

The Behavioral Effects of Combination Therapy of Memantine and Acetylcholinesterase Inhibitors Compared with Acetylcholinesterase Inhibitors Alone in Patients with Moderate Alzheimer's Dementia: A Double-Blind Randomized Placebo-Controlled Trial

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Objective This study aimed to investigate treatment effects of combination therapy of memantine and acetylcholinesterase inhibitors (AChEIs) compared with AChEIs alone on behavioral and psychological symptoms of dementia (BPSD) in patients with moderate Alzheimer's dementia (AD).

Methods This was a 12-week, double-blind, randomized, placebo-controlled trial. A total of 148 patients with moderate AD participated in this study. Mini-Mental State Examination, Neuropsychiatric Inventory (NPI), Clinician's Interview-Based Impression of Change plus caregiver input, Gottfries-Bråne-Steen Scale, and Zarit Burden Interview were used as assessment scales.

Results There were no significant differences in age, sex, or education between AChEIs alone and combination groups. The combination group showed significantly more improvement of NPI-disinhibition score (0.76 ± 2.15) than the AChEIs alone group (-0.14 ± 1.71) after 12 weeks.

Conclusion Our findings suggest that the combination therapy of memantine and AChEIs might be a beneficial option for reducing disinhibition symptoms of patients with moderate AD compared with AChEIs alone. We believe that clinicians need to consider additional memantine treatment when patients with moderate AD complain disinhibition symptom. A larger clinical trial is needed to further determine the efficacy and advantages of such combination therapy of memantine and AChEIs for treating BPSD of patients with moderate AD.

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Key Words Alzheimer's dementia, Memantine, Acetylcholinesterase inhibitors, Behavioral and psychological symptoms of dementia, Disinhibition, Neuropsychiatric inventory.

INTRODUCTION

Dementia has been an important issue in many countries due to worldwide trend of population aging.¹ In South Korea,

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the number of patients with dementia has continuously increased due to a very rapid rate of population aging.² According to the National Institute of Dementia, 750,488 persons were estimated to have dementia (about 10.16% of people aged 65 and over) in South Korea in 2019.³ Social cost per year per patient with dementia was estimated at 20,420,000 Korean Won (KW; 1 USD=1,206 KW as of 2020).³ Total public management cost for patients with dementia was estimated at 15,300 billion KW (i.e., 12,700 million USD).³ It has been predicted that cost for patients with dementia would increase to 3 million by 2050 in South Korea.³ Accordingly, social cost will increase rapidly.

Social cost of dementia is closely associated with behavioral and psychological symptoms of dementia (BPSD)⁴⁻⁶ because BPSD can increase caregiver distress and nursing home placement.^{4,7} Many clinicians and researchers have focused on alleviating BPSD such as insomnia, anxiety, aggression, agitation, delusion, hallucination, disinhibition, and wandering.⁸ Trinh et al.⁹ have shown that the efficacy of acetylcholinesterase inhibitors (AChEIs) commonly used for cognitive symptom of Alzheimer's dementia (AD) is insufficient for treating BPSD. Some studies have recommended low-dose antipsychotics (aripiprazole, olanzapine, risperidone, quetiapine, and haloperidol) for treating agitation and aggression in patients with dementia.^{10,11} Selective serotonin reuptake inhibitors have also been used for reducing depression and agitation.^{11,12} In addition, benzodiazepine and carbamazepine have been studied for treating BPSD, although common use of these medications is not recommended due to side effects and drug interactions.^{13,14} Up to date, consensus and guideline regarding medications for treating BPSD in patients with dementia have not been established yet.

Memantine is an uncompetitive (channel blocking) N-methyl-D-aspartate receptor antagonist. It was approved for treating moderate-to-severe AD by Food and Drug Administration in 2003.^{8,15} Many researchers have studied the effect of memantine in patients with AD.¹⁶⁻¹⁸ Parsons et al.¹⁹ have shown that a combination therapy of memantine and AChEIs has complementary and synergistic effects. However, there is still not enough evidence to verify the effect of memantine for treating BPSD, though memantine has been one candidate medication for treating BPSD in patients with AD.

In this study, we conducted a double-blind, randomized, placebo-controlled trial to investigate the effect of combination therapy of memantine and AChEIs compared with AChEIs alone for treating BPSD in patients with moderate AD.

METHODS

Study design

This was a 12-week, multi-center (six), prospective, double-blind, randomized, placebo-controlled, parallel group trial. The trial was registered (registration number: IIT 16395T). The trial was initiated on Apr. 26, 2016. All visits were completed by Oct. 23, 2019. This study was approved by the Institutional Review Board of Inje University Ilsan Paik Hospital (2015-06-008), Soonchunhyang University Bucheon Hospital (2015-07-018), Gachon University Gil Medical Center, Myongji Hospital (MJH 2017-09-034), Gangdong Sacred Heart Hospital (2018-08-006), and Korea University Ansan Hospital (2015AS0096). All subjects and their legal guardians (family members or caregivers) were informed of the study protocol.

They provided written informed consent.

Subjects

A total of 148 older adults from Inje University Ilsan Paik Hospital (n=48; 32.4%), Soonchunhyang University Bucheon Hospital (n=34; 23.0%), Gachon University Gil Medical Center (n=30; 20.3%), Myongji Hospital (n=27; 18.2%), Gangdong Sacred Heart Hospital (n=5; 3.4%), and Korea University Ansan Hospital (n=4; 2.7%) participated in this study. This study enrolled patients with AD who met the criteria for "major neurocognitive disorder due to Alzheimer's disease" proposed by the fifth version of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5).²⁰ We enrolled patients with moderate AD considering the indication of memantine and the onset timing of BPSD.⁸

Subjects enrolled for this study met the following inclusion criteria: 1) aged over 60 years old, 2) scored 10–20 in Mini-Mental State Examination (MMSE), 3) scored ≥ 11 in Neuropsychiatric Inventory (NPI), 4) took AChEIs for over six months, including donepezil, rivastigmine, and galantamine, 5) had unchanged AChEIs dosages for at least three months, 6) had caregiver who could provide reliable information and accompany participants whenever visiting the hospital during the study period. During screening and diagnostic procedures, we applied the following patient exclusion criteria: 1) those who had experienced cerebrovascular diseases or traumatic brain diseases, 2) those who had alcohol or other substance use disorders, 3) those who had fatal or serious medical diseases, and 4) those who had visual or hearing impairment at a level where assessments for studies including neuropsychological tests and clinical scales were impossible. Geriatric psychiatrists certified by Korean Association for Geriatric Psychiatry were responsible for all screening and diagnostic procedures.

Assessment

At baseline assessment, demographic data such as age, sex, and years of education were obtained. In addition, all participants and their caregivers used the following scales during the study period.

MMSE is a simple measure of cognitive function that has been used in clinical evaluation of patients with dementia.²¹ Among various Korean versions of MMSE, we adopted the MMSE-KC version: MMSE in the Korean version of Consortium to Establish a Registry for Alzheimer's disease (CERAD) assessment packet.²² NPI was conducted to assess behavioral and psychiatric symptoms of dementia.²³ NPI consisted of 12 symptoms. Each symptom was scored according to its frequency and severity.²³ We used Korean version of NPI and adopted the sum of composite scores (frequency x severity).²⁴

This study also used Clinician’s Interview-Based Impression of Change plus caregiver input (CIBIC-Plus).²⁵ CIBIC-Plus is a clinician rating scale that evaluates change in patients’ overall condition. Gottfries–Bråne–Steen Scale (GBS) focuses on the overall assessment of patients with dementia.²⁶ GBS consists of subscales regarding cognition, emotion, activities of daily living, and behavioral and psychological symptoms. We adopted GBS for caregiver interview. In addition, we adopted Zarit Burden Interview (ZBI) for interviewing caregivers of patients with dementia.^{27,28} ZBI has been widely used to assess caregiver burden related to dementia.

Procedure

Subjects were randomized using a stratified block randomization method. Statisticians who were blinded to clinical information conducted a 1:1 ratio randomization using Statistical Analysis System (SAS Institute Inc. Cary, NC, USA). All participants took memantine or placebo two times a day dur-

ing 12 weeks according to their randomized group allocation. Memantine and placebo had the same appearance. They were provided using blister packs. Participants in the combination group initially received 5 mg memantine per day. The dosage of memantine was then increased to 20 mg/day between 3 and 8 weeks considering side effects. Medication adherence was monitored using pill count method referring to remaining empty blister packs. Antidepressants/benzodiazepines/cognitive enhancers–unchanged medication dosages for at least three months–and medications for physical illness were permitted during the study period. However, the following medications were not allowed to be co-administered until the end of this study: amantadine, ketamine, detromethorphan, phenytoin, cimetidine, ranitidine, procainamide, quinidine, quinine, and nicotine. Figure 1 shows the schedule for assessments including effectiveness and safety.

Statistical analysis

Descriptive statistics were calculated for all variables. Percentages were calculated for categorical variables while means and standard deviations were calculated for continuous variables. Independent t-test was used for analyzing differences in baseline characteristics and changes of scale scores between AChEIs alone and combination groups. The last observation carried forward (LOCF) approach was adopted to handle missing data.

A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using R version 3.6.2 (The R Foundation for Statistical Computing Platform, Vienna, Austria).

RESULTS

Table 1 shows basic characteristics of the AChEIs alone and combination groups. The mean age of subjects was 78.18±6.85 years in the AChEIs alone group and 78.23±6.59 years in

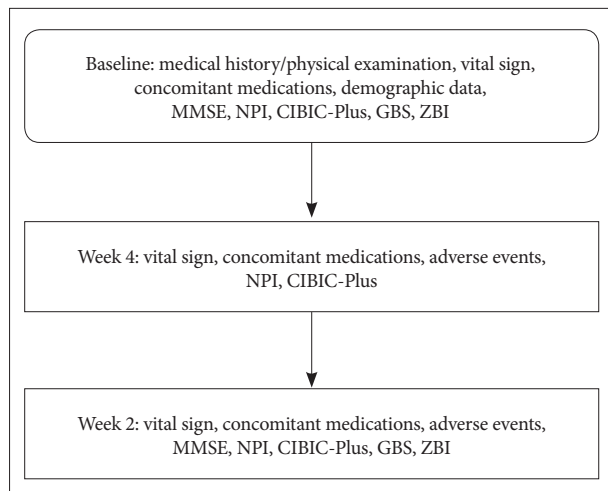


Figure 1. The schedule for assessments. MMSE: Mini-Mental State Examination, NPI: Neuropsychiatric Inventory, CIBIC-Plus: Clinician’s Interview-Based Impression of Change plus caregiver input, GBS: Gottfries– Bråne–Steen Scale, ZBI: Zarit Burden Interview.

Table 1. Baseline characteristics of participants in AchEIs alone and combination groups

	Total (N=148)	AchEIs alone (N=74)	Combination (N=74)	t-value	p-value*
Age (years)	78.20±6.69	78.18±6.85	78.23±6.59	-0.05	0.963
Sex (male/female)	39/109	18/56	21/53	0.56	0.579
Education (years)	6.95±5.07	6.69±5.11	7.22±5.05	-0.63	0.527
MMSE	15.61±3.41	15.71±3.35	15.51±3.50	0.36	0.717
NPI	24.59±16.43	24.73±15.31	24.45±17.60	0.10	0.920
CIBIC-Plus	4.13±0.69	4.10±0.68	4.15±0.71	-0.47	0.641
GBS	43.12±24.04	43.44±24.30	42.79±23.94	0.16	0.872
ZBI	34.59±17.59	36.74±17.15	32.40±17.88	1.49	0.138

*p values were calculated using chi-square test and independent t-test. MMSE: Mini-Mental State Examination, NPI: Neuropsychiatric Inventory, CIBIC-Plus: Clinician’s Interview-Based Impression of Change plus caregiver input, GBS: Gottfries– Bråne–Steen Scale, ZBI: Zarit Burden Interview

the combination group. More females than males participated in both groups. There were no significant differences in age, sex, or education between AChEIs alone and combination groups. No one specifically complained about the symptoms of side effects, and no one stopped taking drugs because of drug adverse events.

Changes of scale scores in AChEIs alone and combination groups during the follow-up period are shown in Tables 2 and 3. The combination group showed significantly more improvement of NPI-disinhibition score (0.76 ± 2.15) than the AChEIs alone group (-0.14 ± 1.71) after 12 weeks, although there was no significant difference in this score between the two groups at week 4. CIBIC-Plus change scores did not differ significantly between the two groups at week 4 or week 12 (Table 4).

DISCUSSION

South Korea has national health insurance system which covers all health services of approximately 50 million Koreans.²⁹ Accordingly, almost all medications are controlled by criteria for National Health Insurance coverage. Recommended National Health Insurance criterion for memantine prescription is MMSE ≤ 20 (and Clinical Dementia Rating 2–3 or Global Deterioration Scale 4–7). According to 2019 statistics of National Institute of Dementia, the target population of memantine use in South Korea was estimated to be approximately 350,000.³ There were about 220,000 patients with moderate degree of AD in that report, consistent with the inclusion criteria of our study.³ Although statistics data are limited, the prevalence of BPSD is relatively high (50–80%) in patients with dementia.^{30–32} Therefore, many older adults can get help if the effect of memantine for treating BPSD is confirmed.

Previous double-blind, randomized, placebo-controlled studies have reported the effect of combination therapy of memantine and AChEIs. Tariot et al.³³ have enrolled 404 patients with AD (MMSE of 5 to 14) and found that patients in the memantine group have significantly better outcomes than those in placebo group based on measures of cognition, activities of daily living, global outcome, and behavior. Grossberg et al.³⁴ have also reported that patients with AD (MMSE of 3 to 14) in the memantine group have cognitive, global, and behavioral benefits. However, some studies on AD patients with relatively less severe stages have shown different results. Porsteinsson et al.³⁵ have included 433 AD patients with MMSE of 10 to 22 and found that those in the memantine group do not show an advantage over those in the placebo group regarding cognition, activities of daily living, global outcome, or behavior. Similarly, Choi et al.³⁶ have reported that the combination therapy of memantine plus rivastigmine patch does not

show an advantage over rivastigmine patch monotherapy in patients with AD (50 to 90 years old with MMSE of 10 to 20). Our study found that patients with moderate AD treated with the combination therapy of memantine and AChEIs had significant improvement in disinhibition symptoms of BPSD compared with those who treated with AChEIs alone. Considering that previous studies did not validate an advantage of combination therapy of memantine plus AChEIs in patients with moderate AD, the result of our study might be used as a reference when treating patients with moderate AD.

Causes and pathophysiology of BPSD are incompletely understood.³⁷ Likewise, pathophysiology, phenomenology, main clinical correlates, and long-term evolution of disinhibition symptom in dementia remain unclear.³⁸ Accordingly, it might be difficult to elucidate the association between memantine and improvement of disinhibition symptoms. Povysheva and Johnson have suggested that memantine can affect excitation-inhibition balance in the prefrontal cortex.³⁹ Araki et al.⁴⁰ have reported that combination treatment of memantine and donepezil can inhibit the reduction of cerebral blood flow in the prefrontal area of a patient with AD. Considering that prefrontal cortex is one of the regions associated with disinhibition symptom, these previous studies might help explain results of our analysis.⁴¹

The question of NPI-disinhibition item is “Does the patient seem to act impulsively, for example, talking to strangers as if he/she knows them, or saying things that may hurt people’s feelings?”²³ Lyketsos et al.⁴² have shown that the prevalence of NPI-disinhibition item is 12.7% in patients with dementia. Kaufer et al.⁴³ have also reported a prevalence of 10–13% of NPI-disinhibition item in patients with moderate to severe dementia. In addition, Starkstein et al.³⁸ have investigated the prevalence of abnormal behaviors in patients with dementia and reported that inappropriate social behavior is one of the most frequent symptoms. Therefore, clinicians may often encounter AD patients with disinhibition symptoms. The use of additional memantine might be considered each time.

Our findings suggest that the combination therapy of memantine and AChEIs might be a beneficial option for reducing disinhibition symptoms of patients with moderate AD compared with AChEIs alone. That is, combination therapy of memantine and AChEIs may be considered when disinhibition symptoms of patients with moderate AD are encountered or when disinhibition symptoms are unresponsive to AChEIs only. An additional implication of this study is that it suggests the possibility of using memantine combination therapy for patients with moderate AD for treating BPSD. A larger clinical trial is needed to further determine the efficacy and advantages of such combination therapy of memantine and AChEIs for treating BPSD of patients with moderate AD.

Table 2. Changes of MMSE and NPI scores in AchEIs alone and combination groups during the follow-up period

	Baseline	Week 4	Baseline-week 4	t-value	p-value*	Week 12	Baseline-week 12	t-value	p-value†
MMSE-placebo	14.98±3.12					15.23±3.60	-0.25±2.84	-0.21	0.833
MMSE-memantine	15.54±3.57					15.67±4.74	-0.13±2.82		
NPI total-placebo	25.12±15.34	20.21±15.44	4.91±12.23	-0.16	0.877	17.05±13.09	6.58±13.04	0.48	0.632
NPI total-memantine	25.26±18.16	20.20±15.23	5.26±13.43			18.49±13.57	5.45±11.26		
Delusions-placebo	1.54±2.80	1.24±2.55	0.30±2.53	-0.49	0.628	0.75±1.76	0.84±2.16	1.40	0.166
Delusions-memantine	1.34±2.60	0.83±1.84	0.51±2.30			0.76±1.78	0.30±1.91		
Hallucinations-placebo	0.84±2.03	0.70±1.93	0.14±1.43	-0.27	0.791	0.50±1.65	0.02±1.31	1.46	0.147
Hallucinations-memantine	0.91±2.41	0.69±2.09	0.22±1.63			0.89±2.24	-0.39±1.60		
Agitation/aggression-placebo	2.04±2.91	1.58±2.59	0.46±2.64	-0.55	0.582	1.02±1.54	0.91±2.47	0.83	0.411
Agitation/aggression-memantine	2.58±2.97	1.83±3.05	0.75±3.54			1.67±2.58	0.50±2.74		
Depression-placebo	3.13±3.21	2.58±3.07	0.55±2.79	0.27	0.790	1.71±2.13	1.23±2.83	1.41	0.161
Depression-memantine	2.46±2.91	2.03±3.43	0.43±2.36			1.94±2.78	0.54±2.29		
Anxiety-placebo	2.06±2.96	1.77±2.26	0.29±2.86	0.58	0.561	1.39±1.95	0.98±2.59	1.87	0.065
Anxiety-memantine	2.12±3.22	2.09±3.18	0.03±2.22			2.17±3.46	0.07±2.51		
Elation/euphoria-placebo	0.32±0.91	0.33±1.02	-0.01±0.85	-1.47	0.144	0.32±1.35	-0.02±1.46	-0.07	0.944
Elation/euphoria-memantine	0.34±1.04	0.12±0.57	0.22±0.96			0.37±0.92	0.00±1.20		
Apathy/indifference-placebo	4.49±3.75	3.36±3.27	1.13±3.32	-0.09	0.931	3.07±3.12	1.04±3.22	0.44	0.658
Apathy/indifference-memantine	4.33±3.92	3.15±3.45	1.18±3.91			3.17±3.62	0.76±3.31		
Disinhibition-placebo	1.15±2.18	0.87±1.91	0.28±2.36	-1.19	0.234	1.09±2.11	-0.14±1.71	-2.44	0.016
Disinhibition-memantine	1.58±2.40	0.80±1.90	0.78±2.58			0.48±1.33	0.76±2.15		
Irritability-placebo	2.48±2.98	1.96±2.82	0.52±3.23	-0.00	0.998	1.41±2.50	0.80±2.32	0.68	0.501
Irritability-memantine	2.37±2.97	1.85±2.84	0.52±2.34			1.46±2.54	0.54±1.77		
Aberrant motor behavior-placebo	1.81±3.40	1.46±2.92	0.35±2.68	-0.58	0.566	1.43±2.87	0.18±3.13	-0.25	0.803
Aberrant motor behavior-memantine	2.12±3.60	1.49±2.83	0.63±3.01			1.85±3.19	0.31±2.55		
Night-time behavior-placebo	2.69±3.20	1.88±2.90	0.81±2.59	0.40	0.694	1.77±3.17	0.50±3.52	-1.32	0.190
Night-time behavior-memantine	2.71±3.54	2.09±2.97	0.62±3.15			1.57±2.45	1.39±3.55		
Appetite/eating abnormalities-placebo	2.25±3.36	1.93±3.37	0.32±3.36	0.02	0.982	2.29±3.19	0.34±4.02	-0.52	0.607
Appetite/eating abnormalities-memantine	2.28±3.14	1.97±3.18	0.31±2.01			1.81±2.92	0.67±2.40		

*p-value for baseline-week 4. †p-value for baseline-week 12. Both p-values were calculated using independent t-test. MMSE: Mini-Mental State Examination, NPI: Neuropsychiatric Inventory

Table 3. Changes of clinician's interview-based impression of change plus caregiver input, GBS, and ZBI scores in AchEis alone and combination groups during the follow-up period

	Baseline	Week 4	Baseline-week 4	t-value	p-value*	Week 12	Baseline-week 12	t-value	p-value†
CIBIC-Plus overall-placebo	4.11±0.66	3.79±0.97	0.32±0.69	0.98	0.329	3.81±0.97	0.28±0.71	-0.99	0.323
CIBIC-Plus overall-memantine	4.17±0.71	3.93±0.75	0.24±0.58			3.75±0.73	0.42±0.72		
Patients-placebo	4.14±0.70	3.82±0.98	0.32±0.68	0.69	0.494	3.81±0.97	0.26±0.71	-1.40	0.164
Patients-memantine	4.23±0.80	3.97±0.80	0.26±0.58			3.72±0.74	0.45±0.72		
Caregiver-placebo	4.12±0.69	3.80±0.97	0.32±0.66	0.53	0.600	3.81±0.97	0.33±0.75	-0.66	0.510
Caregiver-memantine	4.21±0.70	3.95±0.75	0.26±0.66			3.77±0.75	0.43±0.82		
GBS total-placebo	43.02±24.30					40.95±24.03	2.07±16.13	1.64	0.105
GBS total-memantine	43.70±23.94					46.98±29.39	-3.29±18.44		
Intellectual-placebo	23.32±11.90					23.52±11.62	-0.20±6.78	1.52	0.132
Intellectual-memantine	23.75±11.34					26.88±17.47	-3.13±12.75		
Emotional-placebo	4.95±4.18					4.36±3.91	0.59±3.39	1.51	0.135
Emotional-memantine	5.32±4.34					5.71±4.75	-0.39±3.51		
Activities of daily living-placebo	6.16±6.42					5.98±7.29	0.18±4.65	0.90	0.371
Activities of daily living-memantine	6.73±6.78					7.39±7.60	-0.66±5.21		
Behavioral and psychological symptoms of dementia-placebo	8.67±5.86					7.22±5.40	1.45±5.69	0.59	0.556
Behavioral and psychological symptoms of dementia-memantine	7.89±5.73					7.00±5.13	0.89±4.23		
ZBI-placebo	37.33±15.84					36.11±17.40	1.22±1.68	0.89	0.373
ZBI-memantine	32.93±17.19					33.60±17.55	-0.67±1.28		

*p-value for baseline-week 4, †p-value for baseline-week 12. Both p-values were calculated using independent t-test. CIBIC-Plus: Clinician's Interview-Based Impression of Change plus caregiver input, GBS: Gottfries-Bråne-Stein Scale, ZBI: Zarit Burden Interview

Table 4. Clinician’s interview-based impression of change plus caregiver input change scores of participants in AchEIs alone and combination groups

	Week 4	t-value	p-value*	Week 12	t-value	p-value†
CIBIC-Plus overall-placebo (change)	3.65±0.95	0.14	0.890	3.49±0.87	-0.62	0.538
CIBIC-Plus overall-memantine (change)	3.63±0.74			3.58±0.69		
Patients-placebo (change)	3.68±0.95	0.03	0.974	3.49±0.87	-0.38	0.708
Patients-memantine (change)	3.68±0.75			3.55±0.67		
Caregiver-placebo (change)	3.65±0.94	-0.17	0.867	3.51±0.91	-0.70	0.484
Caregiver-memantine (change)	3.68±0.79			3.62±0.74		

*p-value for week 4, †p-value for week 12. Both p-values were calculated using independent t-test. CIBIC-Plus: Clinician’s Interview-Based Impression of Change plus caregiver input

However, this study has some limitations. First, the sample size of this study was relatively small and most of our participants were females, thus limiting the generalizability of our results. Second, this study adopted only the MMSE score as an inclusion criterion for moderate AD. We believe that a more complex neuropsychiatric battery such as CERAD is needed for more appropriate classification. Third, our study analyzed the effect of combination therapy of memantine and AchEIs in patients with moderate AD. Further studies including other AD groups with various severity stages are needed to provide more informative results. Fourth, the follow-up period of this study was 12 weeks. Considering that patients taking memantine and AchEIs tend to maintain their medications for a long time, a longer follow-up period may be necessary. Finally, this study did not match kinds or doses of AchEIs. In addition, we also did not control kinds or doses of other drugs such as antidepressants, antipsychotics, and medications for physical illness. More controlled studies that address this issue are needed to verify the effect of such memantine combination therapy more clearly.

This study conducted a double-blind, randomized, placebo-controlled trial to investigate the effect of combination therapy of memantine and AchEIs compared with AchEIs alone in patients with moderate AD. After 12 weeks of follow-up period, patients in the combination group showed an advantage over those in the AchEIs alone group for NPI-disinhibition items. We believe that clinicians may consider additional memantine treatment when patients with moderate AD complain disinhibition symptoms. Further larger clinical trials are needed to verify and determine advantages of such combination therapy of memantine and AchEIs for treating BPSD of patients with moderate AD.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

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