症し，緩徐に進行する（**図1**）。近時記憶障害で発症することが圧倒的に多く（**図2**），内容はエピソード記憶の障害である。他の認知機能障害に比べて，記憶障害が突出して目立つ場合，数分前の出来事すら覚えていないような場合は，ADを強く疑う。記憶障害に比べると目立たないが，初期から無関心，意欲の低下は存在し，趣味の減少など社会生活範囲の狭小化を認める。進行に伴い見当識障害や頭頂葉症状（視空間認知障害，視覚構成障害）が加わる。見当識障害は，通常進行に伴い，時，場所，さらには人物の順番に障害されるので，初期の認知症の場合は，時刻や季節などを丁寧に尋ねることが重要である。場合わせ，取り繕い反応が目立つ。初期から，局所神経症状を認めることは少ない。比較的初期から，物盗られ妄想が認められる場合がある。

なお，ADの診断基準（**表1**）からも明らかなように，他の認知症性疾患や上述のせん妄など認知症類似状態の除外がADの診断には必須である。したがって，他の認知症性疾患や認知症類似状態の診断に熟達しておくことが，正確なAD診断の必要条件である。

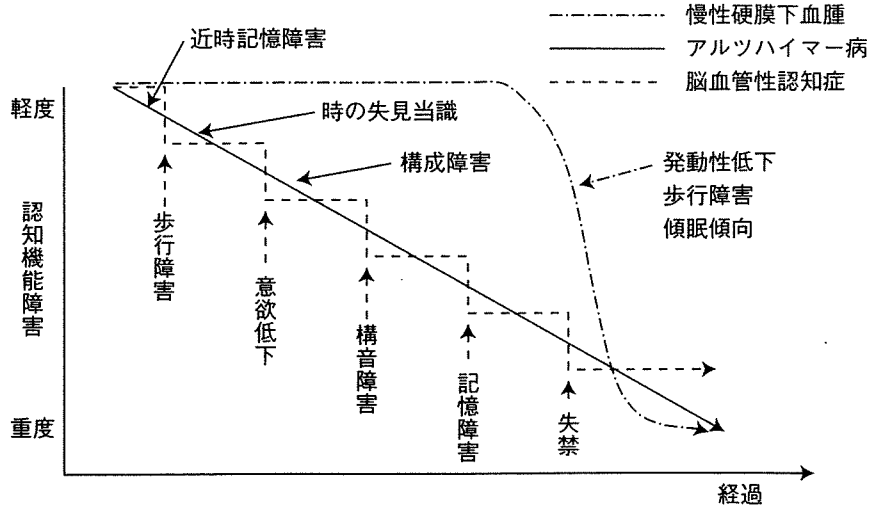

図1　認知症の発症・進行過程

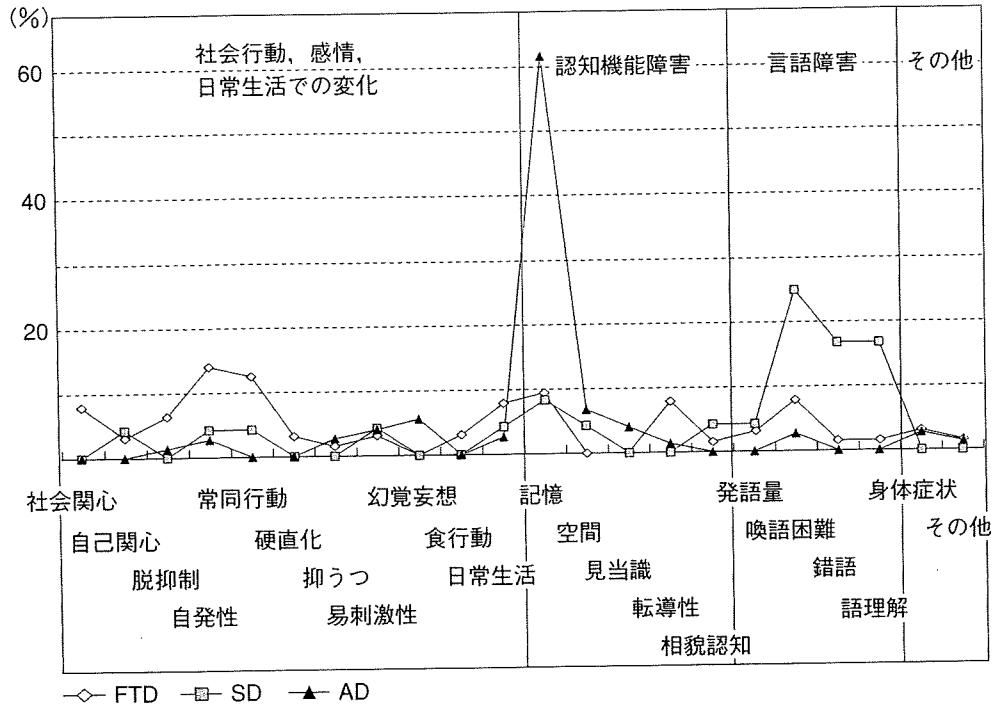

図2　疾患別の初発症状

(Shinagawa, S., Ikeda, M., Fukuhara, R., et al.：Initial symptoms in frontotemporal dementia and semantic dementia compared with Alzheimer's disease. Dement. Geriatr. Cogn. Disord, 21：74-80, 2006 (Epub 2005).)

表1　アルツハイマー型認知症の診断基準（DSM-Ⅳ）

- A. 多彩な認知障害の発現
  - (1) 記憶障害
  - (2) 以下の認知障害の1つ（またはそれ以上）
    - (a) 失語 (b) 失行 (c) 失認 (d) 実行機能
- B. A (1) (2) により，社会的および職業的機能の著しい障害
- C. 緩やかな発症と持続的な認知の低下
- D. A (1) (2) の認知障害は以下のものによらない
  - (1) 記憶や認知に進行性の障害を引き起こす中枢性疾患
    (例：脳血管性疾患，パーキンソン病)
  - (2) 認知症を引き起こす全身性疾患
- E. その障害はせん妄の経過中にのみ現れるものではない
- F. その障害は他のI軸疾患（例：大うつ病）では説明されない

Ⅳ. 脳血管性認知症

脳卒中発作後に発症し，階段状に進行することが，ADなど変性疾患による認知症との鑑別に重要である（**図1**）。潜在性に発症し緩徐に進行する変性疾患の進行経過か，階段状に進行するVaDの進行経過かを，介護者からの問診で把握するよう心がける。ただし，多発性小梗塞，ビンスワンガー病によるものは，脳卒中発作との関連がはっきりせず，緩徐に進行することが多い。脳梗塞や脳

出血の危険因子（高血圧症，糖尿病，高脂血症など）を有することが多い。症状は多彩であるが，視床梗塞など一部の症例を除いて記憶障害は比較的軽度のことが多い。幻覚や妄想が前景に立つことはまれで，発動性の低下・無関心が認められる（表2）。活動の低下によって生じる廃用症候群は単独でも出現するが，しばしば認知症，とくに脳血管性認知症によっても生じ，認知機能障害をさらに増悪させる。局所神経症状を認めることが多いので，認知症の診察には神経学的診察が欠かせない。

Ⅴ．レビー小体型認知症

発症と進行は緩徐で，認知機能障害もADに似る。異なる点は，認知機能が激しく変動することである。状態の良い時は認知症の存在を疑うほどであるが，悪い時にはその場では認知症の有無の判定すら困難な，せん妄といわざるを得ない状態となる。また，鮮明で生々しい幻視（人，動物，虫など）と誤認妄想（夫を父と間違うなど）が特徴的である（図3）。すでに亡くなっている家族が家の中にいると主張するなど，誤認妄想と幻視が一体となったような精神症状が特徴的である。「自宅が自宅でない，本物の自宅は別にある」「夫は偽物で，別に存在する」といったCapgras症候群がみられることもある。パーキンソン症候が認知障害の出現する前からみられることもあれば，認知機能障害が目立ってきた後に出現することもある。寝言や睡眠時の体動（レム睡眠行動障害）を認めることも多い。抗精神病薬をはじめ各種薬剤に過敏性があるので，薬物療法を検討する前にADと鑑別しておくことは重要である。

Ⅵ．前頭側頭葉変性症

発症と進行は緩徐で，多くは初老期に発症する。前頭葉と側頭葉前方部に病変が限局する前頭側頭型認知症（FTD）では，初期から人格変化や行動障害が前景に立つ。側頭葉に病変の主座がある意味性認知症（SD）やシルビウス裂周囲に病変の主座がある進行性非流暢性失語では，初期から失語

表2　アルツハイマー病と脳血管性認知症の精神症状―第1回中山調査から―

NPI item	アルツハイマー病（N=21）			脳血管性認知症（N=28）			
	N	%	Score	N	%	Score	p
下位項目							
妄想	9	42.9	1.4	4	14.3	0.7	0.0349
幻覚	5	23.8	1.0	2	7.1	0.4	0.1148
興奮	10	47.6	2.7	7	25.0	1.5	0.1338
うつ	5	23.8	1.7	6	21.4	0.8	0.6283
不安	5	23.8	1.0	6	21.4	0.8	0.8284
多幸	3	14.3	0.9	1	3.6	0.1	0.1734
無為/無関心	9	42.9	3.4	20	71.4	5.1	0.1288
脱抑制	2	9.5	1.1	3	10.7	0.8	0.9847
易刺激性	10	47.6	2.3	6	21.4	1.2	0.0745
異常行動	12	57.1	4.0	6	21.4	0.9	0.0057
計	19	90.5	19.6	26	92.9	12.2	0.1370

(Ikeda, M., Fukuhara, R., Shigenobu, K., et al.：Dementia associated mental and behavioural disturbances in elderly people in the community；findings from the first Nakayama study. J. Neurol. Neurosurg. Psychiatry, 75：146-148, 2004.)

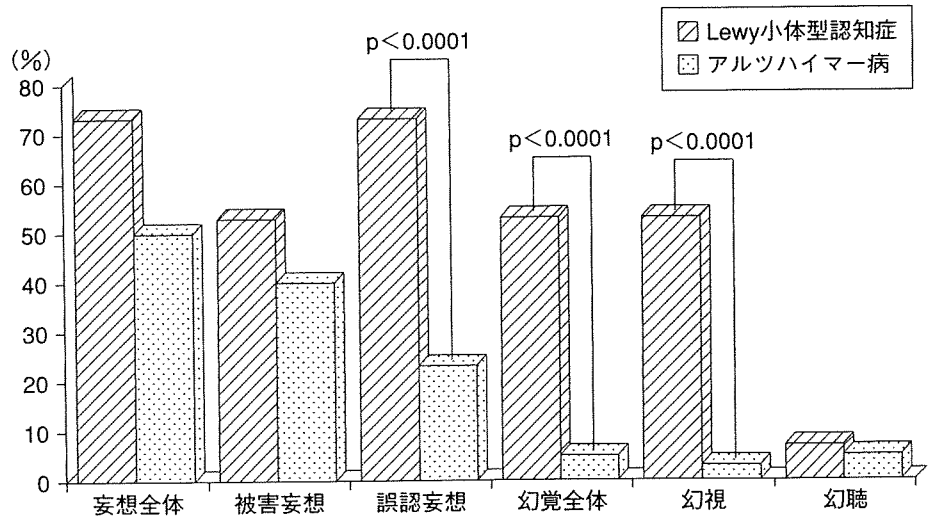

図3　レビー小体型認知症とアルツハイマー病における幻覚・妄想の種類
(博野信次，森　悦朗，今村　徹，ほか：Lewy小体をともなう痴呆とアルツハイマー病における精神症状の比較．脳と神経，50：45-49, 1998. より引用)

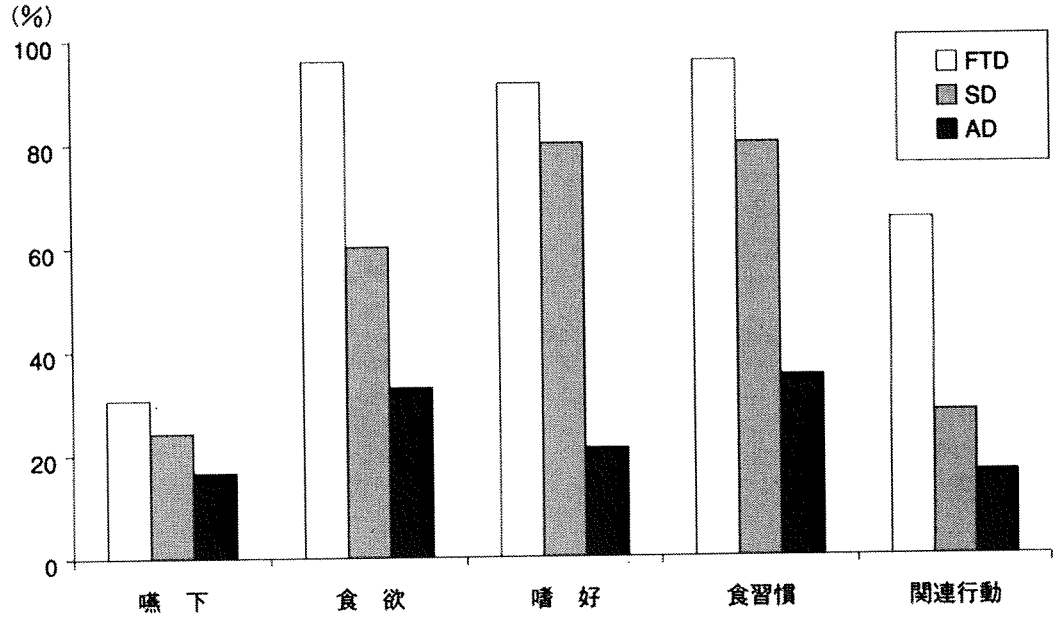

図4　疾患別の食行動異常の頻度
(Ikeda, M., Brown, J., Holland, A. J., et al.：Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry, 73：371-376, 2002.)

症状が前景に立つ（図2）。FTDとSDは，常同行動（時刻表的生活・滞続言語・反復行為）（図4）や食行動異常（過食・嗜好の変化・常同的食行動）（図5）など共通の行動障害を呈し，これらは，他の認知症との鑑別にも役立つ症状である。一方，初期には記憶障害や視空間認知障害は目立たない。幻覚や妄想を呈することもほとんどない。

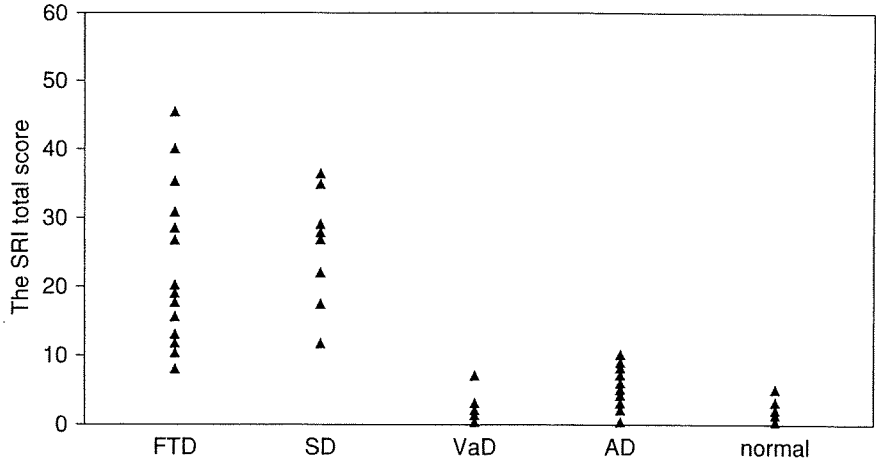

図5 疾患別の常同行動

SRI：Stereotypy Rating Inventory
(Shigenobu, K., Ikeda, M., Fukuhara, R., et al.：The Stereotypy Rating Inventory for frontotemporal lobar degeneration. Psychiatry Res., 110：175-187, 2002.)

おわりに

認知症の原因疾患として代表的な4疾患について，診断に必要な症候学のポイントを述べた。疾患に特徴的な認知機能障害のパターン，精神症状と行動特徴を，診察ならびに検査場面から把握することが重要である。また，信頼できる介護者の情報から，日常生活上の認知機能障害，精神症状を把握し，診察結果から得られた知見を裏付け，修正することが必要である。特定の認知症性疾患の診断には，認知症類似の症状を呈するせん妄やうつ病などの精神障害，他の認知症性疾患が正確に診断できることが条件となる。

謝辞：想い出の地，松山で発表の機会を与えていただいた鹿島晴雄先生，山鳥重先生，ならびに大東祥孝先生に深謝いたします。本講演の内容は，恩師である故田邉敬貴先生からご教授いただいたものです。

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Abstract

Clinical skills for dementia

Manabu Ikeda*

In recent years, there has been considerable progress in expanding the differential diagnosis of Alzheimer's disease (AD) with clinical characterization of vascular dementia (VaD), dementia with Lewy bodies (DLB), and frontotemporal lobar degeneration (FTLD). Each dementia has its own characteristic clinical course, cognitive profile, behavioral profile, and neurologic features. Both the onset and course of the disease are important in assessing its etiology. Neurodegenerative diseases such as AD, DLB, and FTLD have insidious onset with a slowly progressive and chronic course, whereas a stair-step progression suggests VaD. The first symptom of AD is usually progressive difficulty with recent memory. In DLB, visual hallucinations are prominent, whereas in FTLD stereotypic behavior and inappropriate eating behavior are more pronounced. Such cognitive and behavioral symptomatology is essential to early diagnosis and care of dementia.

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doi:10.1111/j.1479-8301.2009.00302.x PSYCHOGERIATRICS 2009; 9: 196–203

ORIGINAL ARTICLE

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

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Received 9 September 2009; accepted 4 November 2009.

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

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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

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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.

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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.

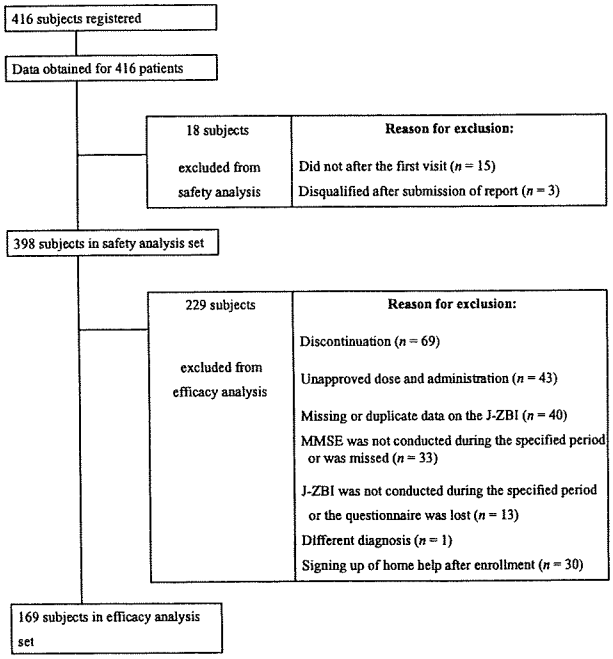

Figure 1 Distribution of subjects throughout the study. MMSE, Mini-Mental State Examination; J-ZBI, Japanese version of the Zarit Caregiver Burden Interview.

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 Baseline	J-ZBI score Week 12	Change from baseline	*P* (paired *t*-test)
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.

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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).

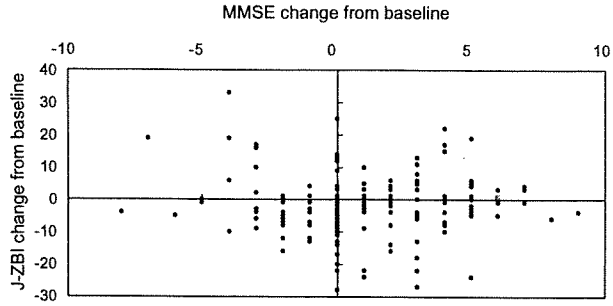

Figure 2 Relationship between the Japanese version of the Zarit Caregiver Burden Interview (J-ZBI) and the Mini-Mental State Examination (MMSE). There was no significant correlation found between the two ($r = -0.015$; $P < 0.844$).

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.

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Table 4 Change in scores on the Japanese version of the Zarit Caregiver Burden Interview depending on the presence of behavioral and psychological symptoms of dementia

BPSD	No. patients	Change from baseline	*P* (paired *t*-test)
Overall	169	−1.9 ± 9.5	0.009
Abulia/apathy			
Overall	71	−0.4 ± 10.3	0.732
Improved	22	−4.1 ± 12.4	0.135
Unchanged	46	0.4 ± 8.3	0.738
Worsened	3	13.7 ± 8.3	0.738
Depression			
Overall	27	−2.0 ± 10.0	0.302
Improved	17	−4.8 ± 9.5	0.053
Unchanged	7	0.3 ± 6.2	0.907
Worsened	3	8.3 ± 15.0	0.437
Delusion			
Overall	30	−2.4 ± 12.4	0.306
Improved	18	−5.6 ± 9.4	0.022
Unchanged	11	2.8 ± 15.8	0.567
Worsened	1	−1.0	–
Hallucination			
Overall	12	−1.8 ± 14.2	0.678
Improved	10	−5.5 ± 9.8	0.110
Unchanged	2	17.0 ± 22.6	0.481
Worsened	0	–	–
Anxiety			
Overall	50	−2.4 ± 9.1	0.074
Improved	25	−4.8 ± 8.5	0.009
Unchanged	21	−1.7 ± 7.5	0.321
Worsened	4	9.3 ± 13.3	0.258
Dependency			
Overall	68	−1.1 ± 10.0	0.349
Improved	22	−4.7 ± 8.1	0.014
Unchanged	42	−0.8 ± 9.7	0.581
Worsened	4	15.0 ± 6.9	0.022
Wandering			
Overall	12	−0.9 ± 16.1	0.848
Improved	5	−7.8 ± 8.4	0.108
Unchanged	4	14.8 ± 14.3	0.132
Worsened	3	−10.3 ± 15.5	0.368
Aggression			
Overall	43	−1.3 ± 9.3	0.361
Improved	16	−2.1 ± 8.4	0.328
Unchanged	23	0.0 ± 10.4	0.984
Worsened	4	−5.8 ± 1.7	0.007
Resistance			
Overall	31	−0.3 ± 10.9	0.896
Improved	3	−8.3 ± 12.3	0.363
Unchanged	25	0.3 ± 10.8	0.884
Worsened	3	3.0 ± 10.1	0.660
Irritation			
Overall	46	−2.3 ± 8.7	0.073
Improved	20	−2.9 ± 9.0	0.175
Unchanged	22	−2.2 ± 8.5	0.240
Worsened	4	−0.8 ± 10.0	0.890

BPSD, behavioral and psychological symptoms of dementia.

Table 5 Number of patients reported adverse reactions

Adverse reaction	No. patients	%
Safety analysis population (398 subjects)	36	9.0
Metabolic and nutritional disorder	4	1.0
Anorexia	2	0.5
Loss of appetite	2	0.5
Psychological disorder	12	3.0
Aggression	2	0.5
Agitation	10	2.5
Anger	1	0.3
Corporalia	1	0.3
Depression	1	0.3
Insomnia	1	0.3
Anxiety	1	0.3
Neurological disorder	3	0.8
Dizziness	1	0.3
Headache	2	0.5
Parkinsonism	1	0.3
Cardiac disorder	1	0.3
Atrial fibrillation	1	0.3
Gastric and intestinal disorder	15	3.8
Diarrhea	5	1.3
Erosive gastritis	1	0.3
Nausea	8	2.0
Vomiting	2	0.5
Skin and subcutaneous disorder	1	0.3
Pruritus	1	0.3
Musculoskeletal and connective tissue disorder	1	0.3
Back pain	1	0.3
Systemic and local disorder	1	0.3
Irritability	1	0.3

company in 2009. In the present study, the frequently observed adverse reactions included agitation ($n = 10$ patients; 2.5%), nausea ($n = 8$ patients; 2.0%), diarrhea ($n = 5$ patients; 1.3%) and two patients each (0.5%) reporting poor appetite, loss of appetite, aggression, headache and vomiting. Other adverse reactions also observed were anger, coprolalia, depression, insomnia, uneasiness, dizziness, parkinsonism, atrial fibrillation, erosive gastritis, pruritus, back pain and irritation ($n = 1$ patient each; Table 3). Severe adverse reactions included agitation and atrial fibrillation ($n = 1$ patient each; 0.3%).

DISCUSSION

In the present study, J-ZBI scores were reduced after donepezil treatment for 12 weeks. This reduction can be attributed to the effects of donepezil because patients who changed nursing services, which may have had potential effects on care burden, were excluded from analysis. Thus, the present results suggest that donepezil is effective in reducing caregiver burden in AD.

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The present study addressed changes in care burden from baseline to Week 12 using J-ZBI and showed a significant difference in the mean J-ZBI score (–1.9 ± 9.5). This result is in line with that of a study conducted in mild to moderate AD patients with a similar drug, rivastigmine,[23] which showed that the mean ZBI score decreased by 1.7 ± 8.6 after 6 months treatment. Although the reduction in J-ZBI score by 2 points seems to be an relatively unimportant improvement, Arai *et al.* defined any reduction in J-ZBI in subjects classified as having mild AD as a successful.[24] Accordingly, because the average care burden was classified as mild in the present study, the change in J-ZBI score observed is considered meaningful for caregivers.

There was no significant correlation between changes in ZBI and MMSE scores. This suggests that a decreased burden is not the direct result of improvements in cognitive function. Conversely, in patients with BPSD, J-ZBI scores were significantly decreased, whereas in patients without BPSD the decrease in J-ZBI scores was not significant. Gort *et al.* reported that BPSD was associated with care burden after assessing care burden and care collapse in relation to various risk factors using the ZBI.[25] In addition, there are many other reports that indicate a correlation between improvements in BPSD and care burden.[11,26–28] Although the correlation between improvements in BPSD and decreased ZBI scores was not analyzed directly in the present study, improvements in BPSD may consequently lead to a reduction in a caregiver's burden.

In the subscales of J-ZBI, there was a significant decrease in personal strain ($P < 0.01$), although a similar decrease was not observed in role strain. Role strain is considered to represent burden that occurs when the caring task restricts established daily activities. This finding shows that donepezil could not reduce everyday life restrictions felt by caregivers. Conversely, it is considered that personal strain was improved along with improvements in BPSD because personal strain reflects subjective difficulty.

It is important to acknowledge that there are some limitations to the present post-marketing observational study. First, there were many drop outs compared with randomized control trials (RCT) and there were only 169 patients for whom valid data were available for analysis. Similarly, in a 6 month post-marketing observational study of rivastigmine conducted in Belgium with an original 434 patients,[23] valid data for analysis was only available for 175 patients, indicated a comparable drop out rate to that seen in the present study. Therefore, it seems inevitable that there will be considerable drop outs in post-marketing observational studies. Second, many patients and caregivers may have dropped out because the care burden worsened. In other words, the patients may have required hospitalization, institutionalization, or the addition of care services because their condition worsened. In any case, these patients were removed from the final analysis. However, this should not have had a major impact on the results because the number of patients who required hospitalization or institusionalization in the present study was small (five patients). Third, because the J-ZBI is a subjective evaluation, the impact of placebo effects cannot be denied. This issue can only be resolved by performing an RCT. However, unlike the RCT, which is conducted under unusual condition with selected patients and families, the present study was performed to elucidate the impact of donepezil under normal clinical settings. For these reasons, the present results must be interpreted with caution.

In conclusion, the results of the present post-marketing survey suggest that donepezil may improve cognitive function, BPSD, and hence care burden and, thus, can be expected to contribute to a better and lasting QOL of family caregivers.

ACKNOWLEDGMENTS

The authors thank the investigators across the 55 institutions who participated in the present study. The authors also thank Mr Takatsuki for his statistical advice.

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