護負担が減少することも確認された。一方、シャント術に起因する重大な有害事象は 3 例のみで生じ、その内訳は硬膜下血腫、腸管穿孔、チューブの閉塞であった。

シャント術をした後の生活指導も重要である。不活発な生活をしているとシャント術の効果が限弱する印象があるため、シャント術後にデイケアなどを利用して活発な生活の維持をはかることが必要である。

他科の先生にどのようにフィードバックするか：髄液排除試験が陰性であったり、陽性であっても身体の他の障害のためにシャント術を施行しなかったりした場合には緩徐進行性の慢性疾患に対する対応が必要となる。ビンスワンガー病を思い浮かべていただくと最もよいと思う。すなわち意欲低下に伴う廃用症候群の予防が最も重要で、転倒、骨折などにも注意を要する。これを紹介医の先生に理解していただく必要がある。逆にシャント術を行った場合は、シャントチューブの管理のために脳外科に定期的に受診する必要がある。本稿で提示した症例はシャント術後にほとんど全ての症状が消失したが、3 徴が残存することも多い。従って、シャント術後も内科系医師の外来通院も並行して行うことが望ましい。

まとめ（再発予防のためにできることなど）：

iNPH は近年、我が国で行われた疫学研究によって、地域在住の一般高齢者の 1.1%[3]に存在すると報告され、これまで考えられていたよりも高頻度の疾患である。治療可能な疾患であるため、見逃さないことが最も重要で、そのために、iNPH の典型的な MR 画像を他科の医師に広く啓発することが最も重要である。

おわりに

認知症の中でも特別な対応が必要な 2 疾患をとりあげ、標準的な診療手順を提示しながら解説した。本稿の情報を全ての精神科医に持っていただきたいと思っている。さらに他科の医師とより円滑に連携できるようになるために、このエッセンスを他科の医師に啓発することも我々の役目であろうと考えている。これらのために本稿が役立てば幸いである。

③参考文献

1. Mori E, Ikeda M, Kosaka K, et al: Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial. Ann Neurol 72:41-52, 2012
2. McKeith IG1, Dickson DW, Lowe J, et al: Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 65:1863-1872, 2005
3. 日本正常圧水頭症学会 特発性正常圧水頭症診療ガイドライン作成委員会. 特発性正常圧水頭症診療ガイドライン第2版. メディカルレビュー社, 大阪, 2011
4. Mori E, Ishikawa M, Kato T, et al: Guidelines for management of idiopathic normal pressure hydrocephalus: second edition. Neurol Med Chir (Tokyo) 52:775-809, 2012
5. Hashimoto M, Ishikawa M, Mori E, et al: Diagnosis of idiopathic normal pressure hydrocephalus is supported by MRI-based scheme: a prospective cohort study. Cerebrospinal Fluid Res 7:18, 2010

Further reading

武田雅俊監修、数井裕光、杉山博通、板東潮子著：認知症 知って安心！症状別対応ガイド、メディカルレビュー社、大阪、2012
（原因疾患別、重症度別に認知症患者のBPSDに対する対応案を具体的に列挙し、まとめている。家族介護者へのBPSD指導にも役立つ。）

Legends

表1　DLBの診断基準（第3回DLB国際ワークショップ）

- 1. central features（DLB診断に必須）
  - 社会的・職業的機能に障害を及ぼす進行性の認知機能障害による認知症。
  - 初期には記憶障害が目立たないこともあるが、進行とともに明らかになる。
  - 注意、遂行機能、視空間機能の障害が特に顕著。
- 2. core features（2つあればprobable DLB、1つでpossible DLB）
  - 注意や覚醒レベルにおける、明らかな変動を伴う認知機能の動揺
  - 詳細で具体的な内容の繰り返される幻視
  - 特発性のパーキンソニズム
- 3. suggestive features（central featuresに加えてこれが1つ以上あればprobable DLB、core featuresがなくてもこれが1つ以上あればpossible DLB）
  - REM睡眠行動異常
  - 抗精神病薬への過敏性の亢進
  - SPECTやPETで認められる基底核のドパミントランスポーターの取り込み低下
- 4. supportive features
  - 繰り返す転倒や失神
  - 一過性で原因不明の意識障害
  - 幻視以外の幻覚
  - 体系だった妄想
  - 重度の自律神経障害（例：起立性低血圧、尿失禁など）
  - うつ症状
  - CT/MRIでの側頭葉内側面の脳萎縮は比較的軽度
  - 脳血流SPECT/PETで後頭葉に目立つ取り込み低下
  - MIBG心筋シンチグラフィーの取り込みの低下
  - 脳波上、側頭葉での一過性鋭波を伴う顕著な徐波
- 5. DLBの可能性を低くするもの
  - 局所神経症状や画像所見で裏付けられる脳血管性障害の存在
  - 臨床的特徴を説明しうる他の身体疾患や脳病変の存在
  - 重度の認知症になって初めて付随するパーキンソニズム

表2　iNPHガイドライン（2004）の診断基準（抜粋）

1. Possible iNPH

(1)60歳台以降に発症。

(2)歩行障害、認知障害および尿失禁の１つ以上を認める。

(3)脳室拡大（Evans index*＞0.3）がある。

*Evans index：両側側脳室前角間最大幅/その同じスライスにおける頭蓋内腔最大幅。

(4)他の神経学的あるいは非神経学的疾患によって上記臨床症状の全てを説明し得ない。

(5)特発性である。

Possible iNPH with MRI support：Possible iNPHの必要項目を満たし、かつMRIで高位円蓋部および正中部の脳溝、くも膜下腔の狭小化が認められる場合このように呼ぶ。

2. Probable iNPH

(1)Possible iNPHの必要項目を満たす。

(2)脳脊髄液圧が200mmH_2O以下で脳脊髄液の性状が正常。

(3)以下のいずれかを認める。

①歩行障害があり、高位円蓋部および正中部の脳溝、くも膜下腔の狭小化が認められる。

②タップテスト（脳脊髄液排除試験）で症状の改善を認める。

③ドレナージテスト（脳脊髄液持続排除試験）で症状の改善を認める。

3. Definite iNPH

シャント術施行後，客観的に症状の改善が示される。

表3　iNPH grading scale

重症度	歩行障害	認知障害	排尿障害
0	正常	正常	正常
1	ふらつき、歩行障害の自覚のみ	注意・記憶障害の自覚のみ	頻尿、または尿意切迫
2	歩行障害を認めるが補助器具（杖、手すり、歩行器）なしで自立歩行可能	注意・記憶障害を認めるが、時間・場所の見当識は良好	時折の失禁（1−3回/週以上）
3	補助器具や介助がなければ歩行不能	時間・場所の見当識障害を認める	頻回の尿失禁（1回/日以上）
4	歩行不能	状況に対する見当識は全くない。または意味ある会話が成立しない。	膀胱機能のコントロールがほとんどまたは全く不可能

地域高齢者うつ病スクリーニング調査で うつ病と診断された群の特徴

藤瀬 昇[1)]、小山 明日香[1)]、西 良知[1)]、中山 智子[1)]
福永 竜太[2)]、阿部 恭久[2)]、向坂 香織[3)]、池田 学[1)]

1）熊本大学大学医学部神経精神科
2）八代更生病院
3）あさぎり町役場保健環境課

背景

- 熊本県は平成19年度より、球磨郡あさぎり町をモデル地域に指定し、3年間の計画で地域自殺対策事業を推進してきた.
- 我々の教室では平成20年度から、高齢者のうつ病予防を目的に「スクリーニング調査」「相談事業」「啓発活動」を中心とした地域介入を行うことで当該事業に関わり、県のモデル事業が終了した後も現在まで継続して介入を行っている
- 我々は、郵送による1次スクリーニング調査で、一定の基準に該当した人を対象に、精神科医による2次面接調査を実施してきた[1)]
- これまで、2次面接調査でうつ病と診断された人たちの中には、自記式の老年期うつ病評価尺度（Geriatric Depression Scale, GDS）[2),3)]にてカットオフ値に満たない人も含まれていることが分かっていた

目的

- 2次面接調査でうつ病と診断された人たちの特徴を明らかにし、高齢者のうつ病スクリーニング調査を効果的に行う方法を検討したい

対象

- 熊本県球磨郡あさぎり町在住の65歳以上の高齢者で、平成21～24年度に「こころの健康アンケート」へ回答のあった住民のうち2次面接調査でうつ病と診断された人
- すでにうつ病の治療を受けている人は除外
- 各年度、対象人口が1500名前後となる1地区を選定し、3年で町全体を網羅する
- 入院中・施設入居中の者は除外し、返信をもって調査への協力に同意があるものとした
- 本調査は熊本大学大学院生命科学研究部倫理委員会の承認を得て実施した

スクリーニング調査の流れ

1次調査
（自記式郵送アンケート）

以下のいずれかに該当する場合、2次調査へ
①GDS（高齢者うつ評価尺度）6点以上
②生活機能評価基本チェックリスト（うつ予防）[4)]2点以上
③強い経済的困窮あり
④希死念慮あり

2次調査
（精神科医による面接）

面接後、町保健師とケースカンファレンスを実施. うつ病を含む何らかの精神障害が認められた者についての対応を協議し、介護サービス、町の健康相談、かかりつけ医、精神科医療機関などに繋いだ

1次アンケート調査項目

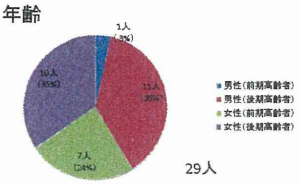
- 年齢、性別、家族構成、就労の有無、持病の有無
- 睡眠時間、睡眠状態（よく眠れている、眠れなくて困る、寝付くのに30分以上かかる、夜中に何度も目が覚めて困る、朝早く目が覚める）
- 食欲（いつもおいしい、時々食欲がない、いつも食欲がない）
- 経済的不安（頭から離れないほど金銭的に大きな不安や心配がありますか？）
- 希死念慮（いつも考える、しばしば考える、たまに考える、考えることはない）：「たまに」「しばしば」「いつも」と回答した人を希死念慮ありとした。
- 飲酒状況（ほぼ毎日、週に数回、年に数回、飲まない）
- 喫煙状況（1日1箱以上、1日数本、吸わない）

スクリーニング調査(65歳以上の在宅高齢者)

	2009	H21	H22	H23	H24	H25
対象地区	あさぎり町全体	免田	岡原	上	須恵・深田・上	上
アンケート配布数	4443	1552	1574	1505	1715	1583
回収率	80%	62.7%	62.8%	65.8%	69.6%	54.4%
有効回答数	3778	964	976	978	1114	845
二次調査参加者	293	60(6%)	44(4.4%)	51(5.2%)	58(5.8%)	269(31.8%)
二次調査参加者	108	33	182	153	151	63
二次調査参加率	36.25	52.1%	41.3%	29.5%	28.9%	(23.4%)
うつ病者数（出現率）	18 (0.48%)	26 (2.7%)	11 (1.1%)	7 (0.7%)	4 (0.34%)	6 (0.7%)

2次調査でうつと診断された人の特徴

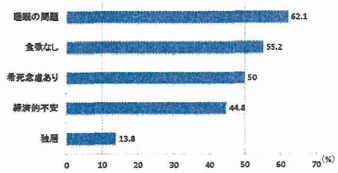
年齢



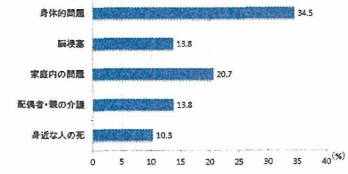
29人

すでに精神科受診中の人や、前年度にも2次調査対象となっていた人を除く

問題や不安を抱える人の割合1

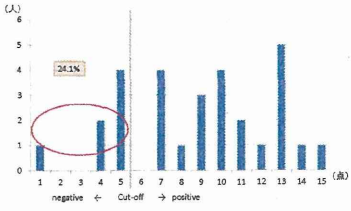


問題や不安を抱える人の割合2

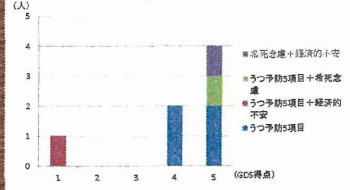


身体的問題：生命に直接的に影響する疾患や日常生活全般に著しい支障を及ぼす疾患に限定した。
整形外科的な疾患や高血圧などは含まない。

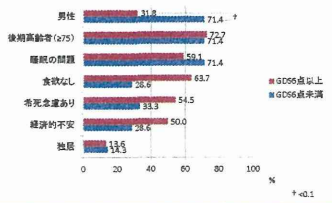
GDS得点の分布



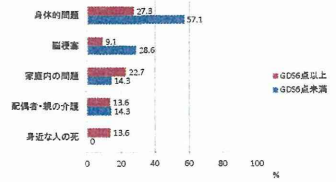
1次調査のGDSがカットオフ値以下であった人が、2次調査対象となった理由



GDS6点以上群と6点未満群の比較1



GDS6点以上群と6点未満群の比較2



結果のまとめ

- 後期高齢者が多かった
- 約1/4（7名）がGDSカットオフ値未満であった
- 上記7名中6名は、高齢者の生活機能評価・うつ予防5項目で陽性を示していた
- GDSカットオフ値未満群とカットオフ値以上群とで、生活や心身の状況に有意な差は認められなかったものの、未満群には男性および身体的問題を抱えている人が多い傾向がみられた

考察

- GDSだけでは地域のうつ病高齢者を拾えていない可能性が示唆された
- 高齢者のうつ病スクリーニングとしては、生活機能評価・うつ予防などを併用することが有効と考えられた
- もともと生活機能評価・うつ予防の5項目は、GDSを外部基準として、その信頼性が示されており[5)]、今後、われわれの調査においても両者の関係を検討したい

文献：

1. Fukunaga R., et al. Living alone is associated with depression among the elderly in a rural community in Japan. Psychogeriatrics 12：179-185, 2012
2. Yesavage J.A. Geriatric Depression Scale. Psychopharmacol. Bull., 24: 709-711, 1988
3. 村岡義明ら. 地域在住高齢者のうつ状態の身体・心理・社会的背景要因について. 老年精神医学雑誌 7：397-407, 1996.
4. 介護予防のための 生活機能評価に関するマニュアル（改訂版） 平成21年3月 主任研究者 鈴木 隆雄
5. Fujisawa D., et al. The development of a brief screening instrument for depression and suicidal ideation for elderly: the Depression and Suicide Screen. Psychiatry Clin. Neurosci. 59: 634-638, 2005.

Journal of Affective Disorders 176 (2015) 56–60

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Preliminary communication

The relationship between post-stroke depression and physical recovery

Shiho Matsuzaki [a], Mamoru Hashimoto [b,*], Seiji Yuki [b], Asuka Koyama [b], Yoshifumi Hirata [c], Manabu Ikeda [b]

[a] Department of Neuropsychiatry, Graduate School of Medical Science, Kumamoto University, Kumamoto, Japan
[b] Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan
[c] Kumamoto Takumadai Rehabilitation Hospital, Kumamoto, Japan

ARTICLE INFO

Article history:
Received 8 January 2015
Accepted 15 January 2015
Available online 28 January 2015

Keywords:
Post-stroke depression
Depression
Apathy
Physical recovery
Rehabilitation

ABSTRACT

Background: Post-stroke depression (PSD) is a serious and common complication of stroke. In this prospective study on the relationship between clinical PSD and physical recovery, we focused on (1) distinguishing between depression and apathy, (2) issues in assessment of PSD, and (3) timing of assessment.

Methods: Japanese stroke patients ($n=117$) were studied. We used self-rating scales [Zung Self-Rating Depression Scale (SDS) for depression; Apathy Scale (AS) for apathy] and observer-rating scales [Montgomery–Åsberg Depression Rating Scale (MADRS) for depression; Neuropsychiatric Inventory-Nursing Home (NPI-NH) for apathy] to assess psychological state. We assessed physical disability using the Functional Independence Measurement (FIM). Two-way analysis of covariance was used to determine effects of depression and apathy on functional outcome. We evaluated PSD twice, within 10 days after hospitalization and four weeks later.

Results: Objective scales gave higher prevalence than subjective scales for both depression and apathy. A significant effect of apathy on FIM recovery was seen with objective scale assessment during hospitalization; there was a marginal effect of depression at the same time.

Limitations: We did not consider the stroke size and location. In addition, we excluded patients with severe comprehension deficits or with a history of stroke.

Conclusions: Our findings indicate that depression and apathy could occur independently after stroke and could individually influence functional recovery. We obtained more accurate estimates of functional recovery using objective measures. Furthermore, our findings suggest that depression and apathy should be assessed not only at admission but also during hospitalization to estimate and enhance the functional recovery of stroke patients.

1. Introduction

Post-stroke depression (PSD) is a serious and common complication of stroke, affecting one third of all stroke patients at any time during the follow up (Hackett et al., 2005). PSD has negative impacts on patient participation in rehabilitation at the most crucial time to functional recovery and leads to poor outcomes (Hinojosa et al., 2011). On the other hand, there is an increasing evidence that antidepressants do treat PSD effectively and improve functional status (Gonzalez-Torrecillas et al., 1995; Dam et al., 1996; Miyai and Reding, 1998; Gainotti et al., 2001; Narushima et al., 2007). Therefore, early detection, correct diagnosis, and appropriate treatment of PSD are essential to enhance the functional recovery of stroke patients.

In this prospective study, we investigated the relationship between the clinical condition of PSD and physical recovery of stroke patients in a rehabilitation hospital. We focused on the following three issues. The first was to distinguish clearly between depression and apathy. Apathy is defined as the absence or lack of feeling, emotion, interest, or concern (Marin, 1990). The symptom has been considered to partially overlap with the expression of depression; however, several recent studies have revealed neuroanatomical and symptomatological differences between the two symptoms (Marin et al., 1994; Levy et al., 1998; Andersson et al., 1999). Apathy is also often observed after stroke and can interfere

Abbreviations: PSD, post-stroke depression; SDS, Zung Self-Rating Depression Scale; AS, Apathy Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; NPI-NH, Neuropsychiatric Inventory-Nursing Home; FIM, Functional Independence Measurement; MMSE, Mini-Mental State Examination

* Corresponding author. Tel.: +81 96 373 5184; fax: +81 96 373 5186.
E-mail address: m-hashi@kumamoto-u.ac.jp (M. Hashimoto).

http://dx.doi.org/10.1016/j.jad.2015.01.020
0165-0327/

with patient's engagement in rehabilitation programs. Depression and apathy require completely different therapeutic approaches. Thus, it is necessary to analyze depression and apathy separately in order to evaluate the influences of PSD on the recovery of physical function.

The second issue we focused on is the assessment of PSD. In a review of the assessment of PSD, Salter et al. (2007) noted that the use of self-report measures may be limited by the reliance of such scales on personal insight, but administration of self-report measures requires few resources and represents little patient burden. In contrast, results obtained via observer-rating scales based on psychiatric interviews are more diagnostically accurate, but the amount of time and level of expertise required for their administration make them less feasible assessment tools in most clinical settings (Salter et al., 2007). As with depression, patients with apathy may also lack insight into their disease. Therefore, we evaluated depression and apathy after stroke using both self-report (subjective) scales and observer-rating (objective) scales.

The third issue is the timing of the assessment of PSD. The majority of cases of PSD were developed between one and six months post stroke (Whyte and Mulsant, 2002). Some patients may develop depression during hospitalization for rehabilitation. Because the mental status of patients might be different according to the time between admission and assessment, a single assessment at admission makes it difficult to evaluate the influence of PSD on the rehabilitation effect. Therefore, we evaluated depression and apathy twice using a first assessment at admission and a second one during hospitalization (four weeks after the first one).

2. Method

All procedures for the present study strictly followed the 2011 Clinical Study Guidelines of the Ethics Committee of Kumamoto Takumadai Rehabilitation Hospital (Kumamoto, Japan) and were approved by the internal Review Board. Written informed consent was obtained from all patients after a complete description of all procedures of the study was provided.

2.1. Subjects

This study was a prospective rehabilitation hospital-based cohort study. The subjects were consecutively selected from patients who were admitted to Kumamoto Takumadai Rehabilitation Hospital between July 2011 and June 2013. All patients underwent routine laboratory tests and standard neuropsychological examinations including the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). The inclusion criterion in the present study was hospitalization for sub-acute stroke rehabilitation. The exclusion criteria were as follows: 1) patients with a rehabilitation plan to be finished within four weeks, 2) patients after sub-arachnoid hemorrhage or transient ischemic attack, 3) history of previous stroke, 4) presence of severe aphasia that would make screening test for PSD difficult, 5) history of major psychiatric illness, such as major depression, bipolar disorder, schizophrenia, or schizoaffective disorder, 6) complication of dementia based on DSM-III-R criteria (American Psychiatric Association, 1987), and 7) inability to obtain informed consent.

2.2. Assessment

In this study, we assessed depression and apathy separately using both subjective and objective scales. The assessments were performed twice, first within 10 days of the admission and then again at four weeks after the first assessment. Depression and apathy were assessed by two experienced neuropsychiatrists (M.S. and Y.S.). Patients with severe depression were treated appropriately through medication by the experienced neuropsychiatrists.

2.2.1. Assessment of depression

2.2.1.1. Subjective assessment. We used the Japanese version of the Self-rating Depression Scale (SDS) to examine the subjective severity of depression (Zung, 1965; Fukuda and Kobayashi, 1973). The SDS scale consists of 20 items and patients choose their answer to each item from 4 categories: always, often, sometimes, or rarely. The total score is the sum of the 20 items and the SDS scores ranged from 20 to 80. We classified the patients into two groups according to their score: a non-depressed group (SDS score <40 points) and a depressed group (SDS score $\geqq 40$) (Zung, 1965; Fukuda and Kobayashi, 1973).

2.3. Objective assessment

We used the Japanese version of the Montgomery–Åsberg Depression Rating Scale (MADRS-J) to examine the objective severity of depression (Montgomery and Asberg, 1979; Takahashi et al, 2004). The MADRS-J consists of 10 items, each of which is scored on a scale that ranges from 0 to 6. The total score is the sum of the 10 items and the MADRS-J scores range from 0 to 60. We classified the patients into two groups according to their score: a non-depressed group (MADRS-J score <12 points) and a depressed group (MADRS-J score $\geqq 12$) (Montgomery and Asberg, 1979; Takahashi et al, 2004).

2.3.1. Assessment of apathy

2.3.1.1. Subjective assessment. To quantify the apathetic state subjectively, we used the Japanese version of the Apathy Scale (AS) (Starkstein et al., 1992; Okada et al., 1998). The AS consists of 14 questions concerning spontaneity, initiation, emotionality, activity level, and interest in hobbies. This scale is self-assessed. The answers to each question are scored against four grades (0–3) and the total score was used for the analysis. We classified the patients into two groups according to their score: a non-apathetic group (apathy score <16 points) and an apathetic group (apathy score $\geqq 16$ points) (Starkstein et al., 1992; Okada et al., 1998).

2.4. Objective assessment

We assessed the patients' apathetic state objectively using a Japanese version of the Neuropsychiatric Inventory-Nursing Home (NPI-NH) (Wood et al., 2000; Shigenobu et al., 2008). The NPI-NH is a structured interview with professional caregivers in which 10 neuropsychiatric symptoms are assessed: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor behaviors. In this study, we focused on the apathy item on the NPI-NH and interviewed patients' primary nurses, physiotherapists (PT), or occupational therapists (OT). Screening questions are asked to determine whether apathy is present. In the case of a positive answer, further questions are asked and the severity and frequency of the symptom are determined. Frequency is rated on a five point scale from 0–4 and severity is rated on a four point scale from 0–3: the larger the score, the higher the severity or frequency. The NPI-NH score (severity $\times$ frequency) was calculated (range of possible scores, 0–12).

2.5. Physical function

Physical function was assessed with the Functional Independence Measurement (FIM) (Data Management Service of the Uniform Data System for Medical Rehabilitation and the Center

for Functional Assessment Research, 1990; Chino, 1997). The FIM is widely used as a measure of disability in stroke patients. The maximum total FIM score is 126; the lower the score, the greater the disability. The FIM was conducted at the time of admission and at discharge by the patients' PT or OT. In the present study, the recovery of physical function was expressed as the change of the FIM score during hospitalization, which was calculated as follows: [(FIM recovery)=(FIM score on discharge)−(FIM score on admission)].

2.6. Data analysis

The relationship between the clinical condition of PSD and physical recovery was assessed in a two-way analysis of covariance (ANCOVA) model with FIM recovery as a dependent variable, depression (depressive versus non-depressive) and apathy (apathetic versus non-apathetic) as main effects, and (depression) × (apathy) as an interaction term, adjusted for the appropriate covariates (gender, age, length of hospitalization, FIM score on admission and MMSE score). The analysis was performed separately on the basis of assessment measures (subjective or objective) and assessment timings (at admission or during hospitalization). All tests were 2-tailed and significance was set at the $p < 0.05$ level. All statistical analyses were performed using IBM SPSS Statistics 21 (IBM Japan, Tokyo, Japan).

3. Results

Of the 153 patients who participated this prospective study, 36 patients withdrew during the study because of discharge within 4 weeks ($n=25$) or worsening physical condition ($n=11$). Thus, 117 patients were enrolled for this study, with 64 women and 53 men. The mean age of these patients was 71.9 ± 13.8 years, the mean time to hospitalization from the onset was 21.0 ± 14.2 days, the mean length of hospitalization was 80.3 ± 39.0 days, the mean MMSE score was 25.0 ± 5.2, the mean FIM score on admission was 85.9 ± 29.5, and the mean FIM score on discharge was 104.7 ± 25.3. Ten patients with depression received antidepressant drug therapy during hospitalization.

Fig. 1 shows the frequency of depression and apathy based on each assessment scale and timing. The frequency of depression measured by MADRS-J was significantly higher than that by SDS at both timings. The second assessment during hospitalization showed a lower frequency of depression compared with that on admission for objective assessments. The objective scale (NPI-NH) gave a significantly higher prevalence than the subjective one (AS) in apathy, just as in depression.

Depression and apathy coexisted in some, but not all patients, and could exist independently, as shown in Table 1. The objective scales gave higher estimates of depression, apathy, and overlapping apathy and depression than the subjective scales. The pattern of overlap between depression and apathy during hospitalization was similar to that on admission.

A two-way ANCOVA (depression × apathy) revealed a significant main effect of apathy ($p=0.025$) on FIM recovery when the symptom was assessed by objective scale and during hospitalization (Table 2). The main effect of depression on FIM recovery was marginal ($p=0.095$) and was assessed only by objective scale and during hospitalization. There was no significant interaction effect of depression and apathy in either assessment scale or timing.

4. Discussion

Depression and apathy are common neuropsychiatric consequences of stroke. Some form of depression is considered to occur

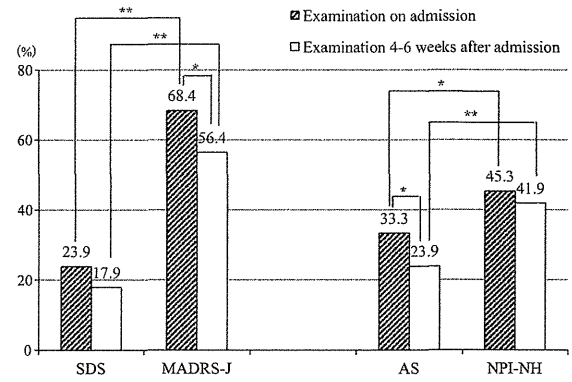


Fig. 1. Prevalence of depression and apathy presented as the percentage using cutoff scores noted in Section 2. The McNemar's test was used to calculate the differences in prevalence between the assessments (**$p < 0.01$, *$p < 0.05$). SDS: Japanese version of the Self-rating Depression Scale, MADRS-J: Japanese version of the Montgomery-Åsberg Depression Rating Scale. AS: Japanese version of the Apathy Scale, NPI-NH: Japanese version of the Neuropsychiatric Inventory-Nursing Home.

in at least one-quarter of patients in the first year after acute stroke (House, 1987; Burvill et al., 1995; Johnson, 1991). In the present study, depression was observed in 23.9% of patients using SDS, and apathy in 33.3% using AS on admission, which were comparable to a previous study conducted by Hama et al. (2007) in a rehabilitation hospital. They assessed psychological status using SDS for depression and AS for apathy in Japanese stroke patients and showed the prevalence of depression (31.6%) and apathy (40.1%).

Depression and apathy can appear simultaneously in the same patient after stroke. In this study, subjective measures revealed 50 patients (42.7%) with depression and/or apathy. Among them, 17 patients (34%) certainly had both depression and apathy at admission while two-thirds of patients had only one of them. This result suggested that depression and apathy could occur independently after stroke.

While investigating the relationships between the clinical condition of PSD and physical recovery after stroke, we also focused on the difference of assessment tools (subjective or objective measure) and timing of assessment (on admission or during hospitalization). There was a considerable discrepancy for prevalence of depression and apathy between self-report measures and observer rating scales. This finding stresses the need to analyze depression and apathy separately and to use appropriate measures for evaluating the influences of PSD on the recovery of physical function.

Apathy had a significant effect on FIM recovery, and depression showed a similar trend. There was no significant interaction effect between depression and apathy. This suggests that apathy and depression may influence functional recovery after stroke independently. It is noteworthy that the influence of apathy and depression on functional recovery was seen only when the symptoms were assessed using an objective scale and during hospitalization, indicating that later objective assessment may be more sensitive in detecting detrimental psychological states. The use of self-report measures to identify the presence of depression or to assess the level of depression has been the focus of considerable debate. It has been suggested that the discrepancies resulting from sole use of self-report measures were due to underreporting of depressive symptomology compared with observer ratings. Gordon et al. (1991) suggest that either patients tend to minimize the severity of their mood disorders or examiners are sensitive to patients' behaviors. Based on results of the current study, assessment using objective scales is essential for

Table 1
Comparisons of the assessments of PSD between groups, *n* (%).

		Depression (−) Apathy (−)	Depression (+) Apathy (−)	Depression (−) Apathy (+)	Depression (+) Apathy (+)
Examination on admission	Subjective assessment	67 (57.3%)	11 (9.4%)	22 (18.8%)	17 (14.5%)
	Objective assessment	33 (28.2%)	31 (26.5%)	4 (3.4%)	49 (41.9%)
Examination 4–6 weeks after admission	Subjective assessment	80 (68.4%)	9 (7.7%)	16 (13.7%)	12 (10.3%)
	Objective assessment	39 (33.3%)	29 (24.8%)	12 (10.3%)	37 (31.6%)

PSD: post-stroke depression.

Table 2
Influences of PSD on the recovery of physical function.

		Depression		Apathy		Depression	Apathy	Interaction
		Non-existence	Existence	Non-existence	Existence	*F*	*F*	*F*
Examination on admission	Subjective assessment	17.2(17.5)	22.2(22.4)	18.8(17.9)	17.6(20.8)	1.6	1.6	2.9
	Objective assessment	15.3(13.4)	19.8(20.8)	19.5(18.1)	17.0(19.7)	1.2	0.04	0.3
Examination 4–6 weeks after admission	Subjective assessment	17.5(17.2)	22.1(25.1)	19.2(16.7)	15.9(24.5)	0.4	1.0	1.2
	Objective assessment	18.3(15.0)	18.4(21.4)	19.5(18.2)	16.7(19.6)	2.8†	5.2*	0.2

Values are mean of FIM recovery (SD).
FIM recovery: (FIM score on discharge)−(FIM score on admission).
PSD: post-stroke depression.
FIM: Functional Independence Measurement.
Two way analysis of covariance (ANCOVA).
* $p < 0.05$.
† $p < 0.1$.

identifying the impact of psychological state on functional recovery.

Our results demonstrated the impact of the timing of assessment after stroke onset and suggested the efficacy of psychological symptom assessment during hospitalization for estimating functional recovery. Why do apathy and depression have a relationship to poor functional recovery only when assessed during hospitalization? Two possible factors might provide an answer to the question. We performed our first assessment of depression and apathy within 10 days after hospitalization. Patients interviewed during the sub-acute phase may still be adjusting to their stroke experience, and depression in these patients may reflect this transition stage. Bhogal et al. (2004) reviewed 26 reports about PSD and showed that the highest rates of depression were noted in patients assessed within the first 28 days of stroke. In fact, the number of patients with depression decreased during hospitalization in this study. Another is the factor on the side of examiners. Performing assessment too early after hospitalization complicates proper PSD screening because medical staff do not have enough time to adequately evaluate patients.

5. Limitations

A few methodological limitations of this study should be acknowledged. First, we did not consider the stroke size and location. Many studies have demonstrated a relationship between left anterior frontal damage and depression soon after an ischemic stroke or intracerebral hemorrhage. On the other hand, right-sided stroke has been associated with the development of anosognosia of depression (denial or unawareness of illness) (Ramasubbu, 1994, Carota et al., 2002). These factors could cause depression or apathy and lead to a poor rehabilitation effect. Further study is needed to examine the influence of lesion site and size on functional recovery. Second, because patients with severe aphasia and patients with a history of stroke were excluded from the study, the results may not be applicable to all stroke patients.

6. Conclusion

Our findings demonstrate that depression and apathy could occur independently after stroke and they could individually influence functional recovery. While we employed both objective and subjective assessment scale, objective measures gave a more accurate estimate of functional recovery. Furthermore, these findings suggest that depression and apathy should be assessed not only at admission but also during hospitalization to estimate and enhance the functional recovery of stroke patients.

Role of funding source
None.

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

Contributors

Shiho Matsuzaki designed this study, collected data, worked on data analysis, and drafted the article. Seiji Yuki helped in collecting data. Asuka Koyama helped to conduct a statistical analysis. Mamoru Hashimoto, Yoshifumi Hirata and Manabu Ikeda designed this study and contributed to supervise and edit the final version of manuscript. All authors revised the paper critically and have approved the final manuscript.

Acknowledgments
The authors gratefully acknowledge the assistance of the staff of the Kumamoto Takumadai Rehabilitation Hospital and Kumamoto University.

References

Andersson, S., Krogstad, J.M., Finset, A., 1999. Apathy and depressed mood in acquired brain damage: relationship to lesion localization and psychophysiological reactivity. Psychol. Med. 29, 447–456.

American Psychiatric Association, 1987. Diagnostic and Statistical Manual of Mental Disorders, third ed., Revised. Washington, D.C.
Bhogal, S.K., Teasell, R., Foley, N., Speechley, M., 2004. Lesion location and poststroke depression: systematic review of the methodological limitations in the literature. Stroke 35, 794–802.
Burvill, P.W., Johnson, G.A., Jamrozik, K.D., Anderson, C.S., Stewart-Wynne, E.G., Chakera, T.M.H., 1995. Prevalence of depression after stroke: the Perth Community Stroke Study. Br. J. Psychiatry 166, 320–327.
Carota, A., Staub, F., Bogousslavsky, J., 2002. Emotions, behaviours and mood changes in stroke. Curr. Opin. Neurol. 15, 57–69.
Chino, N., 1997. FIM Igaku-teki rehabilitation no tame no data set riyou no tebiki, 3rd ed. Keio University, Tokyo.
Dam, M., Tonin, P., De Boni, A., Pizzolato, G., Casson, S., Ermani, M., et al., 1996. Effects of fluoxetine and maprotiline on functional recovery in poststroke hemiplegic patients undergoing rehabilitation therapy. Stroke 27, 1211–1214.
Data Management Service of the Uniform Data System for Medical Rehabilitation and the Center for Functional Assessment Research., 1990. Guide for use of the Uniform Data Set for Medical Rehabilitation Including the Functional Independence Measure (FIM), Version 3.0. Buffalo, NY.
Folstein, MF., Folstein, SE., McHugh, PR., 1975. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198.
Fukuda, K., Kobayashi, S., 1973. Jiko-hyouka-shiki yokuutsu-sei shakudo no kenkyuu. [A study on a self-rating depression scale]. Seishin Shinkeigaku Zassi 75, 673–679.
Gainotti, G., Antonucci, G., Marra, C., Paolucci, S., 2001. Relation between depression after stroke, antidepressant therapy, and functional recovery. J. Neurol. Neurosurg. Psychiatry 71, 258–261.
Gonzalez-Torrecillas, J.L., Mendlewicz, J., Lobo, A., 1995. Effects of early treatment of poststroke depression on neuropsychological rehabilitation. Int. Psychogeriatr. 7, 547–560.
Gordon, W.A., Hibbard, M.R., Egelko, S., Riley, E., Simon, D., Diller, L., et al., 1991. Issues in the diagnosis of post-stroke depression. Rehabil. Psychol. 63, 71–87.
Hackett, M.L., Yapa, C., Parag, V., Anderson, C.S., 2005. Frequency of depression after stroke: a systematic review of observational studies. Stroke 36, 1330–1340.
Hama, S., Yamashita, H., Shigenobu, M., Watanabe, A., Hiramoto, K., Kurisu, K., et al., 2007. Depression or apathy and functional recovery after stroke. Int. J. Geriatr. Psychiatry 22, 1046–1051.
Hinojosa, R., Haun, J., Hinojosa, M.S., Rittman, M., 2011. Social isolation post-stroke: relationship between race/ethnicity, depression, and functional independence. Top Stroke Rehabil. 18, 79–86.
House, A., 1987. Mood disorders after stroke: a review of the evidence. Int. J. Geriatr. Psychiatry 2, 211–221.
Johnson, GA., 1991. Research into psychiatric disorder after stroke: the need for further studies. Aust. N. Z. J. Psychiatry 25, 358–370.
Levy, M.L., Cummings, J.L., Fairbanks, L.A., et al., 1998. Apathy is not depression. J. Neuropsychiatry Clin. Neurosci. 10, 314–319.
Marin, RS., 1990. Differential diagnosis and classification of apathy. Am. J. Psychiatry 147, 22–30.
Marin, R.S., Firinciogullari, S., Biedrzycki, R.C., 1994. Group differences in the relationship between apathy and depression. J. Nerv. Ment. Dis. 182, 235–239.
Miyai, I., Reding, M.J., 1998. Effects of antidepressants on functional recovery following stroke: a double-blind study. Neurorehabil. Neural Repair 12, 5–13.
Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.
Narushima, K., Paradiso, S., Moser, D., Jorge, R., Robinson, R., 2007. Effect of antidepressant therapy on executive function after stroke. Br. J. Psychiatry 190, 260–265.
Okada, K., Kobayashi, S., Aoki, K., Suyama, N., Yamaguchi, S., 1998. Assessment of motivational loss in poststroke patients using the Japanese version of Starkstein's Apathy Scale. Nosotchu 20, 318–323.
Ramasubbu, R., 1994. Denial of illness and depression in stroke. Stroke 25, 226–227.
Salter, K., Bhogal, S.K., Foley, N., Jutai, J., Teasell, R., 2007. The assessment of poststroke depression. Stroke Rehabil. 14, 1–24.
Shigenobu, K., Hirono, N., Tabushi, K., Ikeda, M., 2008. Validity and reliability of the Japanese Version of the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH). Brain Nerve 60, 1463–1469.
Starkstein, SE., Mayberg, HS., Preziosi, TJ., Andrezejewski, P., Leiguarda, R., Robinson, RG., 1992. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J. Neuropsychiatry Clin. Neurosci. 4, 134–139.
Takahashi, N., Tomita, K., Higuchi, T., Inada, T., 2004. The inter-rater reliability of the Japanese version of the Montgomery–Asberg depression rating scale (MADRS) using a structured interview guide for MADRS (SIGMA). Hum. Psychopharmacol. 19, 187–192.
Whyte, E.M., Mulsant, B.H., 2002. Post-stroke depression: epidemiology, pathophysiology, and biological treatment. Biol. Psychiatry 52, 253–264.
Wood, S., Cummings, J.L., Hsu, M-A., Barclay, T., Wheatley, M.V., Yarema, K.T., et al., 2000. The use of the neuropsychiatric inventory in nursing home residents, characterization and measurement. Am. J. Geriatr. Psychiatry 8, 75–83.
Zung, W.W., 1965. A Self-Rating Depression Scale. Arch. Gen. Psychiatry 12, 63–70.

Ikeda et al. Alzheimer's Research & Therapy (2015) 7:4
DOI 10.1186/s13195-014-0083-0

alzheimer's research&therapy

RESEARCH Open Access

Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled, confirmatory phase III trial

Manabu Ikeda[1*], Etsuro Mori[2], Kazutaka Matsuo[3], Masaki Nakagawa[3] and Kenji Kosaka[4]

Abstract

Introduction: The efficacy of a cholinesterase inhibitor, donepezil, in patients with dementia with Lewy bodies (DLB) was investigated to confirm the superiority over placebo in the 12-week, double-blind phase of this phase III study.

Methods: Patients with probable DLB ($n = 142$) were randomly assigned to placebo or to 5 mg or 10 mg of donepezil administered once daily for 12 weeks. The co–primary endpoints were changes in cognitive function assessed using the Mini-Mental State Examination (MMSE) and behavioral and neuropsychiatric symptoms using the Neuropsychiatric Inventory (NPI-2: hallucinations and fluctuations). The superiority of each active group over placebo was determined with simultaneous statistical significance in both endpoints. Safety evaluations included adverse events (AEs) and the unified Parkinson's disease rating scale (UPDRS) part III.

Results: The predefined superiority of donepezil to the placebo was not confirmed in either active group in the primary analysis. MMSE score significantly improved compared to placebo in the 10 mg group (10 mg: 2.2 ± 0.4, placebo: 0.6 ± 0.5 (mean ± standard error); $P = 0.016$). The change in MMSE score in the 5 mg group was not significant (1.4 ± 0.5 (mean ± standard error); $P = 0.232$). Although NPI-2 improved compared to baseline in the active groups, the differences from placebo were not significant. Most AEs were mild or moderate. Although the incidence of parkinsonism was slightly higher in the 10 mg group, the change in the UPDRS score was minimal and without a significant difference from the placebo group.

Conclusions: The co–primary endpoints were not achieved in this trial. However, significant improvement in MMSE score was demonstrated with 10 mg, but not 5 mg, of donepezil. The evaluation of psychiatric symptoms might be affected by advanced education and instructions given to caregivers. Overall, donepezil was well tolerated in patients with DLB. With careful attention on gastrointestinal or parkinsonian symptoms, patients with DLB can safely benefit from treatment with donepezil.

Trial registration: ClinicalTrials.gov Identifier: NCT01278407 (trial registration date: 14 January 2011)

Introduction

Dementia with Lewy bodies (DLB) is the second most common type of senile dementia following Alzheimer's disease (AD) [1]. The core clinical features of DLB are fluctuating cognition, visual hallucinations and motor symptoms of parkinsonism, as well as cognitive impairment characterized by deficits in attention, executive function and visual perception [2]. Other features include neuropsychiatric symptoms such as delusions and depression, as well as autonomic dysfunction. Fluctuating cognition, hallucinations and delusions impose particular challenges and distress on both patients and caregivers. The motor and autonomic features have a further negative impact on activities of daily living and quality of life [3,4].

DLB is associated with a greater loss of cholinergic neurons in the nucleus basalis of Meynert and lower choline acetyltransferase (ChAT) activity than AD, but more postsynaptic muscarinic receptors in the cortex are preserved [5-7]. The cholinergic depletion correlates not only with the cognitive impairment but also with psychiatric symptoms such as hallucinations [8]. On the

* Correspondence: mikeda@kumamoto-u.ac.jp
[1]Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, 1-1-1 Honjo, Chuo-ku, Kumamoto 860-8556, Japan
Full list of author information is available at the end of the article

basis of these pathological features, it has been suggested that cholinesterase inhibitors (ChEIs) may be an effective treatment for DLB [9,10]. However, no ChEIs have been approved for DLB to date.

Previously, we examined the efficacy and safety of donepezil administered at 3, 5 and 10 mg for 12 weeks in patients with DLB in a placebo-controlled, double-blind exploratory study [11]. An open-label, long-term extension study was then conducted in patients who had completed the double-blind study to examine the safety and efficacy of donepezil at 5 mg for 52 weeks [12]. The double-blind study showed that donepezil at 5 mg or 10 mg per day significantly improved cognitive impairment, behavioral and psychiatric symptoms, global clinical symptoms and the caregiver burden compared to placebo. The long-term study showed that donepezil at 5 mg/day was well tolerated and that it sustained improvement in cognitive impairment and psychiatric symptoms over the course of 52 weeks.

The aim of the present phase III study, integrating a placebo-controlled, double-blind comparative study and an open-label long-term extension study, was to further evaluate the efficacy and to confirm the superiority of donepezil administration at 5 mg and 10 mg per day for 12 weeks over placebo, as well as to evaluate the safety and efficacy of long-term administration at 10 mg as well as 5 mg per day, in patients with DLB. This report describes the results of the placebo-controlled, double-blind, 12-week phase. Detailed results of the extension phase are reported elsewhere [13].

Methods

Patients

Patients diagnosed as probable DLB according to the consensus diagnostic criteria [2] were recruited from 72 psychiatric or neurological specialty centers throughout Japan from February 2011 to March 2012. Eligible patients were outpatients aged ≥50 years with mild to moderate or severe dementia (10 to 26 on the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating ≥0.5) and behavioral and psychiatric symptoms (Neuropsychiatric Inventory-plus (NPI-plus) ≥8 and NPI (NPI-2) ≥1). The NPI-plus consisted of 12 items: the original 10 items, sleep [14,15] and cognitive fluctuation, which is reported as the Cognitive Fluctuation Inventory [16,17] (see Additional file 1). The NPI-2 consisted of hallucinations and cognitive fluctuation [11]. The caregivers of the eligible patients had to routinely stay with them 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 exclusion criteria included Parkinson's disease that was diagnosed at least 1 year prior to the onset of dementia; focal vascular lesions visualized on magnetic resonance imaging or computed tomographic scans that might cause cognitive impairment; other neurological or psychiatric diseases; clinically significant systemic disease; complications or a history of severe gastrointestinal ulcer, severe asthma or obstructive pulmonary disease; systolic hypotension (<90 mmHg); bradycardia (<50 m^{-1}); sick sinus syndrome; atrial or atrioventricular conduction block; QT interval prolongation (≥450 ms); hypersensitivity to donepezil or piperidine derivatives; severe parkinsonism (Hoehn and Yahr stage IV or above) [18]; and treatment with ChEIs or any investigational drug within 3 months prior to screening. ChEIs, antipsychotics and antiparkinson drugs other than L-dopa or dopamine agonists were not allowed during the study.

Randomization and masking

This study consisted of two phases: a 16-week, double-blind randomized control (RCT) phase and a subsequent 36-week, open-label extension phase. Treatment with donepezil lasted up to 52 weeks in total. The RCT phase, which was preceded by a 2-week (1 to 3 weeks) prerandomization period, entailed the 12-week confirmatory phase (Figure 1). In this article, we report the results of the confirmatory phase. All patients were given placebo tablets during the prerandomization period, after which the patients were assigned in a 1:1:1 ratio to placebo or 5 mg or 10 mg of donepezil in the RCT phase. Randomization was performed centrally according to a dynamic allocation, adjusting for MMSE and NPI-2 scores at screening. A member of the research staff who was in charge of randomization and who was independent of all the parties concerned with the study securely kept the randomization list with limited access only in an emergency. No other members of the research staff, including the physicians, nurses and study institution staff were aware of the treatment assignment, nor were any of the participants.

Patients received two study drug tablets, which were composed of a combination of 3 mg, 5 mg, or the matched placebo tablets with the same physical appearance, once daily in the morning. The dosage was titrated at the beginning. Treatment began with 3 mg for 2 weeks, and then the dose was increased to 5 mg. Thereafter, the dose was increased to 10 mg at week 6 only in the 10 mg group. The dose was escalated after patient safety was confirmed. Dose reduction was not permitted in the RCT phase.

Procedures

In the confirmatory phase, efficacy was assessed at baseline and at weeks 4, 8 and 12. Co–primary endpoints were cognitive function assessed using the MMSE [19] and behavioral and neuropsychiatric symptoms assessed using the NPI-2 [11], both at week 12. NPI-2 was calculated as the sum of the scores for hallucinations and cognitive

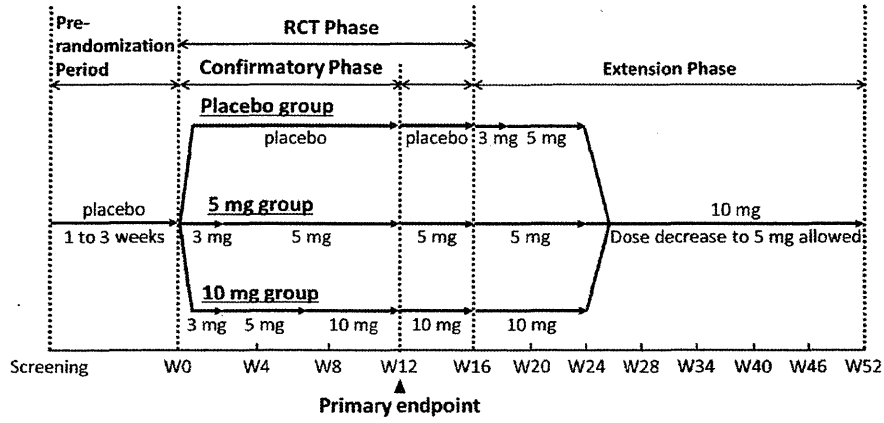


Figure 1 Study flow. RCT, Randomized placebo-controlled trial.

fluctuation, which corresponded to two of the core features of DLB in the consensus criteria. The original NPI-10 (delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability and aberrant motor behavior) was set as a secondary endpoint.

Caregiver burden was assessed using the Zarit Caregiver Burden Interview (ZBI) [20], which evaluates the physical, psychological and social consequences of care activities. The ZBI contains 22 items scored from 0 (best) to 4 (worst), from which a total score of 0 to 88 is calculated.

Safety was assessed based on adverse events (AEs), vital signs, electrocardiograms 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 using the Unified Parkinson's Disease Rating Scale (UPDRS) part III [21] at baseline and week 12.

Written informed consent was obtained from the patients (if at all possible) and their primary caregiving family members before initiating the study procedures. The study was conducted in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the institutional review board at each center (Additional file 2).

Statistical analyses

In a sample size calculation, the mean changes in MMSE score were estimated to be −0.4, 2.0 and 2.0 with standard deviation (SD) of 3.3, and the mean changes in NPI-2 score were estimated to be 1.1, −3.3 and −4.6 with SD of 5.2 in the placebo, 5 mg and 10 mg groups, respectively, according to the results of the previous double-blind study. The Bonferroni-corrected significance level was set at one-sided 1.25%. Detecting the significant difference, predefined to be determined only with statistical significance in both MMSE and NPI-2 results, with at least 80% statistical power between the placebo and 5 mg groups required at least 126 patients (42 per group) (statistical power of 80.7%). The number was expected to provide power of 85.4% to detect a significant difference between the placebo and 10 mg groups. Given that 10% of the patients were excluded from the full analysis set (FAS), the target number of patients in this study was set at 141.

Efficacy was analyzed in the FAS and the per-protocol set (PPS). Analysis using the FAS was positioned for primary analysis. Mean changes from the baseline in each outcome measure were compared between each active group and placebo by analysis of covariance (ANCOVA) with baseline values as covariates. Only the statistical significance in both MMSE and NPI-2 between the placebo group and each active group could determine the superiority of the active drug over placebo. The significance level was adjusted for multiplicity using the Hochberg method. In addition, MMSE improvement was evaluated by responder rate, defined as the proportion of patients with ≥3-point improvement.

The safety analysis set comprised all patients who received at least one dose and had a postbaseline safety assessment. The incidence of AEs was summarized by group. For laboratory parameters and vital signs, descriptive statistics and frequency distributions were calculated. UPDRS part III scores were compared between each active group and the placebo group using ANCOVA with baseline values as covariates.

All analyses were carried out using SAS versions 9.1 and 9.2 software (SAS Institute, Cary, NC, USA).

Results

Patients

Of 161 patients enrolled in the prerandomization 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) (Figure 2). Of these patients, 138 were included in the FAS (44, 45 and 49 patients in the placebo, 5 mg and 10 mg groups, respectively). Four patients (two patients each in the placebo and 5 mg groups) were excluded because of a lack of evaluable efficacy data (three patients) and doubtful diagnosis of probable DLB (one patient). Excluding 19 patients from the FAS, 119 patients (40, 34 and 45 patients in the placebo, 5 mg and 10 mg groups, respectively) constituted the PPS. The reasons for the 19 exclusions were discontinuation within <8 weeks, compliance rate <75% or lack of efficacy data due to a change in the evaluator.

Thirty-one patients discontinued (9, 16 and 6 patients in the placebo, 5 mg and 10 mg groups, respectively) with more discontinuations in the 5 mg group than in the 10 mg group. The total discontinuations in the active groups comprised 22 (22.9%) of the 96 patients, which was similar to the placebo group (19.6%).

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

Co-primary endpoints (MMSE and NPI-2 scores)

Changes in the co-primary endpoints (MMSE and NPI-2 scores) from baseline are shown in Table 2. Primary analysis did not confirm the predefined superiority of either active group to the placebo group.

Cognitive function

Mean changes from baseline in MMSE in the FAS and PPS are shown in Table 3. In the FAS, the mean change from baseline in the MMSE scores at week 12 (last observation carried forward (LOCF)) was higher in each active group (mean ± standard error (SE): 1.4 ± 0.5 and 2.2 ± 0.4 in the 5 mg and 10 mg groups, respectively) than in the placebo group (mean ± SE: 0.6 ± 0.5). Improvement in the 10 mg group was significant compared to that in the placebo group (mean difference from placebo = 1.6; $P = 0.016$), but that in the 5 mg group was not (mean difference from the placebo = 0.8, $P = 0.232$). PPS analysis yielded a significant improvement in both active groups (5 mg: $P = 0.025$, 10 mg: $P = 0.004$). The responder rate (MMSE score change ≥3) was higher in each active group than in the placebo group (29.5%, 41.9% and 42.9% in the placebo, 5 mg and 10 mg groups, respectively).

Behavioral and neuropsychiatric symptoms

Changes from baseline in NPI-2 and NPI-10 scores are shown in Table 4. The changes in NPI-2 scores in both active groups were not significantly different from that in the placebo group. In the active group, NPI-2 improved at week 12 (LOCF) (mean ± SE: −1.8 ± 0.6 and −2.8 ± 0.5 in the 5 mg and 10 mg groups, respectively). However, the placebo group also showed improvement of −2.1 ± 0.6 (mean ± SE). The NPI-10 score improved at week 12 (LOCF) in each active group by −3.3 ± 1.4 and −5.5 ± 1.4 (mean ± SE) in the 5 mg and 10 mg groups, respectively, and also in the placebo group, by −6.4 ± 1.5. There was no significant difference between either of the active groups and the placebo group.

Caregiver burden

ZBI score at week 12 (LOCF) was almost unchanged from the baseline in the placebo group (mean ± SE: −0.1 ± 1.8). In both the 5 mg and 10 mg groups, the score improved by −5.0 ± 1.8 and −0.8 ± 1.7 points (mean ± SE), respectively, but without a significant difference from the placebo group. Subgroup analysis yielded a stronger trend of the ZBI improvement in a group of caregivers who lived with the patient, and a significant difference between the 5 mg group and the placebo group (FAS-LOCF: $P = 0.017$).

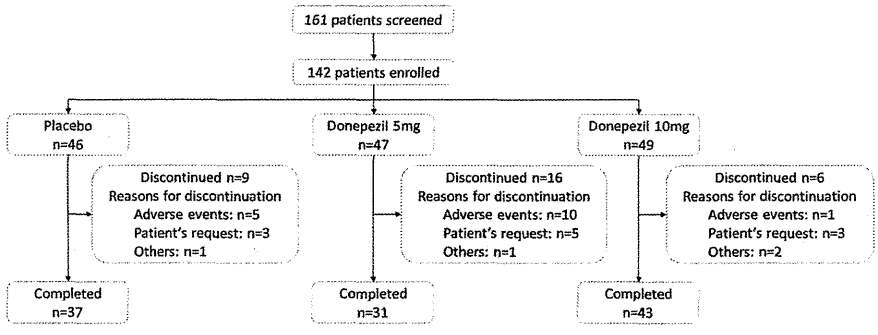


Figure 2 Patient disposition in the confirmatory phase.

Table 1 Patient demographics and baseline characteristics[a] (FAS, *N* = 138)

Characteristics	Placebo (*n* = 44)	Donepezil 5 mg (*n* = 45)	Donepezil 10 mg (*n* = 49)	Overall (*n* = 138)
Sex, *n* (%)				
Male	17 (38.6)	20 (44.4)	21 (42.9)	58 (42.0)
Female	27 (61.4)	25 (55.6)	28 (57.1)	80 (58.0)
Age, yr	77.2 ± 6.1	78.8 ± 5.1	77.7 ± 6.8	77.9 ± 6.1
Weight, kg	50.15 ± 10.75	50.68 ± 9.24	51.72 ± 9.89	50.88 ± 9.92
Duration of dementia, yr	2.0 ± 2.3	2.7 ± 1.8	2.3 ± 1.9	2.3 ± 2.0
History of anti-dementia medication, *n* (%)				
Yes	1 (2.3)	3 (6.7)	4 (8.2)	8 (5.8)
No	43 (97.7)	42 (93.3)	45 (91.8)	130 (94.2)
Cognitive fluctuation, *n* (%)				
Yes	40 (90.9)	41 (91.1)	46 (93.9)	127 (92.0)
No	4 (9.1)	4 (8.9)	3 (6.1)	11 (8.0)
Visual hallucinations, *n* (%)				
Yes	42 (95.5)	39 (86.7)	39 (79.6)	120 (87.0)
No	2 (4.5)	6 (13.3)	10 (20.4)	18 (13.0)
Parkinsonism, *n* (%)				
Yes	38 (86.4)	39 (86.7)	44 (89.8)	121 (87.7)
No	6 (13.6)	6 (13.3)	5 (10.2)	17 (12.3)
Hoehn and Yahr stage, *n* (%)				
I	4 (9.1)	8 (17.8)	7 (14.3)	19 (13.8)
II	15 (34.1)	17 (37.8)	19 (38.8)	51 (37.0)
III	19 (43.2)	14 (31.1)	18 (36.7)	51 (37.0)
MMSE score	20.3 ± 4.2	20.6 ± 4.1	20.3 ± 4.8	20.4 ± 4.3
NPI-2 score	6.9 ± 4.5	6.9 ± 4.5	7.3 ± 4.7	7.1 ± 4.5
NPI-10 score	20.5 ± 15.0	18.9 ± 15.3	16.6 ± 11.7	18.6 ± 14.0
ZBI score	28.4 ± 16.2	28.3 ± 18.5	31.4 ± 17.8	29.4 ± 17.4

[a]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.

Table 2 Co-primary endpoints (MMSE and NPI-2 scores) and changes from baseline (FAS LOCF)[a]

	Groups	*n*	Baseline (week 0) score Mean ± SD	Week 12 (LOCF) change Mean ± SD	*P*-value[b]
MMSE[c]	Placebo	44	20.3 ± 4.2	0.6 ± 3.0	
	5 mg	45[d]	20.6 ± 4.1	1.4 ± 3.4	0.232
	10 mg	49	20.3 ± 4.8	2.2 ± 2.9	0.016
NPI-2[e]	Placebo	44	6.9 ± 4.5	−2.0 ± 4.2	
	5 mg	45	6.9 ± 4.5	−1.7 ± 4.3	0.661
	10 mg	49	7.3 ± 4.7	−2.9 ± 4.7	0.391

[a]FAS, Full analysis set; LOCF, Last observation carried forward; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory. [b]Analysis of covariance with treatment groups as factors and baseline values as covariates. Significance was defined as $P < 0.05$. [c]Positive value of the MMSE change indicates an improvement in cognitive function. [d]The number of patients at week 12 (LOCF) was 43. [e]A negative value of the NPI-2 change indicates an improvement in behavioral and neuropsychiatric symptoms.

Table 3 Mean changes in Mini-Mental State Examination (MMSE) scores from baseline (LOCF)[a]

	Group	n	Mean ± SE[b]	Difference from placebo group[b] (95% CI)	P-value
	Placebo	44	0.6 ± 0.5	–	–
FAS-LOCF	5 mg	43	1.4 ± 0.5	0.8 (−0.5, 2.1)	0.232
	10 mg	49	2.2 ± 0.4	1.6 (0.3, 2.8)	0.016[c]
	Placebo	37	1.0 ± 0.5	–	–
FAS-OC	5 mg	32	2.2 ± 0.5	1.2 (−0.2, 2.7)	0.083
	10 mg	43	2.6 ± 0.4	1.6 (0.3, 2.9)	0.014[c]
	Placebo	40	0.5 ± 0.5	–	–
PPS-LOCF	5 mg	34	2.1 ± 0.5	1.6 (0.2, 2.9)	0.025[c]
	10 mg	45	2.4 ± 0.4	1.9 (0.6, 3.2)	0.004[c]

[a]CI, Confidence interval; FAS, Full analysis set; LOCF, Last observation carried forward; MMSE, Mini-Mental State Examination; OC, Observed case; PPS, Per-protocol set. [b]Least squares mean from analysis of covariance with treatment groups as factors and baseline values as covariates. A positive value of the MMSE change indicates improvement in cognitive function. [c]$P < 0.05$.

Safety

The incidence of AEs and treatment-related AEs did not differ substantially among the groups (AEs: 67.4% (31 of 46), 63.8% (30 of 47) and 69.4% (34 of 49); treatment-related AEs: 23.9% (11 of 46), 25.5% (12 of 47) and 28.6% (14 of 49) in the placebo, 5 mg and 10 mg groups, respectively). The incidence of severe or serious AEs in either of the active groups (severe AEs: 8.5% (4 of 47) and 0% (0 of 49); serious AEs: 8.5% (4 of 47) and 2.0% (1 of 49) in the 5 mg and 10 mg groups, respectively) did not substantially exceed those in the placebo group (severe AEs: 6.5% (3 of 46); serious AEs: 10.9% (5 of 46)). The incidence of the AEs that led to discontinuation was higher in the 5 mg group (21.3% (10 of 47)), but lower in the 10 mg group (4.1% (2 of 49)), than in the placebo group (10.9% (5 of 46)).

AEs with an incidence ≥5% in any treatment group are shown in Table 5. Major AEs with a higher incidence in either of the active groups than in the placebo group were parkinsonism (4.3% (2 of 46), 4.3% (2 of 47) and 8.2% (4 of 49), in the placebo, 5 mg and 10 mg groups, respectively, provided in the same order hereinafter), decreased appetite (2.2% (1 of 46), 6.4% (3 of 47), and 4.1% (2 of 49)) and nausea (2.2% (1 of 46), 6.4% (3 of 47) and 2.0% (1 of 49)). The incidence of contusion in the active groups (0.0% (0 of 47) and 2.0% (1 of 49) in the 5 mg and 10 mg groups, respectively) was low compared to the placebo group (8.7% (4 of 46)).

The incidence of gastrointestinal events in the 5 mg group was higher than in the placebo group, but that in the 10 mg group was similar to the placebo group (13.0% (6 of 46), 21.3% (10 of 47) and 14.3% (7 of 49)). Decreased appetite and nausea were both observed in >5% of patients in the 5 mg group, but the incidence of no gastrointestinal events in the 10 mg group reached 5%. All gastrointestinal events were mild or moderate in severity. When analyzed in 14-day intervals from the baseline, the incidence in the 10 mg group at the interval of days 43 to 56, the first interval following the dose increase from 5 to 10 mg at week 6, was the highest among the periods and the groups (8.3%).

As parkinsonian AEs, only parkinsonism was reported, and its incidence was slightly higher in the 10 mg group than in the placebo and 5 mg groups (4.3% (2 of 46), 4.3% (2 of 47) and 8.2% (4 of 49)), all of which were mild or moderate and not serious. Changes from baseline in the UPDRS part III score were minimal in all of the groups (−0.9 ± 0.9, −1.7 ± 0.9 and 0.4 ± 0.9 points (mean ± SE), respectively) without a significant difference between either of the active groups and the placebo group (5 mg: $P = 0.525$, 10 mg: $P = 0.306$).

Table 4 Change in NPI from baseline (FAS-LOCF)[a]

	Group	n	Mean ± SE[b]	Difference from placebo group[b] (95% CI)	P-value
	Placebo	44	−2.1 ± 0.6	–	–
NPI-2	5 mg	45	−1.8 ± 0.6	0.4 (−1.3, 2.0)	0.661
	10 mg	49	−2.8 ± 0.5	−0.7 (−2.3, 0.9)	0.391
	Placebo	44	−6.4 ± 1.5	–	–
NPI-10	5 mg	45	−3.3 ± 1.4	3.0 (−1.0, 7.1)	0.143
	10 mg	49	−5.5 ± 1.4	0.9 (−3.1, 4.9)	0.660

[a]FAS, Full analysis set; LOCF, Last observation carried forward; NPI, Neuropsychiatric Inventory. [b]Least squares mean from analysis of covariance with treatment groups as factors and baseline values as covariates. A negative value of the NPI change indicates an improvement in behavioral and neuropsychiatric symptoms.

Table 5 Adverse events with an incidence of more than 5% in any treatment groups[a]

	Placebo group ($n = 46$)		5 mg group ($n = 47$)		10 mg group ($n = 49$)	
AE	AEs	Treatment-related AEs[b]	AEs	Treatment-related AEs[b]	AEs	Treatment-related AEs[b]
Total incidence	31 (67.4)	11 (23.9)	30 (63.8)	12 (25.5)	34 (69.4)	14 (28.6)
Nausea	1 (2.2)	1 (2.2)	3 (6.4)	2 (4.3)	1 (2.0)	1 (2.0)
Pyrexia	0	0	0	0	3 (6.1)	0
Nasopharyngitis	7 (15.2)	0	4 (8.5)	0	2 (4.1)	0
Contusion	4 (8.7)	0	0	0	1 (2.0)	0
Decreased appetite	1 (2.2)	1 (2.2)	3 (6.4)	1 (2.1)	2 (4.1)	2 (4.1)
Parkinsonism	2 (4.3)	2 (4.3)	2 (4.3)	2 (4.3)	4 (8.2)	4 (8.2)
Pollakiuria	0	0	3 (6.4)	3 (6.4)	0	0

[a]AE, Adverse event. Incidence shown as number and percentage. [b]AEs for which a causal relationship with the study drug was considered possible or probable.

The incidence of psychiatric events was similar between the 5 mg group and the placebo group, and the incidence in the 10 mg group was lower than that in the placebo group (10.9% (5 of 46), 12.8% (6 of 47) and 4.1% (2 of 49)). The incidence of individual psychiatric events was <5% in each group. Five severe psychiatric events were reported in two patients in the 5 mg group: visual hallucinations, insomnia, paranoia, agitation and irritability, all of which were judged to be related to the treatment.

The incidence of arrhythmic events was similar among the groups (4.3% (2 of 46), 4.3% (2 of 47) and 6.1% (3 of 49)). Each event was reported by only one patient, and the events were of mild to moderate severity.

For vital signs, blood pressure, pulse rate and body weight slightly declined in the active groups. AEs related to vital signs were ventricular extrasystoles ($n = 1$) and hypotension ($n = 1$) in the 10 mg group and weight decrease ($n = 1$) in the 5 mg group. All of these AEs were either mild or moderate. No patients reported any abnormal changes in pulse rate. The incidences of abnormal changes in the electrocardiogram were similar among the groups (4.7% (2 of 43), 4.7% (2 of 43) and 6.3% (3 of 48)).

Discussion

In the primary analysis of the co–primary endpoints (MMSE and NPI-2 scores), predefined superiority over placebo was not confirmed in either the 5 mg or 10 mg group. However, in the evaluation of cognitive function using MMSE score, the difference between the placebo and 10 mg groups was significant, which is consistent with the previous double-blind study [11]. The mean change in the MMSE score in the 10 mg group was 2.2 points, which was almost equal to the score of 2.3 obtained in our previous study [11].

The improvement in the 5 mg group was found to be significant only in the PPS analysis, although it was also found to be significant in all analyses in the previous study [11]. The results of the present study did not replicate our previous finding, which is probably due to a relatively larger number of earlier discontinuations. In the 5 mg group, eight patients (17.0%) discontinued by week 4 when the blood concentrations of 5 mg donepezil reached the steady state, whereas only one patient (3.0%) discontinued in the previous study. The imbalance of discontinuation was not caused by the dose of 5 mg itself, because only one patient in the 10 mg group discontinued by week 4, while taking the same doses as the 5 mg group until week 6.

In two phase III studies in which the efficacy of donepezil in patients with mild to moderate AD was investigated [22,23], a mean change in the MMSE score of 0.24 to 1.35 points with a difference from the change in the placebo groups of 1.02 to 1.36 points was reported. In contrast, in the confirmatory phase of this study and in the previous double-blind study [11] in patients with DLB, the mean change in the MMSE score in the active groups (5 or 10 mg) was 1.4 to 3.4 points with a difference from the placebo groups of 0.8 to 3.8 points, which exceeded the equivalent scores in the two AD studies. Therefore, these results imply that treatment with donepezil for DLB provides greater improvement in cognitive function than for AD, for which donepezil had already been approved, reinforcing the clinical significance of treating DLB with donepezil.

In the phase II study, donepezil clearly showed dose-dependent efficacy against behavioral and neuropsychiatric symptoms [11]. In the present study, however, the placebo group also benefited from improvement in these symptoms, which represents the failure to replicate the findings in the previous study. Which factors affected the unexpected improvement of behavioral and neuropsychiatric symptoms in the placebo group? Two possible reasons are conceivable in terms of the time of the trials: (1) promotion of disease awareness and improved caregiving methodology brought about by quantitatively and qualitatively enriched disease-related information and (2) the emergence of reports on successful psychosocial interventions in behavioral and neuropsychological disorders

related to DLB. Psychosocial factors, as well as brain organic and functional factors, have been reported to cause symptoms such as hallucinations in DLB [24]. Anxiety alleviation, accompanied by enhanced disease understanding, advancement in coping skills and promotion of empathic attitudes through disease education and instructions, may relieve symptoms (for example, frequency or severity of hallucinations) [24,25]. Most of the patients and their caregivers likely received disease education and/or caregiving instructions or acquired information on the disease and its care right before or during the study. The education of and information provided for caregivers may also have increased a positive bias, because NPI is an assessment scale implemented through interviews with caregivers. To lessen the placebo effect, a lead-in period when nonpharmacological treatment is administered has been suggested by a study in which investigators evaluated the efficacy of pimavanserin on psychosis in Parkinson's disease [26]. The results of our present study support our interpretation and the necessity of disease-specific brief psychosocial therapy in the lead-in period in future studies.

In the confirmatory phase, most of the AEs were mild or moderate in severity. The absence of substantial differences in the incidence of AEs or treatment-related AEs, and the existence of fewer reports on AEs that led to discontinuation in the 10 mg group than in the placebo group, suggest tolerability of donepezil in patients with DLB. The incidence of gastrointestinal symptoms, which are typically observed AEs with ChEI administration, did not tend to increase in the active groups. Another expected risk was parkinsonism. Donepezil may possibly induce or exacerbate extrapyramidal symptoms, which are threatening for patients with DLB. Although it is reported with a slightly higher incidence in the 10 mg group, none of these events were serious, and the UPDRS part III score did not represent significant deterioration in each of the active groups. We found no particular concerns about psychiatric symptoms or arrhythmia.

The interpretation of the present results requires taking some points into consideration. First, the number of patients enrolled by each center was generally small (that is, none by 14 of 72 centers and only 1 by 15 of the remaining 58), possibly due to DLB's characteristic features, including the faster progression, severe psychiatric symptoms and greater caregiver burden when compared to those with AD [4,27-30]. Similar recruitment difficulties impeded the previous phase II trial and a placebo-controlled study of rivastigmine in patients with DLB [31]. This may have caused a flaw in the interrater reliability of the clinical ratings. However, in this trial, a training and certification course was mandatory for the investigators. A second limitation is the short duration of the RCT phase. The period was set to 12 weeks, considering the above-noted disease-specific characteristics and the result of the previous phase II trial and its extension. The long-term efficacy of donepezil was evaluated in the open-label extension phase and is reported in another paper [13]. Third, because a global measure was not used, the influence of donepezil administration on the global clinical status cannot be inferred, despite its clinically important effect on improvement in cognitive function demonstrated through evaluation using the MMSE.

Conclusions

The predefined superiority of donepezil over the placebo in the co–primary endpoints was not confirmed. However, significant improvement in MMSE score was demonstrated with 10 mg but not 5 mg. Overall, donepezil was well tolerated in patients with DLB. While paying careful attention to gastrointestinal and parkinsonian symptoms, patients with DLB can safely benefit from treatment with donepezil.

Additional files

Additional file 1: Cognitive Fluctuation Inventory (CFI). This questionnaire was originally developed in Japanese. The English version is not yet validated.

Additional file 2: List of all institutional review boards.

Abbreviations

AD: Alzheimer's disease; AE: Adverse event; ANCOVA: Analysis of covariance; ChAT: Choline acetyltransferase; ChEI: Cholinesterase inhibitors; DLB: Dementia with Lewy bodies; FAS: Full analysis set; LOCF: Last observation carried forward; MMSE: Mini-Mental State Examination; NPI: Neuropsychiatric Inventory; PPS: Per-protocol set; RCT: Randomized placebo-controlled trial; SD: Standard deviation; SE: Standard error; UPDRS: Unified Parkinson's Disease Rating Scale; ZBI: Zarit Caregiver Burden Interview.

Competing interests

MI received personal fees from Eisai during the conduct of the study; grants and personal fees from Daiichi Sankyo, Eisai, FUJIFILM RI, Janssen, Nihon Medi-Physics, Novartis, Pfizer, Takeda and Tsumura; and personal fees from MSD and Ono Pharmaceutical outside the submitted manuscript. All grants were for his department, and he received them as the director of the department. EM received personal fees from Eisai during the conduct of the study; grants and personal fees from Eisai, Janssen, Daiichi Sankyo, Nihon Medi-Physics and FUJIFILM RI; and personal fees from Johnson & Johnson, Lundbeck, Novartis, Ono and Medtronic outside the submitted manuscript. All grants were for his department, and he received them as the director of the department. KM and MN are employees of Eisai. KK received personal fees from Eisai during the conduct of the study and personal fees from Tsumura, Eisai, Janssen, FUJIFILM RI, Novartis, Nihon Medi-Physics, Daiichi Sankyo, Ono, Otsuka and Dainippon Sumitomo outside the submitted manuscript.

Authors' contributions

MI and EM designed the study, analyzed the data and wrote the manuscript. KM designed the study and analyzed the data. MN designed and conducted the study. KK designed and supervised the study. All the authors read and approved the final manuscript.

Acknowledgements

We thank all patients and caregivers for their participation in the study; all investigators and their site staff for their contributions; and the Eisai study team (E Ebisawa, H Yamaguchi, H Yoshida, R Nagai, S Ishizaki and T Kobayashi) for their assistance. This study was sponsored by Eisai Co, Ltd (Tokyo, Japan). The sponsor was involved in the study design and the collection and analysis of

data. The Donepezil-DLB Study Investigators (by whom subjects were enrolled): Yasuto Higashi (Himeji Central Hospital), Naoki Fujii (Omuta Hospital), Yoshiaki Aihara (Shinozuka Hospital), Daisuke Uematsu (Uematsu Neurological Clinic), Yasuhiro Tsugu (Toyokawa City Hospital), Akira Terashima (Hyogo Brain and Heart Center), Kiyohiko Kondo (Yoka Hospital), Hijiri Ito (Miyoshi Neurology Clinic), Rokuro Matsubara (Matsubara Hospital), Eizo Iseki (Juntendo Tokyo Koto Geriatric Medical Center), Koichi Okamoto (Gunma University Hospital), Yuichi Maruki (Saitama Neuropsychiatric Institute), Tomoyuki Ono (Takesato Hospital), Haruo Hanyu (Tokyo Medical University Hospital), Tomonobu Kato (Osaka Red Cross Hospital), Chigusa Watanabe (Hiroshima-Nishi Medical Center), Shinji Ouma (Fukuoka University Hospital), Takemi Kimura (Kikuti National Hospital), Hiroaki Kazui (Osaka University Hospital), Kazuya Okumura (Shirai Hospital), Mitsuhiro Tsujihata (Nagasaki Kita Hospital), Yoko Nakano (Sukoyaka-silver Hospital), Satoshi Orimo (Kanto Central Hospital), Masutaro Kanda (Takeda General Hospital), Yuri Kitamura (Nanohana Clinic), Chika Nishimura (Kurumi Clinic), Tadanori Hamano (University of Fukui Hospital), Chiaki Kudoh (Kudoh Chiaki Hospital), Noriko Kawashima (Kawashima Neurology Clinic), Yusaku Shimizu (Ina Central Hospital), Kuniko Ishikawa (Tenryu Hospital), Yuji Abe (MEDOC Medical Dock & Clinic), Jun Ochiai (Nagoya Ekisaikai Hospital), Norio Taniguchi (Asakayama General Hospital), Yusaku Nakamura (Sakai Hospital Kinki University Faculty of Medicine), Yo Nishimura (Nishi-Kobe Medical Center), Koki Kikugawa (Tsubame Rosai Hospital), Kosuke Nishiyama (Yuge Hospital), Shin Tanaka (Mishima Hospital), Mikiko Kamijo (Chubu Rosai Hospital), Hideyuki Sawada (Utano Hospital), Kazunori Okahara (Keimei Memorial Hospital), Keiko Tokunaga (Ageo Central General Hospital), Masayuki Yokochi (Ebara Hospital), Yasuhiro Kawase (Kawase Neurology Clinic), Koichi Mizoguchi (Shizuoka Institute of Epilepsy and Neurological Disorders), Hiroki Kamada (Oe Hospital), Shogyoku Bun (Hospital Bando), Yasumasa Yoshiyama (Chiba-East Hospital), Tatsuru Kitamura (Takamatsu Hospital), Aki Nakanishi (Osaka City Kosaiin Hospital), Tsukasa Kusuki (Izumino Hospital), Hisashi Yonezawa (Iwate Medical University Hospital), Tsuyoshi Torii (Kure Medical Center), Koichi Mino (Kobe City Medical Center West Hospital), Mamoru Hashimoto (Kumamoto University Hospital), Aoi Yoshiiwa (Oita University Hospital) and Ayumi Okumura (Okumura Clinic).

Author details
[1]Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, 1-1-1 Honjo, Chuo-ku, Kumamoto 860-8556, Japan. [2]Department of Behavioral Neurology and Cognitive Neuroscience, Tohoku University Graduate School of Medicine, 2-1, Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8575, Japan. [3]Eisai Product Creation Systems, Eisai Co. Ltd, 4-6-10 Koishikawa, Bunkyo-ku, Tokyo 112-8088, Japan. [4]Department of Psychiatry, Yokohama City University School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama, Kanagawa 236-0004, Japan.

Received: 28 April 2014 Accepted: 12 November 2014
Published online: 03 February 2015

References

1. McKeith I, Mintzer J, Aarsland D, Burn D, Chiu H, Cohen-Mansfield J, Dickson D, Dubois B, Duda JE, Feldman H, Gauthier S, Halliday G, Lawlor B, Lippa C, Lopez OL, Carlos MJ, O'Brien J, Playfer J, Reid W, International Psychogeriatric Association Expert Meeting on DLB: **Dementia with Lewy bodies.** *Lancet Neurol* 2004, **3**:19–28.
2. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, Salmon DP, Lowe J, Mirra SS, Byrne EJ, Lennox G, Quinn NP, Edwardson JA, Ince PG, Bergeron C, Burns A, Miller BL, Lovestone S, Collerton D, Jansen EN, Ballard C, de Vos RA, Wilcock GK, Jellinger KA, Perry RH: **Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop.** *Neurology* 1996, **47**:1113–1124.
3. Allan L, McKeith I, Ballard C, Kenny RA: **The prevalence of autonomic symptoms in dementia and their association with physical activity, activities of daily living and quality of life.** *Dement Geriatr Cogn Disord* 2006, **22**:230–237.
4. McKeith IG, Rowan E, Askew K, Naidu A, Allan L, Barnett N, Lett D, Mosimann UP, Burn D, O'Brien JT: **More severe functional impairment in dementia with lewy bodies than Alzheimer disease is related to extrapyramidal motor dysfunction.** *Am J Geriatr Psychiatry* 2006, **14**:582–588.
5. Lippa CF, Smith TW, Perry E: **Dementia with Lewy bodies: choline acetyltransferase parallels nucleus basalis pathology.** *J Neural Transm* 1999, **106**:525–535.
6. Perry EK, Haroutunian V, Davis KL, Levy R, Lantos P, Eagger S, Honavar M, Dean A, Griffiths M, McKeith IG, Perry RH: **Neocortical cholinergic activities differentiate Lewy body dementia from classical Alzheimer's disease.** *Neuroreport* 1994, **5**:747–749.
7. Perry EK, Irving D, Kerwin JM, McKeith IG, Thompson P, Collerton D, Fairbairn AF, Ince PG, Morris CM, Cheng AV, Perry RH: **Cholinergic transmitter and neurotrophic activities in Lewy body dementia: similarity to Parkinson's and distinction from Alzheimer disease.** *Alzheimer Dis Assoc Disord* 1993, **7**:69–79.
8. Ballard C, Piggott M, Johnson M, Cairns N, Perry R, McKeith I, Jaros E, O'Brien J, Holmes C, Perry E: **Delusions associated with elevated muscarinic binding in dementia with Lewy bodies.** *Ann Neurol* 2000, **48**:868–876.
9. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, *et al*: **Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium.** *Neurology* 2005, **65**:1863–1872.
10. O'Brien JT, Burns A, BAP Dementia Consensus Group: **Clinical practice with anti-dementia drugs: a revised (second) consensus statement from the British Association for Psychopharmacology.** *J Psychopharmacol* 2011, **25**:997–1019.
11. Mori E, Ikeda M, Kosaka K, Donepezil-DLB Study Investigators: **Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial.** *Ann Neurol* 2012, **72**:41–52.
12. Ikeda M, Mori E, Kosaka K, Iseki E, Hashimoto M, Matsukawa N, Matsuo K, Nakagawa M, Donepezil-DLB Study Investigators: **Long-term safety and efficacy of donepezil in patients with dementia with Lewy bodies: results from a 52-week, open-label, multicenter extension study.** *Dement Geriatr Cogn Disord* 2013, **36**:229–241.
13. Mori E, Ikeda M, Nagai R, Matsuo K, Nakagawa M, Kosaka K: Long-term donepezil use for dementia with Lewy bodies: results from an open-label extension of phase III trial. Alzheimers Res Ther, DOI 10.1186/s13195-014-0081-2.
14. Cummings JL: **The Neuropsychiatric Inventory: assessing psychopathology in dementia patients.** *Neurology* 1997, **48**:S10–S16.
15. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J: **The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia.** *Neurology* 1994, **44**:2308–2314.
16. Hashimoto M, Manabe Y, Mori E, Hirono N, Kosaka K, Ikeda M: **Content validity and inter-rater reliability of the Cognitive Fluctuation Inventory [Article in Japanese].** *Brain Nerve* 2014, **66**:175–183.
17. Mori S, Mori E, Iseki E, Kosaka K: **Efficacy and safety of donepezil in patients with dementia with Lewy bodies: preliminary findings from an open-label study.** *Psychiatry Clin Neurosci* 2006, **60**:190–195.
18. Hoehn MM, Yahr MD: **Parkinsonism: onset, progression and mortality.** *Neurology* 1967, **17**:427–442.
19. Folstein MF, Folstein SE, McHugh PR: **"Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician.** *J Psychiatr Res* 1975, **12**:189–198.
20. Zarit SH, Reever KE, Bach-Peterson J: **Relatives of the impaired elderly: correlates of feelings of burden.** *Gerontologist* 1980, **20**:649–655.
21. Fahn S, Elton R, UPDRS Development Committee: **Unified Parkinson's Disease Rating Scale.** In *Recent Developments in Parkinson's Disease. Volume 2.* Edited by Fahn S, Marsden CD, Calne DB, Goldstein M. New York: Macmillan Healthcare Information; 1987:153–163. 293–304.
22. Rogers SL, Doody RS, Mohs RC, Friedhoff LT: **Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study.** *Donepezil Study Group Arch Intern Med* 1998, **158**:1021–1031.
23. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT, the Donepezil Study Group: **A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease.** *Neurology* 1998, **50**:136–145.
24. Ota K, Iseki E, Murayama N, Fujishiro H, Kasanuki K, Chiba Y, Sato K, Arai H: **Psychosocial risk factors for clinical symptoms in patients with dementia with Lewy bodies compared with Alzheimer's disease [Article in Japanese].** *Jpn J Geriatr Psychiatry* 2012, **23**:457–465.
25. Ota K, Iseki E, Murayama N, Fujishiro H, Arai H, Sato K: **Effect of psychological intervention for visual hallucinations in patients with dementia with Lewy bodies.** *Clin Psychiatry* 2011, **53**:845–853.
26. Cummings J, Isaacson S, Mills R, Williams H, Chi-Burris K, Corbett A, Dhall R, Ballard C: **Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial.** *Lancet* 2013, **383**:533–540.