Original Research Article

Pretreatment Cognitive Profile Likely to Benefit from Donepezil Treatment in Dementia with Lewy Bodies: Pooled Analyses of Two Randomized Controlled Trials

Etsuro Mori^a Manabu Ikeda^{b, c} Masaki Nakagawa^d Hideaki Miyagishi^d
Kenji Kosaka^e

^aDepartment of Behavioral Neurology and Cognitive Neuroscience, Tohoku University Graduate School of Medicine, Sendai, ^bDepartment of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, Kumamoto, ^cDepartment of Psychiatry, Osaka University School of Medicine, Osaka, ^dEisai Co., Ltd., Tokyo, and ^eDepartment of Psychiatry, Yokohama City University School of Medicine, Yokohama, Japan

Key Words

Dementia · Lewy bodies · Cholinesterase inhibitors · Cognitive function · Mini-Mental State Examination

Abstract

Background/Aims: Based on Mini-Mental State Examination (MMSE) subitem scores, in dementia with Lewy bodies (DLB), we aimed to delineate features of cognitive impairment, identify cognitive domains improved by donepezil, and define a pretreatment cognitive profile likely to benefit from donepezil. **Methods:** Pooled data were used from two randomized controlled trials of donepezil in DLB (n = 235). Baseline MMSE subitem scores were calculated for all patients. Mean changes in subitem scores at week 12 were compared between the placebo and the active group. Finally, the subgroup identification based on differential effect search (SIDES) method was applied. **Results:** Baseline subitem scores were relatively low for serial 7's, delayed recall, and copying. Significant improvement by donepezil was found for orientation, serial 7's, repetition, 3-step command, and copying. The subgroup with pretreatment scores of serial 7's = 1, 2, or 3, delayed recall ≥1, and copying = 0 were the best responders. MMSE change in subgroups increased as more of these three conditions were fulfilled. **Conclusion:** Cognitive domains characteristically impaired in DLB are particularly improved by donepezil. The number of fulfilled conditions for serial 7's = 1, 2, or 3, delayed recall ≥1, and copying = 0 (likely to benefit score) may predict the response to donepezil in DLB patients.

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Etsuro Mori
Department of Behavioral Neurology and Cognitive Neuroscience
Tohoku University Graduate School of Medicine
2-1, Seiryō-machi, Aoba-ku, Sendai, Miyagi 980-8575 (Japan)
E-Mail morie@med.tohoku.ac.jp

Introduction

Dementia with Lewy bodies (DLB) is the second most common type of degenerative dementia in the elderly after Alzheimer's disease (AD) [1]. The clinical features of DLB include neuropsychiatric symptoms, parkinsonism, and cognitive impairment [2]. Cholinergic neurotransmission is more defective in patients with DLB than in those with AD [3]. Moreover, cholinergic loss in DLB affects both brainstem and basal forebrain presynaptic nuclei while preserving postsynaptic cortical muscarinic receptors [4]. Thus, cholinesterase inhibitors (ChEIs) have been considered to be more effective for DLB, with galantamine, rivastigmine, and donepezil shown to exert favorable effects in clinical studies [5–10].

In clinical trials as well as clinical practice, cognitive function in DLB patients is often assessed using the Mini-Mental State Examination (MMSE) [5–10]. The MMSE was originally developed as a screening test for cognitive impairment [11]. It readily evaluates overall cognitive function in only about 10 min [11], and is therefore widely used for assessment of cognitive impairment in dementia patients in clinical practice and studies worldwide. The test consists of 11 subitems, with each subitem evaluating different cognitive domains including orientation, memory, attention, and construction. Cognitive impairment in DLB is characterized by deficits in attention, executive function, and visual perception [1], which may be reflected in each MMSE subitem score. Examining treatment changes in subitem scores may identify cognitive domains that are particularly improved by the treatment.

In our previous phase 2 and 3 donepezil trials for DLB, we used the MMSE to assess cognitive function. We found significantly improved cognitive function in patients administered donepezil compared with those given a placebo, with the improvement lasting for at least 1 year [12–15]. Here, based on MMSE scores, we further delineated features of cognitive impairment and identified cognitive domains that are likely improved by donepezil in DLB patients. Furthermore, we identified a pretreatment cognitive profile in individuals who would likely benefit from donepezil treatment. As the MMSE is widely used in clinical practice, such factors, if any, would be useful to predict the response to donepezil and the prognosis of individual patients.

Materials and Methods

Data Analyzed

This analysis used pooled data obtained from two randomized, double-blind, placebo-controlled trials (RCTs) of donepezil treatment for DLB which had been conducted in Japan. A 12-week phase 2 exploratory RCT was conducted from 2007 to investigate the efficacy and safety of donepezil at 3, 5, and 10 mg/day (ClinicalTrials.gov reference: NCT00543855). Subsequently, a confirmatory phase 3 trial, including a 16-week RCT phase, was conducted from 2011 to confirm the superiority of donepezil at 5 and 10 mg/day for 12 weeks over placebo (ClinicalTrials.gov reference: NCT01278407). In both studies, the 5- and 10-mg groups began treatment at 3 mg/day, with the dose increased to 5 mg at week 2 and then to 10 mg at week 6 (in only the 10-mg group). The results of these RCTs have been published previously [12, 14]. Each study was performed in accordance with the principles of the Declaration of Helsinki. Before initiating the study procedures, written informed consent was obtained from the patient (if at all possible) and his/her primary family member.

The inclusion and exclusion criteria were almost identical for both RCTs. The inclusion criteria were: patients aged ≥ 50 years with probable DLB that fulfilled the consensus diagnostic criteria [2], having mild to severe dementia (10–26 points on MMSE and Clinical Dementia Rating score ≥ 0.5) and having behavioral and psychiatric symptoms [Neuropsychiatric Inventory Plus (NPI-plus) (12 items: original 10 NPI items with sleep [16, 17] and cognitive fluctuation reported as Cognitive Fluctuation Inventory [8, 18]) ≥ 8 and NPI-2 (hallucinations and cognitive fluctuation [12], only at phase 3) ≥ 1]. Outpatients were recruited from psychiatric or neurological specialty centers throughout Japan [19]. The diagnosis of each patient was made by investigators from each center and validated after discussion by the central committee.

Fig. 1. Patient disposition in two RCTs. Bold indicates the total number of subjects in two trials. Left/right indicates the number of subjects in phase 2/phase 3 trials. * Patients without MMSE data were excluded.

The exclusion criteria included Parkinson's disease diagnosed at least 1 year prior to dementia onset, focal vascular lesions or multiple infarctions on MRI or CT that might cause cognitive impairment, other neurological or psychiatric diseases, complications or a history of severe gastrointestinal ulcers, severe asthma or obstructive pulmonary disease, systolic hypotension (<90 mm Hg), bradycardia (<50 bpm), sick sinus syndrome, atrial or atrioventricular conduction block, QT interval prolongation (≥ 450 ms), severe parkinsonism (Hoehn and Yahr stage ≥ 4) [20], and treatment with ChEIs or any investigational drug within 3 months prior to screening. Furthermore, except for stable doses of levodopa and dopamine agonists, ChEIs, antipsychotics, and anti-Parkinson drugs were not allowed during the trials.

From the full analysis set of these two RCTs ($n = 273$), the data of patients with MMSE scores at baseline and at least one post-baseline visit in the placebo, 5-mg, and 10-mg groups were incorporated into this analysis (fig. 1). The data of the 3-mg arm ($n = 35$) of the phase 2 trial was not used as there was no significant difference from the placebo arm after adjusting for multiple comparisons; furthermore, 3 mg was not tested in the phase 3 trial. As a clear dose-response relationship between the 5- and 10-mg groups was not noted in the two trials, both dose groups were combined into a single group in the present analysis ($n = 235$; incorporating 99 from phase 2 and 136 from phase 3).

MMSE Assessment

In both RCTs, the MMSE was used to assess cognitive function. MMSE scores ranging from 0 to 30 encompassed the following 11 subitems: orientation for time (5 points), orientation for place (5 points), immediate recall (3 points), attention/calculation (5 points), delayed recall (3 points), naming (2 points), repetition (1 point), 3-step command (3 points), reading (1 point), writing (1 point), and copying (1 point) [11]. In both trials, only the serial 7's test was applied and the spelling backwards substitution not allowed, as the two tests are not equivalent: the former produces lower scores than the latter [21], has merit in terms of variability, internal consistency, and measurement error [22], and is not affected by the orthographic systems of different languages. Above all, to detect serial changes in longitudinal studies, consistent use of the test is desirable.

Statistical Analysis

The patients were divided into two groups: the placebo group and the active drug group (which was administered 5 or 10 mg donepezil). For all patients, the mean score of each MMSE subitem at baseline was

Table 1. Patient demographics and clinical characteristics at baseline

	All (n = 235)	Placebo group (n = 75)	Active group (n = 160)
Sex			
Male	86 (36.6%)	26 (34.7%)	60 (37.5%)
Female	149 (63.4%)	49 (65.3%)	100 (62.5%)
Age, years	78.1 ± 6.0	77.7 ± 5.5	78.2 ± 6.2
Weight, kg	49.5 ± 9.8	49.3 ± 10.0	49.6 ± 9.8
Disease duration, years	2.2 ± 1.9	2.4 ± 2.3	2.2 ± 1.8
Core features			
Cognitive fluctuation	220 (93.6%)	70 (93.3%)	150 (93.8%)
Visual hallucination	201 (85.5%)	69 (92.0%)	132 (82.5%)
Parkinsonism	203 (86.4%)	65 (86.7%)	138 (86.3%)
MMSE	20.0 ± 4.5	19.5 ± 4.5	20.2 ± 4.4
NPI-10	18.0 ± 12.7	19.5 ± 12.8	17.3 ± 12.7
NPI-2	7.0 ± 4.6	6.8 ± 4.2	7.2 ± 4.8
UPDRS part III	20.2 ± 11.6	21.2 ± 11.4	19.7 ± 11.7

Values are expressed as mean ± SD or n (%).

UPDRS = Unified Parkinson's disease rating scale.

calculated. As the full score of each MMSE subitem varies, a proportional score was obtained by dividing the obtained score by the highest possible score, thereby allowing direct comparison of performance between subitems. Mean MMSE change in total score and individual item scores from baseline to week 12 were calculated in each treatment group. If the MMSE score at week 12 was unavailable, a value from the final evaluation point was imputed using a last observation carried forward method. Intergroup comparisons of mean change were performed by analysis of covariance, with baseline values as the covariate. These statistical analyses were performed with a two-tailed 0.05 significance level using SAS for Windows, version 9.3 (SAS Institute Inc., Cary, N.C., USA).

Subsequently, the subgroup identification based on differential effect search (SIDES) method [23] was applied to identify subgroups defined by baseline MMSE subitem score profile, which in terms of total MMSE score likely improved at week 12 with donepezil treatment. A common approach to identify subgroups is regression-based analysis of subsets (via models with main effects and interactions), in which subgroups are identified based on significant interaction terms. However, this approach usually lacks statistical power and has difficulties in specifying interaction terms and covariate cutoffs. The SIDES method, which is flexible in terms of search criterion, can focus on the treatment effect and therefore directly search for predictive covariates. Furthermore, this method can search for subgroups with a large differential effect relative to the overall population. There are three steps in the SIDES method. In the first step, subgroups with an enhanced treatment effect are identified recursively under the constraints of a maximum number of covariates defining subgroups and a minimal sample size. In the second step, only subgroups in which the treatment effect is below a prespecified threshold value are retained. In the third step, a multiplicity adjustment is applied to correct p values for the treatment effect within the identified subgroups. In the present analysis, the splitting criterion was set as the differential, and the minimal sample size per treatment arm in a subgroup as 20. The default settings in the SIDEScreen Excel Macro provided by Lipkovich and Dmitrienko [24] were used for the other criteria.

Results

Baseline Patient Characteristics

The demographics and clinical characteristics of all 235 patients at baseline are summarized in table 1. There were no notable differences between the placebo and the active drug

Fig. 2. Mean proportional MMSE subitem scores at baseline in overall patients. Proportional scores ranging from 0 to 1 were calculated by dividing each MMSE item score by the full item score. Error bars indicate SD.

group. Overall, females accounted for 63.4%. Mean age ($\pm$ standard deviation, SD) was 78.1 ± 6.0 , and all but 2 patients were 65 years or older. The mean MMSE score ($\pm$ SD) was 20.0 ± 4.5 .

Baseline MMSE Subitem Score Profiles

The mean proportional scores for MMSE subitems at baseline in the overall patient group are shown in figure 2. The proportional scores for the following items were relatively low: serial 7's (0.31 ± 0.28), delayed recall (0.47 ± 0.35), and copying (0.54 ± 0.50). In contrast, the scores for immediate recall (0.93 ± 0.17), naming (1.00 ± 0.05), and reading (0.95 ± 0.21) were high.

Changes in MMSE Subitem Scores from Baseline to Week 12

The mean changes in total MMSE score and in each subitem score from baseline to week 12 are shown in table 2. The mean change ($\pm$ SD) in total MMSE score was 0.20 ± 2.93 in the placebo group and 2.19 ± 3.25 in the active drug group, with a significant difference between groups ($p < 0.001$). The mean change in the 5- and 10-mg groups was comparable (2.27 ± 3.46 and 2.12 ± 3.06 , respectively). There were also significant intergroup (placebo versus active) differences in mean change of orientation for time ($p < 0.001$), orientation for place ($p = 0.026$), serial 7's ($p = 0.022$), repetition ($p = 0.045$), 3-step command ($p = 0.018$), and copying ($p = 0.030$).

Subgroups Likely to Benefit from Donepezil Treatment in Terms of MMSE Score

The SIDES method selected the following three covariates: delayed recall, serial 7's, and copying. Four subgroups, namely (1) serial 7's ≥ 1 and delayed recall ≥ 1 , (2) serial 7's ≥ 1 and copying = 0, (3) delayed recall ≥ 1 and copying = 0, and (4) serial 7's ≤ 3 , delayed recall ≥ 1 , and copying = 0, were identified as the best responders, in which large changes in total MMSE

Table 2. Mean changes in total MMSE score and in each subitem score from baseline to week 12 (last observation carried forward method)

MMSE item	Placebo group (n = 75)	Active group (n = 160)	p value ^a
Total score	0.20 ± 2.93	2.19 ± 3.25	<0.001
Orientation for time	−0.21 ± 1.30	0.41 ± 1.42	<0.001
Orientation for place	0.04 ± 0.91	0.28 ± 1.02	0.026
Immediate recall	−0.01 ± 0.45	0.06 ± 0.47	0.277
Serial 7's	0.23 ± 1.37	0.72 ± 1.68	0.022
Delayed recall	0.16 ± 1.03	0.32 ± 1.04	0.152
Naming	0.00 ± 0.16	0.00 ± 0.11	0.581
Repetition	−0.07 ± 0.53	0.03 ± 0.47	0.045
3-step command	0.13 ± 0.93	0.26 ± 0.80	0.018
Reading	0.01 ± 0.26	−0.03 ± 0.22	0.625
Writing	−0.08 ± 0.36	0.02 ± 0.40	0.097
Copying	0.00 ± 0.37	0.11 ± 0.50	0.030

Values are expressed as mean ± SD.

^a Analysis of covariance, with the treatment group as the factor and baseline values as the covariate.

Table 3. SIDES results

Selected subgroup	Group	n	Mean change in total MMSE	Effect size	p value ^a
All subjects	A	160	2.2	0.631	<0.001
	P	75	0.2		
Serial 7's ≥ 1 and delayed recall ≥ 1	A	103	2.4	1.030	<0.001
	P	38	−0.7		
Serial 7's ≥ 1 and copying = 0	A	45	3.6	1.197	<0.001
	P	25	0.0		
Delayed recall ≥ 1 and copying = 0	A	58	3.1	1.164	<0.001
	P	24	−0.4		
Serial 7's ≤ 3 and delayed recall ≥ 1 and copying = 0	A	57	3.1	1.114	<0.001
	P	20	−0.2		

A = Active group; P = placebo group.

^a One-tailed p value using Student's t test.

score from baseline to on-treatment were detected in the active drug group compared with the placebo group (table 3). In the population included within all four subgroups (i.e., serial 7's = 1, 2, or 3, delayed recall ≥ 1, and copying = 0), the mean total MMSE score improved from 19.6 to 23.1, with a mean change of 3.5 ± 3.1 in the active drug group (n = 36) (fig. 3), while the mean change for the overall population was 2.19 ± 3.25 . According to the definition of the number of conditions fulfilled among the following: serial 7's = 1, 2 or 3, delayed recall ≥ 1, and copying = 0 as the likely to benefit (LTB) score, the mean change of total MMSE score in the active group was 3.5 ± 3.1 for LTB score = 3, 2.2 ± 3.2 for LTB score = 2, 1.8 ± 2.4 for LTB score = 1, and -2.1 ± 3.7 for LTB score = 0 (fig. 4). The Jonckheere-Terpstra trend test showed

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Fig. 3. Mean change in total MMSE score in the population included within all the four subgroups identified by the SIDES method. LOCF = Last observation carried forward method. Error bars indicate SD. The population included in all the four subgroups: patients with serial 7's scores of 1–3, delayed recall scores of ≥ 1 , and copying scores of 0.

Fig. 4. Mean change in total MMSE score by LTB score. Error bars indicate SD. LTB score (0–3) represents the number of fulfilled conditions among the following conditions: (1) serial 7's = 1, 2, or 3, (2) delayed recall ≥ 1 , and (3) copying = 0.

a statistically significant trend ($p = 0.001$) of higher LTB scores with greater total MMSE score change. Furthermore, the Cochran-Armitage trend test showed a statistically significant trend ($p = 0.001$) between LTB score and a proportion of individuals whose MMSE improved by 3 points or more (58% for LTB score = 3, 49% for LTB score = 2, 42% for LTB score = 1, and 0% for LTB score = 0).

Discussion

Using pooled data from two donepezil RCTs, we analyzed the pattern of MMSE subitem scores in DLB patients likely to respond to donepezil in terms of cognitive impairment. We found evidence for a specific MMSE profile that may indicate a favorable cognitive response to donepezil treatment in DLB patients.

First of all, the subitem scores of serial 7's, delayed recall, and copying were found to be disproportionately reduced compared with other domains. This is similar to a previous study

[25], which suggests that in terms of cognitive impairment, the present study population is likely to be representative of DLB patients. Relatively low MMSE subitem scores for serial 7's and copying may reflect cognitive impairment characteristics of DLB, with greater deficits in attention and visual perception/construction [2]. Additionally, the delayed recall score was disproportionately low among the subitems. However, compared with AD patients, the performance of DLB patients appears relatively good, as the subitem score (1.41 ± 1.04) indicates that patients successfully recalled approximately half of the three words.

Using the SIDES approach, we found that patients with serial 7's scores of 1–3, delayed recall scores of ≥ 1 , and copying scores of 0 particularly showed cognitive improvement by donepezil treatment. Considering the findings discussed above, donepezil is likely to be more effective in the subgroup with a typical DLB cognitive impairment pattern. This is consistent with the finding that DLB patients who do not show imaging features of a coexistent AD-related pathology are more likely to cognitively improve with ChEI treatment [26]. In the group of patients who met more of the conditions for serial 7's = 1, 2, or 3, delayed recall ≥ 1 , and copying = 0, the mean change in total MMSE score was larger (fig. 4). The LTB score may predict the response to donepezil and the prognosis of the individual patient. Conversely, the subgroup of patients with serial 7's or delayed recall scores of 0 is unlikely to benefit from donepezil. This subgroup includes those with an advanced stage of DLB or with concomitant AD pathology. Therefore, in any case, early initiation of donepezil treatment is recommended.

With regard to the effect of donepezil on different cognitive domains, significant improvements were shown for the following items: orientation for time and place, serial 7's, repetition, 3-step command, and copying. These items supposedly relate to measurements of attention, working memory, and visual perception, which are characteristically defective in DLB patients [2, 27]. The effect of donepezil on these cognitive domains has also been demonstrated by other specific neuropsychological tests in our phase 2 trial, including the Wechsler Memory Scale-Revised (WMS-R) attention/concentration subscale and the Wechsler Adult Intelligence Scale (WAIS) symbol digit modality subscale [12]. These findings indicate that donepezil particularly works on cognitive impairments that are characteristic of DLB. However, it should be noted that our findings do not necessarily mean that donepezil has no positive effect on other cognitive functions (e.g., memory). Indeed, due to the smallest range of subitem MMSE scores, the change might not be detected by a floor or ceiling effect. Rather, our analysis shows that donepezil has more favorable effects on cognitive impairment as a whole, as total MMSE score and most of the subitem scores show significant improvements. Moreover, donepezil was found to be associated with improved cognitive fluctuation [12]. Thus, in addition to improved basic cognitive function, reduction of depth and frequency of cognitive dips may lower the probability that a patient is in the cognitive dip phase when the MMSE is administered, thereby resulting in an increased mean score.

We cannot conclude that our findings are specific for DLB, as similar analyses have not been performed in AD populations. In previous AD trials, a considerable number of subjects meeting the criteria for DLB were reportedly included [28, 29]. Although a similar trend as in our present DLB study might be shown in such populations, this would not necessarily mean that it is the case in AD patients.

There are some limitations to our analysis. First, the present study is exploratory in nature, therefore the sample size was not predefined and no adjustment for multiplicity was applied. Thus, our statistical test results should be interpreted with caution, and further confirmatory studies are needed to reinforce our findings. Furthermore, it should be noted that our study is based on data from 12-week RCT phases. Considering our findings as well as the aforementioned characteristics of DLB, longer-term studies are indicated to further

delineate the long-term efficacy of donepezil in relation to changes in individual MMSE item scores along with disease progression. There are also limitations inherent in the cognitive measurements: only the MMSE was considered as predictive and outcome measures, which is neuropsychologically insufficient but practically relevant, and changes in MMSE scores may include a practice effect, although differences between the donepezil and placebo groups suggest that a substantial part of the changes is likely attributable to the effect of donepezil. Additionally, since serial 7's alone was used as the test for attention in our trials, the findings cannot be applied to the spelling backwards score. There are also methodological limitations inherent in our selection of subjects: incorporation of behavioral and psychiatric symptoms with a cutoff of NPI-plus ≥ 8 and NPI-2 ≥ 1 in the inclusion criteria will exclude DLB patients without neuropsychiatric issues. Furthermore, the original consensus diagnostic criteria rather than the revised criteria [30] were used because of the unavailability of dopamine transporter imaging in Japan when the studies were conducted, as well as unfeasibility of polysomnographic confirmation of REM sleep behavior disorder. These may somewhat limit the generalizability of our findings, in return raising diagnostic specificity. Finally, the dose of donepezil was not considered here, although plasma donepezil concentration was shown to correlate positively with change in MMSE score [31].

In conclusion, donepezil treatment in DLB patients positively affects performance on the following MMSE items: orientation for time and place, serial 7's, repetition, 3-step command, and copying, which are supposedly related to attention, working memory, and visual perception. In terms of cognition defined as total MMSE score, DLB patients that fulfill the following three conditions of baseline MMSE subitem scores are likely to benefit from donepezil: serial 7's = 1, 2, or 3, delayed recall ≥ 1 , and copying = 0. Response to donepezil increases as the number of fulfilled conditions (LTB score) increases.

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