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ARTICLE

Combined Effects of Donepezil and Memantine on Behavioral and Psychological Symptoms, Cognitive Function, and Daily Living Abilities in Patients With Alzheimer's Disease

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Abstract

Aims/Background Combined with memantine, donepezil has a beneficial impact on the treatment of moderate to severe Alzheimer's disease (AD), but it can potentially increase the risk of adverse events. The aim of this study is to compare the effects of low-dose and high-dose donepezil combined with memantine on the behavioral and psychological symptoms, cognitive function, and daily living abilities of patients with moderate to severe AD, and to explore their safety.

Methods This retrospective study includes 106 AD patients who received treatment in the Third People's Hospital of Fuyang from January 2022 to January 2024. The patients were grouped according to treatment regimen: patients receiving low-dose donepezil (5 mg/day) combined with memantine were included in the low-dose group ($n = 45$), and those receiving high-dose donepezil (10 mg/day) combined with memantine were included in the high-dose group ($n = 61$). The assessment results of behavioral and psychological symptoms, cognitive function, daily living ability, quality of life, sleep quality, as well as the occurrence of adverse reactions during treatment were obtained from electronic medical records for the two groups of patients before and after 24 weeks of treatment, and were compared using appropriate statistical tests.

Results After 24 weeks of treatment, the scores of neuropsychiatric inventory (NPI) and behavioral pathology in Alzheimer's disease rating scale (BEHAVE-AD) were similar between the two groups ($p > 0.05$). The scores of Mini-Mental State Examination (MMSE) and Alzheimer's disease assessment scale-cognitive section (ADAS-Cog) were similar between the two groups ($p > 0.05$). The scores of activities of daily living (ADL) were comparable between the two groups ($p > 0.05$), and the low-dose group had significantly higher quality of life-Alzheimer's disease (QOL-AD) scores compared to the high-dose group ($p < 0.05$). The Pittsburgh sleep quality index (PSQI) scores of patients in the high-dose group were significantly higher than those before treatment and those in the low-dose group ($p < 0.05$). There was no statistically significant difference in PSQI scores between the low-dose group before and after treatment ($p > 0.05$). During the treatment period, the total incidence of adverse reactions in the low-dose group was significantly lower than that in the high-dose group (11.11% vs. 27.87%, $p < 0.05$).

Conclusion Both 5 mg/day or 10 mg/day donepezil in combination with memantine holds the potential to improve behavioral and psychological symptoms, cognitive function and daily living abilities in patients with moderate-to-severe AD. In addition, high doses of donepezil may lead to decreased sleep quality in patients, increased risk of adverse reactions, and less improvement in quality of life than low doses.

Key words: dose-response relationship, drug; donepezil; memantine; Alzheimer's disease; behavioral symptoms; cognition

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Introduction

Alzheimer's disease (AD) is a chronic degenerative disease with a severe implication for the health of the elderly, characterized by high incidence, poor prognosis, and complex etiology (Rostagno, 2022; Scheltens et al, 2021). In recent years, with the accelerated population aging, the incidence of AD has been increasing year by year (Silva et al, 2019; Stefaniak et al, 2022). Research has shown that an AD progression to moderate and severe stages, patients experience a profound decline in quality of life due to worsening cognitive impairment and decreased daily living abilities, placing a heavy burden on their families and the healthcare system (Collins et al, 2024; Wilkinson et al, 2014).

Memantine and donepezil are both commonly used in the treatment of AD. Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist, which protects neurons by non-competitive blocking of NMDA receptors and reducing the overexcitation of NMDA receptors induced by glutamate (Marotta et al, 2020; Singh and Kumar, 2024; Vaz and Silvestre, 2020). Donepezil is a specific reversible inhibitor of acetylcholinesterase (AChE), a key enzyme responsible for biological conduction in central nervous system, which can stably regulate the activity of AChE and delay the conversion of acetylcholine (ACh) released in the synaptic gap (Birks and Harvey, 2018; Zhang and Gordon, 2018). In a 6-month prospective randomized clinical trial on 85 patients with moderate AD, Bago Rožanković et al (2021) found that both donepezil and memantine had a good safety profile and could effectively improve the behavioral and psychological symptoms of patients with moderate AD.

At present, studies on combining memantine and donepezil for maximizing the therapeutic efficacy for AD have been showing a growing trend. Most of the research results showed that the effect of donepezil combined with memantine was better than that of the drugs in isolation, although Howard et al (2012) pointed out that the combination demonstrated no significant benefits. For example, Tariot et al (2004) found that in AD patients who received a stable dose of donepezil combined memantine therapy experienced further improvements in cognition, activities of daily living, overall prognosis, and behavior. Calhoun et al (2018) reported out that the clinical efficacy of donepezil combined with memantine was superior to that of donepezil alone in the treatment of AD. Matsuzono et al (2015) found that the addition of memantine to donepezil therapy led to stabilization of the cognitive scores of Alzheimer's patients at 6 months and emotional scores at 12 months. In addition, the combination was also advocated by Matsunaga et al (2014) for being able to better improve cognition, behavior disorders and daily living ability of patients with moderate and severe AD. It has been revealed that the main molecular mechanism of the combination of donepezil and memantine in alleviating cognitive impairment involves endocrine disrupting chemicals (EDCs) (Nguyen, 2022). In addition, from a cost perspective, the drug fusion regimen is actually less costly compared to when the constituents drugs—donepezil or memantine—are used separately, underscoring the cost-effectiveness of this combination for treating AD (Pfeil et al, 2012).

Although the above-mentioned studies confirmed that the combination of memantine and donepezil had better efficacy in the treatment of AD, Isaac et al (2022) found that patients treated with the combination of donepezil and memantine experienced a significantly higher risk of side effects than patients treated with memantine monotherapy. In view of this observation, the author hypothesized that reducing the dose of donepezil could reduce the safety while ensuring the efficacy. At present, the clinical efficacy and safety of low-dose donepezil combined with memantine in the treatment of AD have not been reported. In order to mitigate this gap, we conducted a retrospective analysis of 106 patients with AD treated in the Third People's Hospital of Fuyang (Hangzhou, China) from January 2022 to January 2024, and compared the effects of low- and high-dose donepezil combined with memantine on behavioral and psychological symptoms, cognitive function, daily living ability and other aspects of patients with moderate and severe AD. In addition, the safety profile of this combination was explored to generate more data to facilitate donepezil dose selection in the future.

Methods

Study Participants

This retrospective study includes 106 AD patients who received treatment in the Third People's Hospital of Fuyang from January 2022 to January 2024.

Inclusion and Exclusion Criteria

Inclusion criteria for this study are as follows: (1) patients meeting the diagnostic criteria for AD; (2) patients having Mini-Mental State Examination (MMSE) score ranging from 0 to 20 points, with 10 to 20 points indicating moderate AD and 0 to 9 points indicating severe AD; (3) patients not receiving any other relevant treatment before admission; and (4) patients having complete medical records.

Individuals with the following conditions were excluded from the present study: (1) individuals with cognitive impairment caused by vascular diseases, Parkinson's disease, and other factors; (2) individuals who had taken medication that affects cognitive function before admission; (3) patients with hematological disease, autoimmune diseases and infectious diseases; (4) individuals with malignant tumors; (5) individuals who are allergic to treatment drugs; and (6) patients with severe liver, heart, and kidney dysfunction.

Research Methods

The patients recruited were categorized according to treatment regimen received into two groups: patients receiving low-dose donepezil (5 mg/day) combined with memantine were included in the low-dose group (n = 45), whereas those receiving high-dose donepezil (10 mg/day) combined with memantine were included in the high-dose group (n = 61).

Patients in both groups were treated with memantine hydrochloride tablets (Sinomedical code H20203016, Hunan Dongting Pharmaceutical Co., Ltd., Changde, China), the initial dose was 5 mg/time, once/day, orally for 1 week. From the second week onward, the dose was increased to 10 mg/day, including 5 mg in the morning

and 5 mg in the evening. From the third week onward, the dose was increased to 15 mg/day, including 10 mg in the morning and 5 mg in the evening. From the fourth week onward, the dose was increased to 20 mg/day, with 10 mg in the morning and 10 mg in the evening, and this particular dose was maintained for a consecutive 24 weeks.

For the patients in the high-dose group, donepezil hydrochloride tablets (National drug approval number H20183417, Zhejiang Huahai Pharmaceutical Co., Ltd., Taizhou, China) were combined with the memantine treatment, with a dose of 5 mg/time, once/day, orally before going to bed; the dose was increased to 10 mg/day after 4 weeks, once per day, orally before going to bed, which was maintained for a consecutive 24 weeks.

For patients in the low-dose group, donepezil hydrochloride tablets (National drug approval number H20183417, Zhejiang Huahai Pharmaceutical Co., Ltd., Taizhou, China) were added to the memantine treatment, with a dose of 5 mg/time, once per day, orally before going to bed, which was maintained for a consecutive 24 weeks.

Observation Indicators

The baseline data (gender, age, body mass index [BMI], course of disease, educational level, severity of AD, smoking history, hypertension and diabetes mellitus) of 106 AD patients were obtained from electronic medical records, and the scores of various scales (neuropsychiatric inventory (NPI), behavioral pathology in Alzheimer's disease rating scale (BEHAVE-AD), Mini-Mental State Examination (MMSE), Alzheimer's disease assessment scale-cognitive section (ADAS-Cog), activities of daily living (ADL), quality of life-Alzheimer's disease (QOL-AD), Pittsburgh sleep quality index (PSQI)) before and after treatment, and the occurrence of adverse reactions (dizziness, fatigue, nausea, diarrhea) during treatment. Details of the research scale are as follows:

(1) NPI (Cummings et al, 1994): The scale covers 12 parts, including delusion, hallucination, agitation/aggression, depression/dysthymia, anxiety, euphoria/euphoria, lack of desire/apathy, loss of self-control, irritability/emotional instability, abnormal motor behavior, sleep/night behavior, and appetite/diet. These symptoms were queried in two parts: frequency and severity, with the former scored with a range of 1–4 points and the latter with 1–3 points. The score for each item is calculated by multiplication of the two component subscores obtained: frequency score × severity score. The total score is the sum of the scores of each item, ranging from 0 to 144 points. By default, the higher the total score value, the more serious the behavioral and psychological symptoms of a patient.

(2) BEHAVE-AD (Noroozian et al, 2025): The scale covers 7 parts, including affective disorder, hallucination, circadian rhythm disorder, behavior disorder, aggressive behavior, paranoid and delusional ideas, anxiety and fear, covering a total of 25 items, with each item scored from a range of 0–3 points. The total score of this scale is the sum of the scores of each part, ranging from 0 to 75 points. A higher score measured with this scale indicates the more serious behavioral and psychological symptoms faced by a patient.

(3) MMSE (Katzman et al, 1988): The scale covers 6 parts: time orientation (0–5 points), place orientation (0–5 points), immediate memory (0–3 points), attention and computation (0–5 points), delayed memory (0–3 points), language and visual space (0–9 points), totaling 30 items. The total score is the sum of the scores of each part, ranging from 0 to 30 points. A lower score indicates greater cognitive impairment.

(4) ADAS-Cog (Peña-Casanova, 1997): The scale covers 12 items: word recall, naming, executing instructions, orientation, intentionality exercise, structural exercise, word recognition, verbal expression, word-finding ability, language expression, attention, and recall test instructions. Among these, 1 item is rated 0–10 points, 9 items are each rated 0–5 points, 1 item is rated 0–8 points, and 1 item is rated 0–12 points. The total score is the sum of the scores of each part, ranging from 0 to 75 points, and the lower the score value, the better the cognitive function of the patient.

(5) ADL (Reisberg et al, 2001): This scale covers 20 daily living abilities, including taking public transportation, going to places near home, cooking, doing household chores, taking medicine, eating, dressing/undressing, combing hair/brushing teeth, washing one's own clothes, walking in flat rooms, going up and down stairs, getting up and down/sitting/standing up, fetching water and cooking, taking a shower, cutting toenails, window shopping/shopping, being able to use bathroom without others' assistance, making phone calls, handling one's own money, and being alone at home. Each living ability is scored from 1 to 4 points: 1 point denotes "completely capable", 2 points "somewhat difficult", 3 points "in need of help", and 4 points "simply unable to do". The total score is the sum of the scores of each part, ranging from 20 to 80 points. A higher total score reflects a more diminished daily living ability.

(6) QOL-AD (Yamada et al, 2020): The scale covers 13 parts, including physical health, energy, mood, living conditions, memory, relationship with family members, marital status, relationship with friends, overall feeling of oneself, ability to do housework, ability to engage in recreational activities, economic status, and overall situation of life. Each part is scored 1–4 points. The total score ranges from 13 to 52, with higher scores indicating better quality of life.

(7) PSQI (Buysse et al, 1989): The scale covers 7 parts: subjective sleep quality, time to fall asleep, sleep time, sleep efficiency, sleep disorders, hypnotic drugs, and daytime dysfunction. Each part is scored 0–3 points, and the total score is the sum of the scores of each part. The total score ranges from 0 to 21 points, with a higher score indicating poorer sleep quality.

The score measurements for the above-mentioned scales were conducted by the same group of survey personnel, and the entire survey staff have received unified training to ensure that they fully mastered the purpose, process, and scoring methods of the questionnaire survey. Before the questionnaire survey, the survey personnel team was given a detailed briefing on the relevant precautions that they should exercise while conducting the survey, such as avoiding the utilization of inductive language, and ensuring data accuracy.

Statistical Analysis

Statistical analysis was performed using SPSS 23.0 software (IBM Corp, Armonk, NY, USA). Continuous variables (e.g., age, BMI, course of disease and the scores of NPI, BEHAVE-AD, MMSE, ADAS-Cog, ADL, QOL-AD, PSQI) were assessed for normality using the Kolmogorov–Smirnov test. Variables conforming to normal distribution were expressed as mean ± standard deviation (SD) and compared using the *t*-test. Categorical variables (e.g., gender, course of disease, educational level, severity of AD, smoking history, hypertension, diabetes mellitus and adverse reactions) were expressed as counts and percentages, with comparisons analyzed using chi-square test. A p-value < 0.05 was considered statistically significant.

Results

Comparison of Clinical Baseline Characteristics

The low-dose and high-dose groups had no significant differences in clinical baseline characteristics such as gender, age, BMI, course of disease, educational level, severity of AD, smoking history, hypertension and diabetes mellitus ($p > 0.05$), as shown in Table 1.

Comparison of Behavioral and Psychological Symptoms

Baseline NPI and BEHAVE-AD scores were statistically comparable between the two groups ($p > 0.05$). After 24 weeks of treatment, both groups experienced significant reductions in NPI and BEHAVE-AD scores ($p < 0.05$). After 24 weeks of treatment, the scores of NPI and BEHAVE-AD were statistically comparable between the two groups ($p > 0.05$), as shown in Table 2.

Comparison of Cognitive Function

No statistically significant differences between the low-dose and high-dose donepezil groups were observed in baseline levels of the scores of MMSE and ADAS-Cog ($p > 0.05$). After 24 weeks of treatment, both groups exhibited significant increases in the scores of MMSE and a significant reduction in the scores of ADAS-Cog, compared to the pre-treatment scores ($p < 0.05$). After 24 weeks of treatment, the scores of MMSE and ADAS-Cog were similar between the two groups ($p > 0.05$), as shown in Table 3.

Comparison of Daily Living Ability and Quality of Life

No statistically significant differences between the low-dose and high-dose donepezil groups were observed in baseline levels of the scores of ADL and QOL-AD ($p > 0.05$). After 24 weeks of treatment, both groups exhibited significant decreases in the scores of ADL, and both groups exhibited significant increases in the scores of QOL-AD ($p < 0.05$). After 24 weeks of treatment, the scores of ADL were comparable between the two groups ($p > 0.05$), but the low-dose group had significantly higher QOL-AD scores compared to the high-dose group ($p < 0.05$), as shown in Table 4.

Table 1. Comparison of demographic and clinical baseline characteristics between low-dose and high-dose donepezil groups.

Characteristics	Low-dose group ($n = 45$)	High-dose group ($n = 61$)	χ^2/t	p
Gender, *n* (%)			0.126	0.722
Male	17 (37.78)	21 (34.43)		
Female	28 (62.22)	40 (65.57)		
Age, mean ± SD (years)	67.24 ± 8.14	65.48 ± 8.06	1.113	0.268
BMI, mean ± SD (kg/m^2)	25.23 ± 2.10	24.94 ± 2.18	0.692	0.490
Course of disease, mean ± SD (years)	3.93 ± 1.66	3.79 ± 1.82	0.426	0.671
Educational level, *n* (%)			0.006	0.938
Primary and below	21 (46.67)	28 (45.90)		
Junior high school and above	24 (53.33)	33 (54.10)		
Severity of AD, *n* (%)			0.172	0.679
Moderate	24 (53.33)	35 (57.38)		
Severe	21 (46.67)	26 (42.62)		
Smoking history, *n* (%)			0.171	0.680
Yes	18 (40.00)	22 (36.07)		
No	27 (60.00)	39 (63.93)		
Hypertension, *n* (%)			0.573	0.449
Yes	11 (24.44)	19 (31.15)		
No	34 (75.56)	42 (68.85)		
Diabetes mellitus, *n* (%)			0.558	0.455
Yes	9 (20.00)	16 (26.23)		
No	36 (80.00)	45 (73.77)		

Abbreviations: AD, Alzheimer's disease; BMI, body mass index; SD, standard deviation.

Table 2. Comparison of the scores of NPI and BEHAVE-AD between the low-dose and high-dose donepezil groups before and after treatment (mean ± SD, points).

Grouping	*n*	NPI		BEHAVE-AD	
		Before treatment	After treatment	Before treatment	After treatment
Low-dose group	45	37.18 ± 3.93	27.78 ± 3.51*	20.78 ± 3.48	11.91 ± 3.35*
High-dose group	61	37.05 ± 3.82	26.80 ± 3.57*	20.36 ± 3.46	11.10 ± 3.60*
t		0.169	1.400	0.612	1.183
p		0.866	0.165	0.542	0.239

Notes: * indicates a significant difference between data before and after 24 weeks of treatment within the same group ($p < 0.05$).
Abbreviations: BEHAVE-AD, behavioral pathology in Alzheimer's disease rating scale; NPI, neuropsychiatric inventory.

Comparison of Sleep Quality

No statistically significant differences between the low-dose and high-dose donepezil groups were observed in baseline levels of the score of PSQI($p > 0.05$).

Table 3. Comparison of the scores of MMSE and ADAS-Cog between the low-dose and high-dose donepezil groups before and after treatment (mean ± SD, points).

Grouping	*n*	MMSE		ADAS-Cog	
		Before treatment	After treatment	Before treatment	After treatment
Low-dose group	45	14.69 ± 2.79	21.91 ± 2.59*	44.71 ± 6.14	37.02 ± 5.61*
High-dose group	61	14.62 ± 2.78	22.67 ± 2.72*	43.57 ± 5.78	36.59 ± 6.05*
t		0.121	1.451	0.975	0.375
p		0.904	0.150	0.332	0.709

Notes: * indicates a significant difference between data before and after 24 weeks of treatment within the same group ($p < 0.05$).
Abbreviations: ADAS-Cog, Alzheimer's disease assessment scale-cognitive section; MMSE, Mini-Mental State Examination.

Table 4. Comparison of the scores of ADL and QOL-AD between the low-dose and high-dose donepezil groups before and after treatment (mean ± SD, points).

Grouping	*n*	ADL		QOL-AD	
		Before treatment	After treatment	Before treatment	After treatment
Low-dose group	45	47.20 ± 7.86	29.93 ± 4.18*	26.64 ± 3.97	32.82 ± 3.97*
High-dose group	61	47.61 ± 7.31	28.92 ± 3.80*	26.77 ± 4.40	30.28 ± 5.25*
t		0.274	1.304	0.152	2.724
p		0.784	0.195	0.880	0.008

Notes: * indicates a significant difference between data before and after 24 weeks of treatment within the same group ($p < 0.05$).
Abbreviations: ADL, activities of daily living; QOL-AD, quality of life-Alzheimer's disease.

After 24 weeks of treatment, the PSQI scores of patients in the high-dose group were significantly post-treatment compared to pre-treatment and to those in the low-dose group ($p < 0.05$). There was no statistically significant difference in PSQI scores before and after the low-dose treatment ($p > 0.05$), as shown in Table 5.

Table 5. Comparison of the score of PSQI between the low-dose and high-dose donepezil groups before and after treatment (mean ± SD, points).

Grouping	*n*	Before treatment	After treatment
Low-dose group	45	9.40 ± 1.85	9.42 ± 1.59
High-dose group	61	9.05 ± 2.12	10.15 ± 1.79*
t		0.889	2.164
p		0.376	0.033

Notes: * indicates a significant difference between data before and after 24 weeks of treatment within the same group ($p < 0.05$).
Abbreviation: PSQI, Pittsburgh sleep quality index.

Comparison of Adverse Reactions

During the treatment period, the total incidence of adverse reactions in the low-dose donepezil group was significantly lower than that in the high-dose donepezil group (11.11% vs. 27.87%, $p < 0.05$), as shown in Table 6.

Table 6. Comparison of the adverse reaction incidences between the low-dose and high-dose donepezil groups during treatment period [n (%)].

Grouping	*n*	Dizziness	Fatigue	Nausea	Diarrhea	Total
Low-dose group	45	1 (2.22)	1 (2.22)	2 (4.44)	1 (2.22)	5 (11.11)
High-dose group	61	3 (4.92)	5 (8.20)	6 (9.84)	3 (4.92)	17 (27.87)
χ^2						4.422
p						0.035

Discussion

The present study presents a comprehensive comparisons of the efficacy and safety parameters between low-dose and high-dose donepezil treatments, both combined with memantine, for treating moderate to severe AD. We found that after 24 weeks of treatment, there were no significant differences in NPI, BEHAVE-AD, MMSE, ADAS-Cog, and ADL scores between the two groups of patients. The QOL-AD score of the low-dose group was higher than that of the high-dose group, the PSQI score of the low-dose group was lower than that of the high-dose group, and the overall incidence of adverse reactions during the treatment period was lower in the low-dose group than in the high-dose group.

Traditionally, donepezil treatment for AD was believed to follow a dose-response relationship, where higher dose led to stronger AChE inhibition and better therapeutic effects (Lee et al, 2015). However, recent research challenges this assumption. In 2010, the USA Food and Drug Administration (FDA) approved a high-dose donepezil tablet at a recommended dose of 23 mg/day for the treatment of moderate to severe AD patients. However, Farlow et al (2010) revealed that the overall functional improvement achieved by a dose of 10 mg/day in patients with moderate to severe AD was comparable to that by a higher dose of 23 mg/day. Another research revealed that the efficacy endpoint of 23 mg/day donepezil was not superior to 10 mg/day in severe AD patients in Japan (Homma et al, 2016). In addition, Salloway et al (2012) found that patients with moderate to severe AD who received treatment with 23 mg/day donepezil had a higher overall incidence of adverse events during the treatment process and manifested poorer compliance with treatment. In light of these prior observations, we hypothesize that a higher dose of donepezil is not necessarily more effective in treating AD, especially when this drug is combined with other drugs.

In terms of clinical efficacy, in this study, different doses of donepezil combined with memantine showed no significant differences in improving the behavioral and psychological symptoms, cognitive function, and daily living abilities of patients with moderate to severe AD. Concerning the comparison between the two

donepezil doses of 5 mg/day and 10 mg/day, most studies have shown that the 10 mg/day donepezil is more therapeutically effective for AD. For example, Mori et al (2016) reported that 10 mg/day donepezil was superior to the lower dose of 5 mg/day in improving cognitive function of patients with Lewy body dementia. Nozawa et al (2009) found that increasing the dose of donepezil to 10 mg/day was conducive to delaying cognitive dysfunction in patients with advanced AD. A meta-analysis conducted by Sheikh and Ammar (2024) on the results of 18 dose-response studies of donepezil showed that a dose of 10 mg/day was more effective in improving patients' cognitive function. However, there are also a few studies that suggest that the effects of the two doses are equivalent. For instance, Dubois et al (2012) reported that both 5 mg/day and 10 mg/day donepezil doses are equivalently effective in improving cognitive function, ADL scores, and behavior in patients with Parkinson's dementia. It has also been revealed that increasing the dose of donepezil to 10 mg/day did not significantly improve the clinical symptoms in children and adolescents with seizures and attention deficit/hyperactivity disorder (Cubo et al, 2008). Similarly, Friedman et al (2002) also reported the same finding for patients with schizophrenia. In regard with interpreting the current set of findings in the context of AD, the author' hypothesis is as follows: Donepezil can increase acetylcholine levels, thereby improving cognitive impairment caused by the low acetylcholine levels. Memantine can increase the concentration of brain-derived neurotrophic factor in the marginal cortex, thereby improving cognitive function loss and learning disabilities. The combination of the two can exert a synergistic effect to enhance the therapeutic effect, but this effect has a maximal threshold, explaining why increasing the dose of donepezil does not necessarily amplify the therapeutic effect in a proportional fashion.

In terms of safety, in our study, the overall incidence of adverse events during treatment period was lower in the patients receiving low-dose donepezil, who also reported better quality of sleep and life, suggesting that the 5 mg/day dosage is safer and more acceptable by patients, a postulation consistent with the following research conclusions. Yang et al (2024) pointed out that most patients begin to experience adverse events within one month of receiving treatment with donepezil combined with memantine, and some patients continue to experience these adverse events after one year of treatment. Guo et al (2020) found that the acceptability of combination therapy of donepezil plus memantine by AD patients is lower than that the case of monotherapy. When ethnicity and regionality factors are taken into the context, Park et al (2021) found that the discontinuation rate of donepezil among AD patients in Asia is as high as 20.9%, with adverse events cited as the primary reason. A Japanese study by Otani et al (2024) also reported that multidrug treatments such as donepezil and memantine are significantly associated with an increased incidence of adverse events in AD patients, including changes in consciousness, decreased appetite, vomiting, and falls. Tan et al (2014) found that 10 mg/day donepezil can increase the risk of adverse events and treatment withdrawal. In a survey of 241 patients with moderate to severe AD, approximately 17.43% of the patients discontinued medication (donepezil) due to adverse events such as diarrhea, vomiting, and nausea (Jia et al, 2020). In a separate study, patients with

AD and Parkinson's dementia receiving low-dose donepezil treatment were found to be more likely to experience disorders in appetite and sleep compared to those receiving high-dose treatment (Bittner et al, 2023). Nozawa et al (2009) reported that compared with 10 mg/day donepezil, a long-term 5 mg/day dose can reduce the incidence of adverse events in advanced AD patients.

Several limitations in this investigation deserve our attention. First, our study was a single-center trial using a limited sample size. Secondly, the observation time of efficacy and safety in this study spanned only 24 weeks, which is relatively short. In fact, it is critical to acknowledge that a pre-defined research duration may impact the ultimate results as efficacy of drug administered at low doses may be satisfactory in the short term but may plateau in the long run. Also, the incidence of certain uncommon adverse reactions cannot be captured if a rather short observation duration is applied in clinical research. Besides, cost-benefit analysis was not performed in this study, since drug cost is also an important factor affecting clinical care decisions for patients with AD. In future studies, we will further validate the efficacy and safety of different doses of donepezil combined with memantine, including increasing the sample size and factoring in diversity for patient recruitment in terms of geographical regions, ethnic backgrounds, age groups, and disease severity so as to improve the reliability and universality of the study results. Furthermore, this study only investigated the efficacy and safety of different doses of donepezil combined with memantine treatment, but did not analyze its pharmacological mechanism; therefore, future research could consider investigating the pharmacological aspects of these two drugs. In addition, our further work in this line of research will consider an extension of the follow-up time and an expansion of the range of psychosocial indicators as well as drug-related adverse reactions in order to examine the long-term health status of these patients after treatment by evaluating a broader range of parameters.

Through this study, a comprehensive set of data was yield to facilitate the selection of drug treatment plans for patients with moderate to severe AD. While conducive for reducing the risk of adverse reactions caused by donepezil, the combination of low-dose donepezil combined with memantine is also cost-effective, alongside other benefits such as improved patient compliance, and avoidance of drug abuse and waste. Thus, this regimen offers a safe and feasible treatment plan for this particular patient group.

Conclusion

In conclusion, different doses of donepezil combined with memantine improve behavioral and psychological symptoms, cognitive function, and daily living abilities in patients with moderate to severe AD. However, low-dose donepezil has very minimal effect on sleep quality and causes a lower incidence of adverse reactions, which are the foundations for safeguarding their quality of life. Therefore, it is recommended to use donepezil at a dose of 5 mg/day in clinical practice for the treatment of AD.

Key Points

- Different doses of donepezil combined with memantine have an equivalent beneficial potential in improving behavioral and psychological symptoms, cognitive function, and daily living ability of patients with moderate to severe AD.
- Low-dose donepezil combined with memantine is more beneficial for improving the quality of life of patients with moderate to severe AD.
- Low-dose donepezil combined with memantine does not adversely impact sleep quality in patients with moderate to severe AD.
- The incidence of adverse reactions in patients with moderate to severe AD receiving low-dose donepezil combined with memantine is relatively low.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

HYT and SZ designed the research study and wrote the first draft. SZ and JXL performed the research. HYT and SZ analyzed the data. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The data of the subjects in this study were obtained from the Third People's Hospital of Fuyang and the study complied with the basic principles of medical ethics outlined in the Declaration of Helsinki. This study was approved by the Institutional Ethical Committee of the Third People's Hospital of Fuyang (2025-2-001-01). The family members of the patients in this study signed informed consent forms.

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Conflict of Interest

The authors declare no conflict of interest.

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