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ORIGINAL RESEARCH

A Multicentre, Randomised, Open-Label, Prospective Study to Estimate the Add-On Effects Of Memantine as Ebixa® Oral Pump (Solution) on Language in Patients with Moderate to Severe Alzheimer's Disease Already Receiving Donepezil (ROMEO-AD)

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ABSTRACT

Introduction: This multicentre, randomised, open-label, and prospective study aimed to evaluate the effectiveness of memantine (memantine solution) on speech function in patients with moderate to severe Alzheimer's disease (AD) who were already on donepezil therapy.

Methods: Participants were divided into two groups: the drug trial group was administered donepezil + memantine (memantine solution), while the control group was administered only donepezil. Patients in the test group were required to increase the dose of memantine by 5 mg/day per week for the first 4 weeks and were maintained at 20 mg/day until the end of the

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trial.
Results: Of the 188 participants, 24 dropped out, and 164 completed the final research process. As the primary outcome, K-WAB showed an increase in scores in both groups compared to baseline scores; however, the difference was not statistically significant ($P = 0.678$). After 12 weeks, the donepezil treatment group had higher K-MMSE and lower CDR-SB scores than the donepezil and memantine combination group, indicating better cognitive and functional status. However, this effect was not sustained for 24 weeks. Patients who were assigned to receive only donepezil had Relevant Outcome Scale for AD (ROSA) scores that were higher by an average of 4.6 points compared to the donepezil and memantine combination group. The NPI-Q index improved compared to baseline values in both groups.
Conclusions: Although several clinical studies have reported significant improvements in speech function after the administration of memantine, clinical studies on speech function improvement in patients with Alzheimer's disease are still insignificant. There are no studies on the effect of donepezil and memantine in combination treatment on language function in the moderate and severe stages of AD. Therefore, we investigated the effect of memantine (memantine solution) on speech function in patients with moderate to severe AD who were administered donepezil at a stable dose. Although the efficacy of the combination therapy was not superior to that of donepezil monotherapy alone, memantine was effective in improving behavioural symptoms in patients with moderate or severe AD.

Keywords: Alzheimer's disease; Donepezil; Language; Memantine

Key Summary Points

Why carry out this study?

Although several clinical studies have reported significant improvement in speech function after administration of memantine, clinical studies on speech function improvement in Alzheimer's disease (AD) patients are still insignificant.

There are no studies worldwide on the effect of donepezil and memantine on language function in combination treatment in moderate and severe stages of AD.

What was learned from this study?

The addition of memantine to donepezil therapy did not provide benefits in terms of cognition and behavioural symptoms of dementia in patients with moderate to severe Alzheimer's disease in this study. Although there were some improvements in these outcomes in both the groups, the benefits were not sustained for 24 weeks, and the progression of the disease continued.

The change in K-WAB was not significant in the addition of memantine to donepezil therapy. ROSA shows the result of improvement in donepezil only group. In addition, NPI also shows improved symptoms in combination group.

The study's findings indicate that the combination of donepezil and memantine may not be more effective than donepezil alone in treating AD. The results challenge the initial hypothesis that adding memantine to donepezil therapy would provide significant benefits in patients with AD.

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The short duration of the study and the dose adjustment limitation of memantine may have affected the assessment of the response to memantine. A longer duration of the study could have provided more insight into the long-term effects of combination therapy with donepezil and memantine in patients with moderate to severe AD. In the future, it is considered necessary to study detailed results on the drug concentration according to the method of taking memantine solutions and tablets based on real-world data.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterised by cognitive impairment, gradual decline in daily functioning, and neuropsychiatric symptoms that ultimately result in complete dependence on caregiver support [1]. AD dementia affects 3–4% of adults in their late working or retirement years, and meta-analysis found AD affected 3.31% of men and 7.13% of women [2]. Memantine is a moderate-affinity, uncompetitive, voltage-dependent N-methyl-D-aspartate (NMDA) receptor antagonist with rapid blocking/unblocking properties [3, 4]. Clinical studies in patients with AD have demonstrated that memantine can produce significant benefits compared with placebo in clinical global measures, as well as in cognition, function, and behaviour with a favourable safety profile [4–10]. However, the clinical benefits of memantine in patients with AD remain inconclusive, especially when compared to donepezil. Some studies have reported that patients with moderate or severe AD who continued treatment with donepezil had cognitive benefits that exceeded the minimum clinically important difference and had significant functional benefits over the course of 12 months compared to those who received memantine [11]. In 2017, meta-analyses suggested credible efficacy and safety of memantine in treating AD when used alone or in combination with cholinesterase inhibitors [12]. Among cognitive functions, language impairment is one of the most striking and distressing manifestations of AD [13–15]. Difficulties in communication can be an obstacle to activities of daily living in patients with AD. Therefore, we evaluated the effectiveness of cognition and behavioural symptoms, including speech function, in the additional treatment with memantine (memantine solution) in patients with moderate to severe AD who were receiving donepezil in comparison to those who received donepezil-monotherapy.

METHODS

Study Population and Data Collection

A multicentre, randomised, open-label, prospective study to estimate the add-on effects of memantine as a memantine oral pump on language in moderate to severe AD patients already receiving donepezil (ROMEO-AD) study was a randomised, open-label, and prospective study. Outcomes were assessed for 24 weeks. We recruited patients with moderate-to-severe AD who were stably being administered donepezil at 13 university hospitals. Patients with dementia who satisfied the criteria for probable AD issued by the National Institute of Neurologic and Communicative Disorders and Stroke and the AD and Related Disorders Association were considered to have AD [16]. Eligible participants, who met the standardised clinical criteria [16] for probable or possible moderate or severe AD, had been prescribed donepezil continuously for at least 3 months and had received a dose of 10 mg for at least the previous 6 weeks. They also had a score below 20 on the Korean Mini–Mental State Examination (K-MMSE; scores range from 0 to 30, with higher scores indicating better cognitive function) [17]. Written consent to participate in the study was obtained from the participants if they were considered to have the capacity to give informed consent. The main caregivers also provided written informed consent for their own involvement and assent for patients' involvement. Patients were excluded if they had

one of the following indications: severe or unstable medical conditions, received memantine, or were considered unlikely to

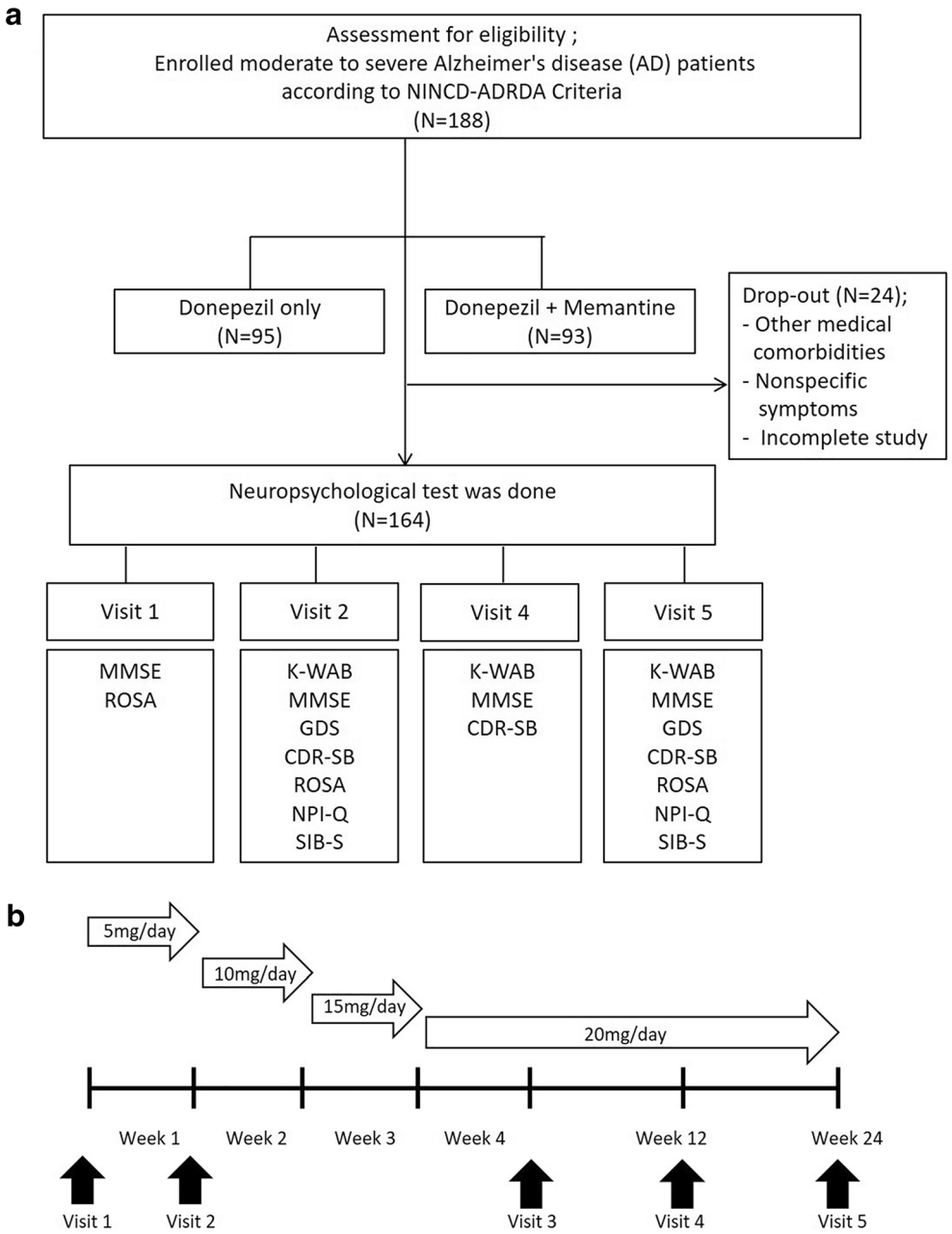

Fig. 1 **a** Participant selection. A total of 188 clinical probable patients with AD were enrolled. A neuropsychological test was performed on 163 patients. **b** *Visit 1* screening; *Visit 2* baseline and randomisation; *Visit 4* week 12; and *Visit 5* week 24. *K-MMSE* the Korean version of the Mini-Mental Status Examination, *CDR-SB* Clinical Dementia Rating Scale sum of Boxes, *GDS* Global Deterioration Scale, *K-WAB* the Korean version of the Western Aphasia Battery, *ROSA* Relevant Outcome Scale for Alzheimer's Disease, NPI-Q Korean Version of the Brief Clinical Form of the Neuropsychiatric Inventory, *SIB-S* Severe Impairment Battery Language scale

adhere to the study regimens. Details of the design are shown in Fig. 1A.

A total of 188 patients with AD were enrolled in this study. Twenty-four participants dropped out, and 164 participants completed the final research process. The reasons for dropping out were: 1 patient was lost to follow-up, 2 patients had other medical disorders, 3 patients withdrew their consent due to side effects related to the trial drug but were not judged to have severe adverse events, and 18 patients withdrew their consent. Side effects included dizziness, faecal incontinence, vertigo, and headache; all side effects were mild. The exclusion criteria included the following: (1) patients who had participated in other clinical trials within 4 weeks prior to screening; (2) evidence of severe or unstable physical illness: acute and severe asthma, acute or unstable cardiovascular disease, active peptic ulcer, severe liver disease, renal failure with dialysis, or any medical condition that may interfere with completion of clinical trials; (3) patients with bradycardia (pulse rate of less than 50 bpm), synchronous dysfunction syndrome, or conduction disorder (e.g., 2–3° room block); (4) patients with laboratory abnormalities (hypothyroidism, vitamin B12 or folic acid deficiency, syphilis, etc.) that could cause cognitive impairment; (5) patients with degenerative brain disease or mental illness other than AD; (6) patients with a history of drugs or alcohol (more than 3 glasses a day) abuse within the last 10 years; (7) patients with severe hearing or vision impairment who cannot evaluate their efficacy; (8) patients living alone without a guardian to provide sufficient information about the patient's condition; (9) patients with a history of hypersensitivity including severe drug allergies or allergies to clinical drugs; (10) patients taking other drugs to treat AD or other cognitive impairment; and (11) patients with primary speech loss and disability. Participants underwent extensive screening consisting of medical, neurological, psychiatric, and neuropsychological examinations. Ninety-three participants were randomly allocated to a combination of donepezil and memantine, and 95 patients were assigned to the donepezil-only group (Fig. 1a).

Study Procedures and Outcome Measures

Participants were randomly assigned to one of two treatments: continuation of donepezil (at a dose of 10 mg per day starting in week 1) and continuation of donepezil and initiation of memantine (continuation of donepezil at a dose of 10 mg and memantine at a dose of 5 mg in week 1, with the dose increased in 5 mg increments weekly to a dose of 20 mg from week 4, as shown in Fig. 1b). The primary outcome was language ability measured using the Korean version of the Western Aphasia Battery (K-WAB) [18]. The secondary outcome was cognitive function and degree of disease progression measured using the K-MMSE, Clinical Dementia Rating (CDR) scale [19], the Korean Version of the Brief Clinical Form of the Neuropsychiatric Inventory (NPI-Q) [20], Relevant Outcome Scale for Alzheimer's Disease (ROSA) [21], Severe Impairment Battery Language scale (SIB-S) [22], and Global Deterioration Score (GDS) [23]. Assessment of compliance was by a doctor and evaluation of compliance through the medication position ratio (MPR). All procedures are presented in Fig. 1 (Visit 1, screening; Visit 2, baseline and randomisation; the Visit 4, week 12; Visit 5, week 24).

Statistical Analyses

To verify whether there was a statistical difference between the two groups at the time of clinical trial registration, continuous data were obtained from the mean, standard deviation, median, minimum, and maximum values and compared between groups using a two-sample *t* test or the Wilcoxon rank sum test. For the K-WAB test, descriptive values (number, mean, standard deviation, median, and maximum value) for the change in the base at termination were presented for the combination group. Comparisons between the two groups were analysed using the two-sample *t* test or the Wilcoxon rank sum test. Descriptive statistics for the K-MMSE, CDR-SB, NPI, ROSA, SIB-S, and GDS are also presented. Because the baseline scores were worse in the combination therapy group, all outcomes were also compared using

repeated-measures ANOVA with MMSE and CDR scores as covariates. For clinician compliance evaluation and medication position ratio (MPR), descriptive statistics for baseline and comparison between the two groups are presented. All statistical analyses were performed using Statistical Package for the Social Sciences version 24.0 (IBM, New York, NY, USA).

Compliance with Ethics Guidelines

All authors and this article comply with the relevant ethics guidelines and regulations. This study was completed in accordance with the declaration of Helsinki. Informed consent was obtained from all participants according to IRB regulations. All ethical approval numbers have been provided in the supplementary material.

RESULTS

Characteristics of the Study Population

The mean age of the combination group (donepezil + memantine) was 74.9 years old (SD ± 8.1), which was lower than that of the donepezil group was (75.8 years old, SD ± 6.9). Education level and family history of dementia in the combination group did not significantly differ from those in the donepezil group. Clinical parameters, including the CDR-SB and SIB scores, differed between the groups (Table 1).

Table 1 Participants' demographics, clinical severity, neuropsychological test

	Donepezil only ($n = 95$)	Donepezil + Memantine ($n = 93$)
Age (years)	75.8 ± 6.8*	75.0 ± 8.1*
Female (%)	16 (84.2)*	11 (45.8)*
Education (years)	6.4 ± 4.6	7.1 ± 5.2
History of alcohol %	14*	9*
History of smoking %	4*	12*
K-MMSE	16.2 ± 3.4	15.9 ± 4.2
CDR-SB	6.8 ± 3.0*	7.4 ± 3.3*
GDS	4.5 ± 0.7	4.6 ± 0.8
K-WAB	80.0 ± 10.0	78.4 ± 13.7
ROSA	211.1 ± 58.2	199.7 ± 63.7
NPI-Q	7.1 ± 6.3	7.4 ± 6.7
SIB	45.9 ± 3.4*	45.6 ± 4.8*

Data are means ± SD

K-MMSE the Korean version of the Mini-Mental Status Examination, *CDR-SB* Clinical Dementia Rating Scale sum of Boxes, *GDS* Global Deterioration Scale, *K-WAB* the Korean version of the Western Aphasia Battery, *ROSA* Relevant Outcome Scale for Alzheimer's Disease, NPI-Q the Korean Version of the Brief Clinical Form of the Neuropsychiatric Inventory, *SIB-S* Severe Impairment Battery Language scale

*$p < 0.05$, compared with Wilcoxon rank sum test

Primary Outcome Measures

Donepezil therapy, compared with donepezil with memantine, resulted in minimal average increases (indicating improved language function) across visit 4 (week 12) in the K-WAB scores (a 0.43-point increase with donepezil; 99% CI − 0.01 to 1.0; $P < 0.001$; and a 0.5-point decrease at visit 4 in combination of donepezil with memantine vs. baseline; 95% CI − 0.1 to 0.9; $P = 0.03$) (Fig. 2). However, the effect of K-WAB was not statistically significant in the donepezil-only group until week 24 (Table 2). There was no difference between the two groups in the repeated measures ANOVA (Supp Fig. 1).

Secondary Outcome Measures

The mean scores on the secondary outcome measures in all the study groups and at all visits are shown in Table 2 and Fig. 3. The between-group differences in the primary outcome measures at all the trial visits are shown in Table 2. Patients who were assigned to take donepezil, compared with those assigned to combination donepezil and memantine, had scores on the K-MMSE that were higher

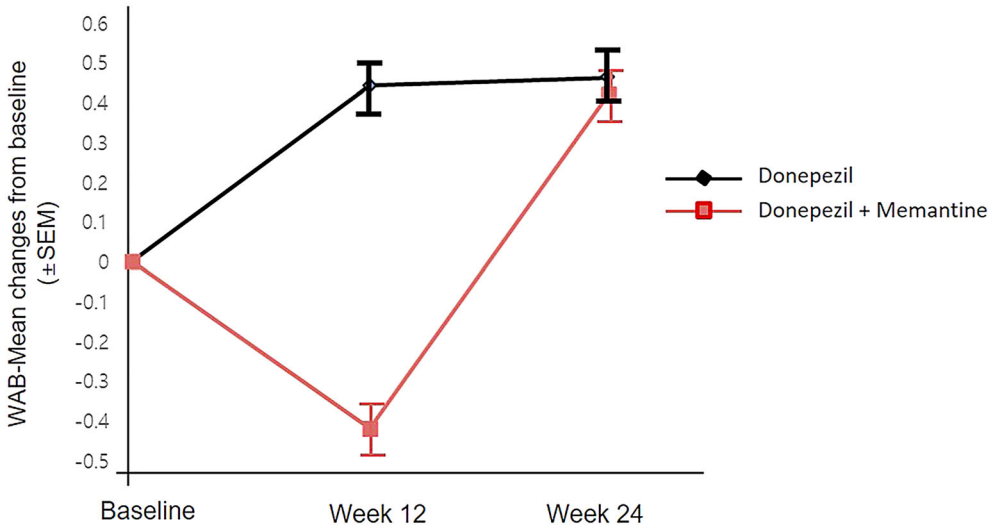

Fig. 2 Primary outcome measure. donepezil therapy, compared to donepezil with memantine, resulted in minimal average increases (indicating improved language function) across visit 4 in the K-WAB scores (a 0.43-point increase with donepezil; 99% CI − 0.01 to 1.0; $P < 0.001$; and a 0.5-point decrease at visit 4 in combination with donepezil with memantine vs. baseline; 95% CI − 0.1 to 0.9; $P = 0.03$). However, the effect on K-WAB was not statistically significant in the donepezil-only group until week 24

(indicating better cognitive function) by an average of 0.45 points ($P = 0.09$). They also had scores on the CDR-SB that were lower (indicating less functional impairment) by an average of 0.57 points (95% CI 0.34–1.48; $P = 0.035$). For both groups, these outcomes showed significant heterogeneity in treatment efficacy over time ($P < 0.0001$), with less apparent benefit at the 24-week assessment than at baseline time points. At 12 weeks, the donepezil treatment groups presented higher K-MMSE and lower CDR-SB scores than the combination donepezil and memantine. This indicated a better cognitive and functional status. However, this effect was not sustained for 24 weeks. The combination group slowly progressed in the clinical course ($P < 0.0001$). Patients who were assigned to receive donepezil, compared with those who were assigned to receive donepezil and memantine, had ROSA that were higher by an average of 4.6 points (95% CI − 28.9 to 6.13; $P = 0.19$) at baseline and scores at 24 weeks (visit 5). However, the combination of donepezil and memantine group showed a decreasing trend in ROSA scores. This reflects that memantine add-on therapy failed to show a better effect on the relevant outcome for AD compared to donepezil-only treatment. For both groups, the benefits with respect to scores on the NPI-Q reflecting behavioural symptoms of dementia appeared to decrease after treatment at 24 weeks, but these differences were not significant ($P = 0.28$). The donepezil-only therapy group showed a higher score on the SIB-S that was not significant (0.23 points higher than baseline; $P = 0.925$). There was no added benefit of adding memantine to donepezil with respect to SIB-S (0.46 points lower than baseline; 95% CI 0.03 to 1.85; $P = 0.04$). Both groups showed higher scores on the GDS (0.13 points in donepezil compared to baseline scores, and − 0.12 point with memantine; $P = 0.012$ and $P = 0.012$, respectively). These results showed clinical progression in both groups, and were the same as those of the repeated measures ANOVA (Supp Fig. 1).

DISCUSSION

Although several clinical studies have reported significant improvements in speech function

Table 2 Primary and secondary outcomes

Outcome	Screening Visit 1	Baseline[a] Visit 2	Week 12 Visit 4	Week 24 Visit 5
K-WAB				
Don		80.0 ± 10.0	80.5 ± 9.83**	80.5 ± 9.87
Don + Mem		78.4 ± 13.7	78.1 ± 13.9**	78.8 ± 13.6**
K-MMSE				
Don	15.9 ± 3.2	16.2 ± 3.4	16.8 ± 3.9**	16.1 ± 4.1**
Don + Mem	15.8 ± 3.9	15.9 ± 4.2	15.8 ± 4.9**	16.0 ± 5.0**
CDR-SB				
Don		6.78 ± 3.0	6.91 ± 3.2**	7.23 ± 3.0**
Don + Mem		7.35 ± 3.3	7.63 ± 3.5**	8.04 ± 3.6**
ROSA				
Don	210.4 ± 54.8	211.1 ± 58.2*		215.7 ± 51.2*
Don + Mem	206.7 ± 64.3	199.7 ± 63.7		200.1 ± 59.7
GDS				
Don		4.54 ± 0.7*		4.63 ± 0.7*
Don + Mem		4.66 ± 0.8*		4.76 ± 0.8*
NPI-Q				
Don		7.09 ± 6.3		6.12 ± 5.8
Don + Mem		7.43 ± 6.7		6.65 ± 6.1
SIB-S				
Don		45.9 ± 3.4		46.0 ± 4.2
Don + Mem		45.6 ± 4.8*		44.8 ± 6.3*

Data are means ± SD

Don donepezil, *Mem* memantine, *K-MMSE* Korean version of the Mini-Mental Status Examination, *CDR-SB* Clinical Dementia Rating Scale sum of boxes, *GDS* Global Deterioration Scale, *K-WAB* Korean version of the Western Aphasia Battery, *ROSA* Relevant Outcome Scale for Alzheimer's Disease, NPI-Q the Korean Version of the Brief Clinical Form of the Neuropsychiatric Inventory, *SIB-S* Severe Impairment Battery Language scale

[a]Reference group

**$p < 0.05$ compared with Kruskal–Wallis one-way ANOVA

*$p < 0.05$, compared with paired sampled t test

after memantine administration, clinical studies on speech function improvement in patients with AD are still limited. Studies worldwide have examined the effect of donepezil and memantine on language function in combination treatments for AD [24]. According to this review, there are four prospective studies and three post hoc analyses of the effects of memantine on language and communication in patients with AD [25]. Other studies provide evidence for the benefits of memantine in slowing the clinical progression of AD, either

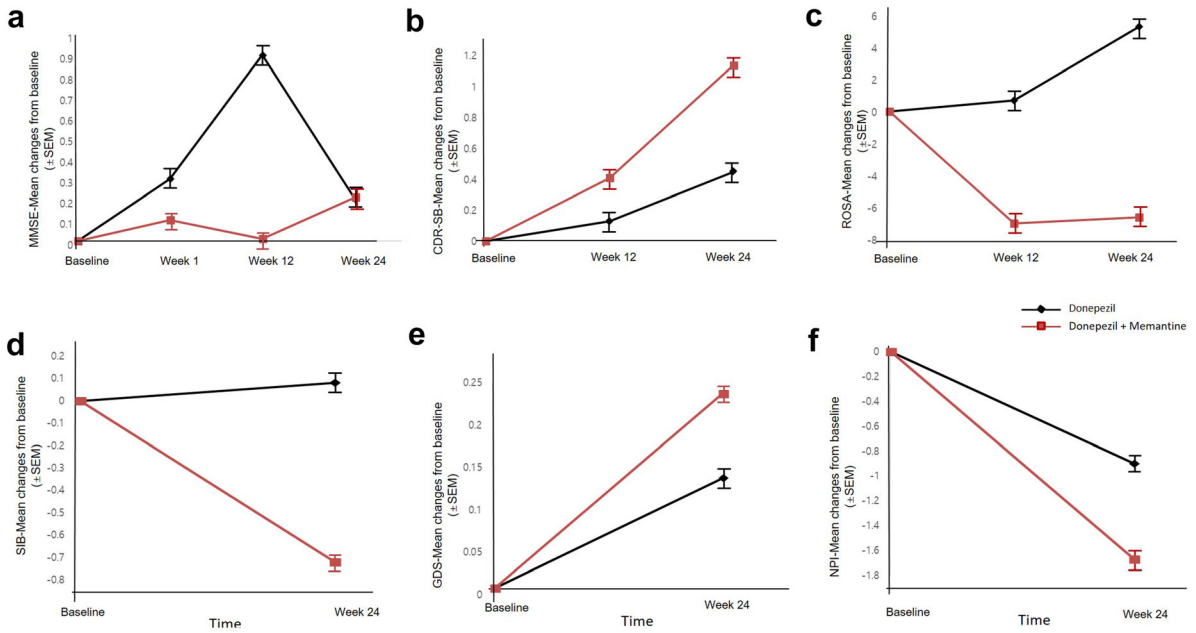

Fig. 3 Secondary outcome measures. **a** K-MMSE that were higher (indicating better cognitive function) by an average of 0.45 points ($P = 0.09$) and scores on the **b** CDR-SB that were lower (indicating less functional impairment) by an average of 0.57 points (95% CI 0.34 to 1.48; $P = 0.035$). For both these outcomes, there was significant heterogeneity in treatment efficacy over time ($P < 0.0001$), with less benefit apparent at the 24 weeks assessment than at baseline time points. **c** ROSA reflects memantine add-on therapy that fails to show a better effect on the relevant outcome for AD compared to donepezil-only treatment group. **d** There was no better benefit of adding memantine to donepezil, with respect to scores on the SIB. **e** Both groups showed higher scores on the GDS. **f** For both groups, the benefits with respect to scores on the NPI-Q reflecting behavioural symptoms of dementia appeared to be decreased after treatment at 24 weeks but these differences were not significant ($P = 0.28$)

alone or in combination with an acetylcholinesterase inhibitor (ChEI). This indicates that early treatment initiation may maximise clinical success [26]. The benefits of memantine increase over time, allowing patients to remain independent for longer, alleviating caregiver burden, and delaying institutionalisation [26]. Meta-analyses suggest credible efficacy and safety of memantine in treating AD when used alone or in combination with ChEIs [11].

Therefore, we evaluated the effect, efficacy, and effectiveness of memantine (memantine solution) on the clinical status of speech function in patients with moderate to severe AD who were taking donepezil at a stable dose. According to this result, as the primary outcome, K-WAB had an increase in scores in both groups compared to baseline scores, but the difference was not statistically significant. At 12 weeks, the donepezil treatment group had higher K-MMSE and lower CDR-SB scores than the combination of donepezil and memantine, indicating better cognitive and functional status. However, this effect was not sustained for 24 weeks. The combination group had a slow progression in clinical course according to CDR-SB. As a secondary outcome, ROSA was higher in patients who were treated with donepezil than in those who were assigned to receive the combination therapy. This indicates that memantine add-on therapy did not show any clinical improvement in patients with AD in this study. The SIB-S scale did not change significantly compared to baseline values in either group. The NPI-Q index improved significantly compared to baseline in both groups. This

means that donepezil showed clinical improvement in cognition and general condition in patients with AD.

Regarding the WAB test reflecting language function, both groups showed a trend toward improvement in language at 24 weeks compared to baseline. The donepezil group showed steady improvement, but the combination group was aggravated in the dose-up process and then recovered after adding up to the full dose. This trend suggests the possibility that memantine would be effective for long-term language functioning. Other parameters regarding cognition and donepezil treatment groups showed improvements in cognition (MMSE and SIB-S) and clinical status (CDR-SB, ROSA, GDS, and NPI-Q). In contrast, the memantine group generally showed gradual deterioration, except for BPSD. In this study, the NPI-Q index improved compared to the baseline in both groups, which is consistent with the findings of other studies [26].

Memantine is a moderate-affinity, uncompetitive, voltage-dependent N-methyl-D-aspartate (NMDA) receptor antagonist with rapid blocking/unblocking properties [3, 4]. The glutamatergic system has been implicated in the pathophysiology of neurodegenerative diseases, including AD, and memantine has been suggested to have therapeutic potential in several central nervous system disorders without undesirable adverse events associated with high-affinity NMDA receptor antagonists. In general, it is true that shorter study durations can limit the ability to assess the full impact of a treatment, and longer studies can provide more comprehensive information. Additionally, if the dosing of memantine was increased during the study period, this may confound the interpretation of the results. Further research may be needed to fully understand the effects of memantine on cognitive function in patients with moderate to severe AD.

Considering the pharmacological effects of memantine, it is likely to have a better effect when used for a long time. However, the observation period was too short to observe any desired improvement in language function in this study. Reviewing several studies that indicate good results, it seems that a long observation period of at least 2 years is required in memantine studies [6, 11, 24, 25, 27].

The second point was the differences in drug formulation compared with those of previous studies. The formulation is a key factor that determines the overall mechanism, such as the absorption rate of drugs [28]. In a rat experiment, the original oral solution was categorised as highly aversive/nontolerated, while solutions of excipients only were well tolerated, which revealed that medicine palatability remains important for acceptability in older populations [29]. The rate and extent of oral drug absorption are determined by a complex interaction between a drug's physicochemical properties, gastrointestinal physiological factors, and the nature of the formulation administered. The pH of the gastrointestinal tract is an important factor that can markedly affect oral drug absorption and bioavailability, as it may have a significant influence on drug dissolution and solubility, drug release, drug stability, and intestinal permeability [28]. Up to 9 August, 2010, seven cases of administration errors with pump devices had been reported worldwide due to confusion between doses delivered by the new pump device and doses delivered by the dropper [30]. In the interpretation of the findings of this study, it is necessary to consider the possibility that participants or caregivers encountered errors in the method of administering solutions. In the future, it will be necessary to study detailed results on drug concentration according to the method of administration of memantine solutions and tablets based on real-world data.

Another point of discussion was that patients who were assigned to receive memantine, compared with those who were assigned to receive donepezil, had lower and higher scores on the MMSE and CDR-SB, respectively; this indicates that the group had more advanced-stage patients compared to those in the donepezil group. It is possible that the memantine group had many patients with a natural deterioration. Therefore, the difference in dementia severity between the two groups may have affected the drug results.

Although there was no superior effectiveness in the memantine add-on over the donepezil monotherapy group in language function according to the K-WAB test, memantine was effective in improving behavioural symptoms in patients with moderate or severe AD. The short duration of the study and the dose adjustment limitation of memantine may have affected the assessment of the response to memantine. A longer duration of the study could have provided more insight into the long-term effects of combination therapy with donepezil and memantine in patients with moderate to severe AD. Furthermore, it would have allowed for a more comprehensive evaluation of the potential benefits and limitations of memantine in improving cognitive function and other outcomes in these patients. However, it is important to note that the study's findings are still significant, as they contribute to the current knowledge on the effectiveness of combination therapy in treating AD. Despite its limitations, the study's results challenge the initial hypothesis and demonstrate that the addition of memantine to donepezil therapy may not provide significant benefits in terms of language function, cognitive function, functional impairment, and behavioural symptoms of dementia in patients with moderate to severe AD. This information can be used to guide future research and treatment strategies for AD.

CONCLUSIONS

Based on the results of this study, it is concluded that the addition of memantine to donepezil therapy did not significantly improve speech function in patients with moderate to severe AD. While both the donepezil-only group and the combination therapy group showed some improvement in cognitive and functional status, the donepezil-only group had higher scores on cognitive and functional measures after 12 weeks, although this effect was not sustained for 24 weeks. The ROSA scores were also higher in patients who received donepezil alone compared to those who received the combination therapy, and there were no significant differences between the groups in terms of changes in the SIB-S scores. Overall, the study suggests that the addition of memantine to donepezil therapy may not have significant benefits for speech function in patients with moderate to severe AD, and further research may be needed to fully understand the effects of combination therapy on other outcomes.

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Disclosures. Hee-Jin Kim, YongSoo Shim, Hyun Jeong Han, Byeong C. Kim, Kee Hyung Park, So Young Moon, Seong Hye Choi, Dong Won Yang, Bora Yoon, Eun-Joo Kim, Jee Hyang Jeong and Seol-Heui Han have no conflicts of interest to declare.

Compliance with Ethics Guidelines. All authors and this article comply with the relevant ethics guidelines and regulations. This study was completed in accordance with the declaration of Helsinki. Informed consent was obtained from all participants according to IRB regulations. All ethical approval numbers have been provided in the supplementary material.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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