doi.org/10.36721/PJPS.2026.39.4.REG.15270.1

Comparative assessment of donepezil memantine and sodium oligomannate on cognitive decline and neuroinflammation in early Alzheimer's disease

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Abstract: **Background**: Early Alzheimer's disease (AD) treatments include donepezil, memantine and sodium oligomannate, but their comparative effects on cognitive decline and neuroinflammation are understudied. **Objectives**: This study compares three drugs' validity in improving two aspects in early AD patients. **Methods**: 132 early AD patients from XX Hospital (Jan 2022–Dec 2024) were retrospectively included. After exclusion, 126 patients were divided into 3 groups (42 each): Group A (donepezil), Group B (memantine), Group C (sodium oligomannate). Cognitive function was assessed using the Mini-Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale--Cognitive Subscale (ADAS-cog), the Activity of Daily Living Scale (ADL), the Montreal Cognitive Assessment Scale (MoCA), levels of inflammatory mediators, including Tumour Necrosis Factor-α (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8), neuronal marker levels including β-Amyloid (1-42) (Aβ42), Total tau protein (T-tau protein) and adverse reaction incidence. **Results**: After treatment, compared with Group A, Groups B/C had significantly higher MMSE, ADL, MoCA, Aβ42 (all $P<0.05$) and lower ADAS-cog, TNF-α, IL-6, IL-8, T-tau (all $P<0.05$); compared with Group B, Group C had no significant difference in MMSE, ADAS-cog, ADL, MoCA (all $P>0.05$), but higher Aβ42 and lower TNF-α, IL-6, IL-8, T-tau (all $P<0.05$); adverse reaction incidence did not differ significantly among the three groups ($P>0.05$). **Conclusion**: Memantine and sodium oligomannate outperform donepezil in improving cognitive function and neuroinflammation, with sodium oligomannate suggesting the best effect on neuroinflammation. This study provides a scientific basis for optimizing early AD medication.

Keywords: Donepezil; Early Alzheimer's disease; Memantine; Sodium oligomannate

Submitted on 23-09-2025 – Revised on 07-11-2025 – Accepted on 01-12-2025

INTRODUCTION

Neurological disorders stand as a key focus in today's medical research. Among them, Alzheimer's disease (AD) stands as a widespread neurodegenerative disorder. Its research, diagnosis and treatment are an important part of neurological medicine (Scheltens *et al*., 2021). AD is a continuous spectrum of diseases and the 2023 American Alzheimer's Association Clinical Diagnostic Criteria classifies the clinical staging of the AD spectrum of diseases into 7 stages, stage 0: asymptomatic, with a positive familial genetic predisposition; *stage 1*: asymptomatic, with evidence of biomarkers only; *stage 2*: transitional decline, with minor changes detected and minimal impact on daily functioning; *stage 3*: cognitive impairment affecting functioning at an early stage; *stage 4*: mildly dysfunctional dementia; *stage 5*: moderately dysfunctional dementia; and *stage 6*: dementia with severe functional impairment. Mild cognitive impairment (MCI) due to AD corresponds to some of the stages 2 and 3 of the clinical staging and is an early stage of the AD continuum of disease spectrum. The 2020 epidemiological survey pointed out that in China, approximately 38.77 million people aged 60 and over have MCI, while roughly 15.07 million live with dementia-of these, around 9.83 million have AD. The main clinical manifestations of MCI of AD origin are classified into the following three parts: 1. cognitive impairment, 2. mild impairment of complex instrumental daily living skills and 3. non-cognitive neuropsychiatric symptoms (Chen and Zhang, 2022).

AD has several key pathological hallmarks: β-amyloid (Aβ) builds up to form amyloid plaques; Microtubule-associated proteins (tau proteins) become abnormally phosphorylated, which in turn forms neurofibrillary tangles; there's also neuronal death, loss of synapses, granule vacuolar degeneration and glioblast proliferation (Rostagno, 2022, Knapskog *et al*., 2021). In people with Alzheimer's, the formation of Aβ plaques starts as much as 30 years before cognitive symptoms first appear. Findings show that Aβ deposition starts in the neocortex and gradually spreads to the limbic system and temporal lobe and finally reaches the brainstem and cerebellum. When AD is developing, tau protein phosphorylation accelerates and spurs tau protein buildup following Braak staging patterns, accompanied by hypometabolism, hippocampal volume reduction and cortical atrophy in the corresponding brain regions and cognitive deficits ultimately appear (Zhang *et al*., 2023). A 20-year longitudinal follow-up study of preclinical AD in China found that cerebrospinal fluid biomarkers, including Aβ42, Aβ42/40, phosphorylated tau 181 and neurofilament

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light chain, showed a specific pattern of changes over time before the onset of symptoms. Lately, more and more research has found that neuroinflammation is closely tied to how AD progresses (Monteiro *et al*., 2023). In fact, many believe that neuroinflammation counts among the causes of AD. The presence of an inflammatory response introduces more inflammatory cells and cellular molecules into the centre, which leads to apoptosis and further exacerbation of neuronal death and more deposition and aggregation of Aβ and tau proteins (Twarowski and Herbet, 2023). In addition, numerous studies indicate that neuroinflammation and the pathogenesis of AD are also associated with microglia dysfunction, abnormal neuroinflammatory mechanisms and altered neuronal dendritic morphology (Wang *et al*., 2023). The inflammatory response is a defensive reaction of the organism to external stimuli (e.g., infection, ischaemia, etc.) aimed at clearing pathogens and damaged tissues, while activating other biological processes in the circuit. Within the central nervous system, it shows that microglia and astrocytes act in the role of the principal categories of immune cells (Leng and Edison, 2021). Microglia are a class of immunocompetent leukocytes whose infiltration into the central nervous system requires activation in order to proliferate and serve to clear pathogens. When microglia become activated, they can trigger an inflammatory response. Also, astrocytes have a buffering effect on neurons, removing some ions and neurotransmitters when there is activity in the neuron, thus keeping the neural circuit stable. However, when the nervous system is injured or infected, astrocytes are also activated, triggering pathological processes such as neuroinflammation and keratinocyte hyperplasia (Thakur *et al*., 2023).

At present, in the clinic, drugs are mainly used to control the deterioration and development of this disease, donepezil belongs to the second generation of cholinesterase, the drug acts on the neurotransmitter receptor, produces inhibition of acetylcholine secretion and affects calcium ion channels (Adelman and Louis, 2023, Balazs *et al*., 2021). Meanwhile, it helps repair damaged areas of the nervous system to some extent, eases dementia symptoms and boosts patients' cognitive function—though it often causes side effects too. Memantine functions as an N-methyl-D-aspartate (NMDA) receptor antagonist, which makes glutamate release delayed as well as reduces toxic impairment to neurons by blocking NMDA receptors and subsequently calcium channels (Balazs *et al*., 2021). Sodium Oligomannate is a new drug, by remodelling the balance of intestinal flora, so that the metabolites of intestinal flora can be reduced to reduce Aβ buildup in the brain and the over-phosphorylation of tau proteins, which can produce an improvement in cognitive dysfunction. In addition to targeting and regulating ta disruption in the balance of the intestinal flora, sodium oligomannate can directly penetrate the blood-brain barrier, block the development of Aβ aggregates through the capture of Aβ by multisite, multifractal and multistate and cause the already formed Aβ aggregates to form. and depolymerisation of formed aggregates, thereby improving cognitive function in patients (He *et al*., 2024).

As a core biomarker for early pathological changes in AD, the level of Aβ42 in cerebrospinal fluid is significantly reduced due to abnormal aggregation and deposition, making it a crucial indicator for early screening and differential diagnosis of AD (Scheltens *et al*., 2021). Total-tau (T-tau) can reflect the extent of neuronal damage; its elevated level is one of the typical biological characteristics of AD, which not only aids in diagnosis to distinguish AD from other neurodegenerative diseases but also monitors disease progression to assess the degree of neuronal damage. As key pro-inflammatory cytokines, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are extensively released when glial cells are activated by pathological deposits in the AD brain. The elevated levels of these two cytokines not only reflect the severity of neuroinflammation, assist in monitoring disease course and evaluating disease risk but also provide an important direction for the development of anti-inflammatory therapeutic targets for AD. (Wang *et al*., 2023) The combined detection of these biomarkers can fully cover the core pathological characteristics and mechanisms of AD, significantly improve the accuracy of disease diagnosis and monitoring and facilitate mechanism research and therapeutic exploration.

In this study, we investigated the therapeutic effects of donepezil, memantine and sodium oligomannate in patients with early AD and analysed the comprehensive therapeutic effects mainly from the patients' cognitive function, inflammatory mediators, neuronal markers and the incidence of adverse reactions, It is expected to compare and evaluate the effects of donepezil, memantine and sodium oligomannate on cognitive decline and neuroinflammation in patients with early AD, to bring better results and personalized treatment plans for patients and it also provides theoretical value for promoting the construction of neurological discipline system and diversified pharmacological treatment.

MATERIALS AND METHODS

General information

This study retrospectively selected 132 patients with early AD admitted to Yichun People's Hospital from January 2022 to December 2024 with the aim of evaluating the effects of donepezil, memantine and sodium oligomannate in cognitive decline and neuroinflammation. As the experimental design flowchart in fig. 1 shows, all 132 patients were collected, 6 patients were excluded and finally a total of 126 cases were analysed, which split into three groups based on the treatment modalities recorded in electronic medical records, namely, Group A (donepezil

treatment), Group B (memantine treatment) and Group C (sodium oligomannate treatment), with 42 cases in each group.

Inclusion criteria

(1) Meet the diagnostic criteria for AD in the Diagnostic and Treatment Criteria for Alzheimer's Disease (2020 Edition) (Tian *et al*., 2021) published by the Chinese Journal of Geriatrics and written by Tian Jinzhou *et al*. (2) Diagnosed with early-stage AD by neurological examination, physical examination and examination of mental status; (3) Age > 18 years old; and (4) Clinical data and relevant examinations were complete.

Exclusion criteria

(1) Combined with intracranial organic diseases; (2) Combined with other psychiatric diseases; (3) Recently applied psychotropic drug treatment; (4) Family genetic history of psychiatric diseases; (5) Accompanied by heart, lung and other organ diseases; (6) Patients with allergy to drugs and the existence of other drug contraindications (Bago Rozankovic *et al*., 2021).

Treatment modes

Early-stage AD patients were grouped into three based on their treatment approaches and these 3 groups were treated with conventional nursing care with different medication regimens.

Group A patients were given Donepezil hydrochloride tablets (Weicai Pharmaceutical Co., Ltd.; State Pharmaceutical Certificate H20070181; Specification: 10 mg×7 tablets) at a dose of 5 mg/d orally and the drug level was gradually increased to 10 mg/d after a 2-week interval for a continuous period of treatment for 12 weeks.

Group B patients were given Memantine hydrochloride tablets (Zhuhai United Laboratories Co., Ltd.; State Drug Permit H20130086; Specification: 10 mg×24 tablets) at a dose of 20 mg/d once/d orally for 12 weeks (Buccellato *et al*., 2023).

Group C patients were given Sodium oligomannate capsules (Shanghai Green Valley Pharmaceutical Co., Ltd.; State Pharmaceutical Standard H20190031; Specification: 150 mg×42 tablets) at a dose of 450 mg/dose, 2 times/d, orally, for 12 weeks (Xiao *et al*., 2021).

Observation indicators

Patient cognitive function scale

Mini-Mental State Examination (MMSE) scale is one of the most influential standardised intellectual status screening tools and its use as a cognitive impairment screening method can work for screening AD in a simple and easy way. It includes sense of direction, memory, attention and calculation abilities, recall skills and language proficiency with 11 entries and a total score of 30, 27-30: normal, 21-26: mild cognitive impairment, 10-20: moderate cognitive impairment and 0-9: severe cognitive impairment (Jia *et al*., 2021).

Montreal Cognitive Assessment (MoCA) scale is chiefly used to screen patients with MCI and includes 11 examination items in 8 cognitive domains, including attention and concentration, executive function, memory, language, visual-structural skills, abstract thinking, calculation and orientation. The total score is 30 points, with≥26 points being normal (Jia *et al*., 2021).

Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) (Yu *et al*., 2021) serves to evaluate a variety of cognitive functions including word recall tasks, naming objects or fingers, commands, structured practice, intentional practice, orientation, word recognition tasks, recalling quiz instructions, verbal language skills, word finding difficulties, verbal language comprehension and attention. It has 12 items, amounting to 70 in total, with higher scores indicating more serious cognitive problems.

Activities of Daily Living Scale (ADL) is mainly used to assess the subject's daily living ability, which helps in the diagnosis of dementia and it has 14 items, mainly checking the ability of somatic self-care and instrumental daily living ability. Its rating items include using public vehicles, walking, cooking, doing housework, taking medication, eating, dressing, combing hair, brushing teeth, doing laundry, bathing, shopping, going to the toilet regularly, making phone calls and handling one's own money. The assessment criteria are divided into 4 levels, with a total score of 100. A score of 100 indicates that the ability to perform activities of daily living is good and does not need to rely on others; a score of > 60 is assessed as good, which indicates that there is a mild degree of dysfunction, but the basic daily life is basically self-care; a score of 60-41 indicates that there is moderate dysfunction and a certain degree of help is needed in daily life; a score of 40-21 indicates that there is a severe degree of dysfunction and the need to rely on others is obvious in daily life; A score of < 20 indicates total disability and complete dependence on others for daily living (Yan *et al*., 2023).

Inflammatory mediators like TNF-α: IL-6: interleukin-8 (IL-8) and neuronal marker Aβ42: T-tau protein

procoagulant tubes 5 mL of fasting venous blood of the patient was collected as test samples and after centrifugation for 10 min at 3000 r/min using Beckman Microfuge® 20R centrifuge, the serum fraction was separated and the serum was tested for TNF-α, IL-6, IL-8 and Aβ42, T-tau protein using the enzyme linked immunoassay kits of Shanghai Beyotime Biotechnology Co. Immunoassay Kit Beyotime PT518/PI330/PI640/PA082 to detect the concentrations of TNF-α, IL-6, IL-8 and Aβ42 in serum and Huamei Biological Enzyme-Linked Immunoassay Kit CSB-E12011h to detect T-tau protein.

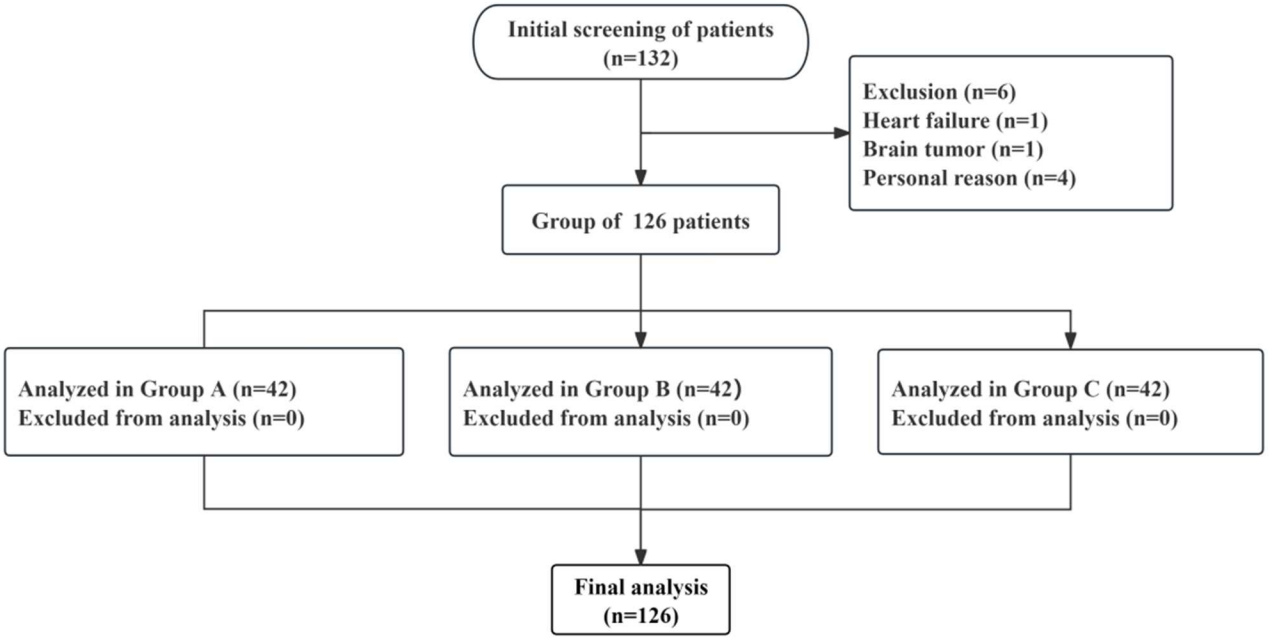

Fig. 1: Experimental flow design diagram (the flowchart outlines the patient recruitment (n=132), inclusion (n=130) and exclusion (n=2) criteria, treatment allocation, loss of follow-up (n=4) and analysis (n=126). The final Group A/B/C each have 42 patients)

Table 1: Baseline characteristics [$\bar{x}\pm s$, *n* (%)]

Variables	Group A (n=42)	Group B (n=42)	Group C (n=42)	*P*	Effect size (η^2 /Cramer' s V)
Age (years)	62.83±10.45	61.31±11.50	59.69±10.07	0.406	0.015
BMI(kg/m^2)	22.73±1.70	22.68±1.77	22.67±1.82	0.986	<0.001
Gender					
Male	20	21	22	0.909	0.039
Female	22	21	20		
Clinical stage					
Phase 2	10	11	13	0.754	0.067
Phase 3	32	31	29		
HR(bpm)	77.05±6.98	73.83±9.03	76.67±8.74	0.157	0.030
HAMD score	3.48±1.44	3.86±1.39	3.90±1.28	0.295	0.020
HIS	1.74±1.15	1.83±1.12	1.93±1.13	0.745	0.005
Course of disease (years)	3.29±1.04	3.17±0.99	3.26±1.01	0.851	0.003

Note: BMI: Body Mass Index; HR: Heart Rate; HAMD: Hamilton Depression Scale. HIS: Hachinski Ischemia Score.

All detections were conducted in the Clinical Laboratory Department of our hospital. This department has obtained ISO 15189 accreditation, is equipped with corresponding professional testing instruments and operates in accordance with standardized procedures by certified technicians. Additionally, it regularly passes national and provincial external quality assessments. The detection methods have undergone verification of precision, accuracy, linear range and specificity in line with relevant standards. The intra-assay coefficient of variation (CV) is < 5%, the inter-assay CV is < 8% and the correlation coefficient when compared with the standard method is > 0.95. Intra-assay variability was evaluated through 10 repeated measurements in the same batch; the intra-assay CV of each indicator ranges from 2.1% to 4.5%, which falls within the acceptable range of low levels. During data analysis, outlier testing was performed to ensure the reliability of the results.

Incidence of adverse reactions during treatment

In this study, donepezil, memantine and sodium oligomannate were used to treat patients with early AD and adverse reactions included nausea, drowsiness, headache and diarrhoea (Chen *et al*., 2024).

The formula for calculating the incidence of adverse reactions is shown as follows:
Adverse reaction incidence rate = (number of patients with adverse reactions/total number of patients in each group) * 100%

Clinical stage
Stage 1: MCI Stage: Cognitive function scores, measured by scales such as MMSE and MoCA, are lower than the normal level of peers, but do not meet the diagnostic criteria for dementia. Meanwhile, other etiologies causing cognitive decline (e.g., cerebrovascular disease, Parkinson's disease, depression) must be excluded.
Stage 2: Mild AD Stage: Patients meet the core diagnostic criteria for AD dementia. Cognitive impairment affects their social or occupational functions, but does not reach a state of severe dependence. (Tian *et al*., 2021)

Sample size calculation methods
The sample size was based on analyses conducted using the G*Power 3.1.9.7, with the samples being calculated based on the cognitive dysfunction score MMSE as an outcome. Referring to previous studies (e.g., Ida (Mohebpour *et al*., 2022) on the neuropathological validation of AD questionnaires where an effect size of 0.58 was considered clinically significant, 2022), based on a one-way Analysis of Variance (ANOVA) with an alpha level of 0.05 (bilaterally) and a statistical efficacy of 85%, we calculated that a sample size of 36 patients was required for each group. Considering the potential uncertainty, the sample size chosen for analysis in this study was 42 patients in each group and we believe that the sample size of this study allows for reliable conclusions to be drawn.

Statistical analysis
We analyzed the data using SPSS 28.0 software. For data that followed a normal distribution—like MMSE scores, ADAS-cog scores, ADL scores, MoCA scores, etc., intergroup comparisons were tested using one-way ANOVA and are presented as $\bar{x}\pm s$. For categorical count data such as adverse reactions, intergroup comparisons were tested using the chi-square test and presented using *n*(%). All statistical tests were two-sided, with $P<0.05$ indicating a statistically significant difference.

RESULTS

Comparison of baseline data among the three groups
In this retrospective cohort study, We statistically analyzed patients' baseline characteristics (Table 1), age (P=0.406), body mass index (BMI) (P=0.986), gender (P=0.909), clinical stage (P=0.754), heart rate (HR) (P=0.157), Hamilton Depression Scale (HAMD) scores (P=0.295), Hachinski Ischemic Index (HIS) (P=0.745) and course of disease (P=0.851) suggested no significant difference between the three groups, which means the patients in these groups were comparable before treatment.

Comparison of MMSE scores and ADAS-cog scores among the three groups of patients
As can be seen in figs. 2 and 3, before treatment, there was no significant difference between the three groups of patients in terms of MMSE scores (P=0.992). When the three groups of patients were compared separately after treatment, compared with Group A, MMSE scores were significantly higher in Group B (P=0.022) and Group C (P=0.009) and ADAS-cog scores were significantly lower in Group B (P=0.021) and Group C (P=0.022), with no significant difference between Group B (P=0.752) compared to Group C (P=0.978).

Comparison of ADL scores among the three groups of patients
The ADL scores of the three groups of patients were compared and the results are suggested in fig. 4. There was no statistically significant difference in the ADL scores of the three groups of patients before the treatment (P=0.991). After treatment, Group B (P=0.009) and Group C (P=0.004) suggested notably higher ADL scores compared to Group A, with no notable difference between Group B and Group C (P=0.753).

Comparison of MoCA scores among the three groups of patients
As can be seen in fig. 5, there was no significant difference in the MoCA scores of the three groups of patients before treatment (P=0.744), After treatment, Group B (P=0.019) and Group C (P=0.041) suggested significantly higher MoCA scores compared with Group A after treatment. Group B and Group C didn't differ in any statistically meaningful way (P=0.754).

Comparison of the amounts of inflammatory mediators TNF-α: IL-6 and IL-8 among the three groups of patients
As can be seen in figs. 6, 7 and 8, before treatment, no significant difference was observed in the levels of TNF-α, IL-6 and IL-8 among the three groups (P=0.991). After treatment, compared with the levels of TNF-α (P=0.041), IL-6(P=0.007) and IL-8(P=0.048) in Group A, the amounts of these three inflammatory mediators were significantly lower in Group B and also had these three inflammatory mediators reduced in Group C (all $P<0.001$). As opposed to Group B, where these three inflammatory mediators were significantly lower in Group C (P=0.016; P=0.013; P=0.044).

Comparison of Aβ42 and T-tau among the three groups of patients
As can be seen in figs. 9 and 10, before treatment, no notable difference emerged in the concentrations of Aβ42 and T-tau among the three groups (P=0.308; P=0.817). When the three groups of patients were compared separately after treatment, Group B (P=0.022) and Group C ($P<0.001$) exhibited significantly higher Aβ42 concentrations compared with Group A Aβ42 and both T-

tau concentrations were reduced (P=0.041; P<0.001); and significantly higher concentrations of Group C Aβ42 compared with Group B (P=0.048); T-tau concentration was significantly lower (P=0.016).

Comparison of the incidence of adverse reactions

Table 2 suggested that no significant difference in the incidence of adverse reactions between donepezil, memantine and sodium oligomannate in the treatment of early AD patients (P=0.86).

DISCUSSION

As the most common cognitive impairment disorder, AD is characterized by insidious onset, which makes early diagnosis difficult. The cognitive decline, neuropsychiatric symptoms and reduced activities of daily living caused by disease progression not only lead to gradual disability and eventual death from complications in patients, but also impose a heavy care burden and economic pressure on their families, while resulting in significant social cost consumption (Testo *et al*., 2025). Therefore, achieving early diagnosis and precise intervention of AD is crucial for slowing disease progression and maintaining patients' quality of life, which also serves as the core starting point for this study to focus on comparing the efficacy of drugs for early-stage AD.

This study quantitatively evaluated the effects of donepezil, memantine and sodium oligomannate on improving cognitive function in patients with early-stage AD from multiple dimensions using four scales: MMSE, MoCA, ADL and ADAS-cog. The results suggested that all three groups of patients exhibited significant cognitive improvement after treatment.(Kwon *et al*., 2024) The increases in MMSE and MoCA scores intuitively reflected enhancements in patients' overall cognitive ability and specific cognitive domains; this improvement can support patients in maintaining basic social interactions and simple decision-making capabilities. The elevation in ADL scores indicated the recovery of patients' ability to perform activities of daily living independently, which can reduce their reliance on family care and significantly improve their quality of life. Additionally, the decrease in ADAS-cog scores further confirmed the clinical superior effects of the three drugs in alleviating the core symptoms of dementia. In terms of the magnitude of improvement and stratified differences, the changes in the aforementioned scale scores in the memantine group and sodium oligomannate group were significantly superior to those in the donepezil group, suggesting that the latter two drugs have greater advantages in the intervention of cognitive function in early-stage AD. This result aligns with the conclusions of previous studies: a prospective study (Bago Rozankovic *et al*., 2021) confirmed that memantine and donepezil suggested better results in treating neuropsychiatric symptoms in AD patients with good safety, while a study (Zhang *et al*., 2022) pointed out that the efficacy of sodium oligomannate in treating AD is non-inferior to, or even superior to, that of donepezil. Notably, there was no significant difference in cognitive function scale scores between the memantine group and the sodium oligomannate group, indicating that the two drugs have similar clinical efficacy in improving the overall cognitive performance and daily living abilities of patients with early-stage AD and both can meet the core needs of early intervention. This equivalence may be related to the pathological characteristics of early-stage AD: during this phase, neuronal damage has not yet entered a period of rapid progression. The mechanism by which memantine inhibits excitotoxic damage by regulating NMDA receptor activity, together with the unique action pathway of sodium oligomannate, can exert comparable cognitive protective effects.

Clinical studies have clearly established a bidirectional driving relationship between neuroinflammation and the pathological progression of AD. Pathological changes in AD can induce the release of inflammatory factors, triggering local inflammatory responses in the brain, which in turn lead to neuronal metabolic disorders and loss, ultimately manifesting as progressive cognitive decline (Singh, 2022, Dhapola *et al*., 2021). Analysis of three core proinflammatory factors (TNF-α, IL-6 and IL-8) in this study suggested that all three drugs could reduce inflammatory responses, but there were significant differences in the magnitude of improvement. Among them, the memantine group exhibited the most significant reduction in proinflammatory factor levels, demonstrating the optimal neuroinflammation-regulating efficacy. From a mechanistic perspective, the anti-inflammatory pathways of different drugs are fundamentally distinct, Donepezil indirectly alleviates neuroinflammation by improving mitophagy (Youn *et al*., 2024) and its regulatory effect on inflammatory factors is relatively mild, resulting in a limited reduction in proinflammatory factors. Memantine primarily blocks endogenous NMDA receptors, protects neurons by regulating Ca^{2+} homeostasis, thereby inhibiting excessive activation of neuroglial cells and reducing the release of inflammatory factors (Yu *et al*., 2023). As a targeted anti-neuroinflammatory drug, sodium oligomannate can block the transmission of peripheral inflammation to the central nervous system by regulating the balance of intestinal flora, achieving a more direct and efficient neuroinflammation intervention effect (Thangwaritorn *et al*., 2024). This difference in efficacy is closely related to the pathological roles of the three inflammatory factors: TNF-α can directly or indirectly induce neuronal death (Dhapola *et al*., 2021); IL-6 is involved in neuronal pathology and senile plaque formation in the AD brain and its overexpression is positively correlated with the inflammatory process; IL-8 exacerbates local inflammatory responses by recruiting leukocytes (Wei *et al*., 2023).

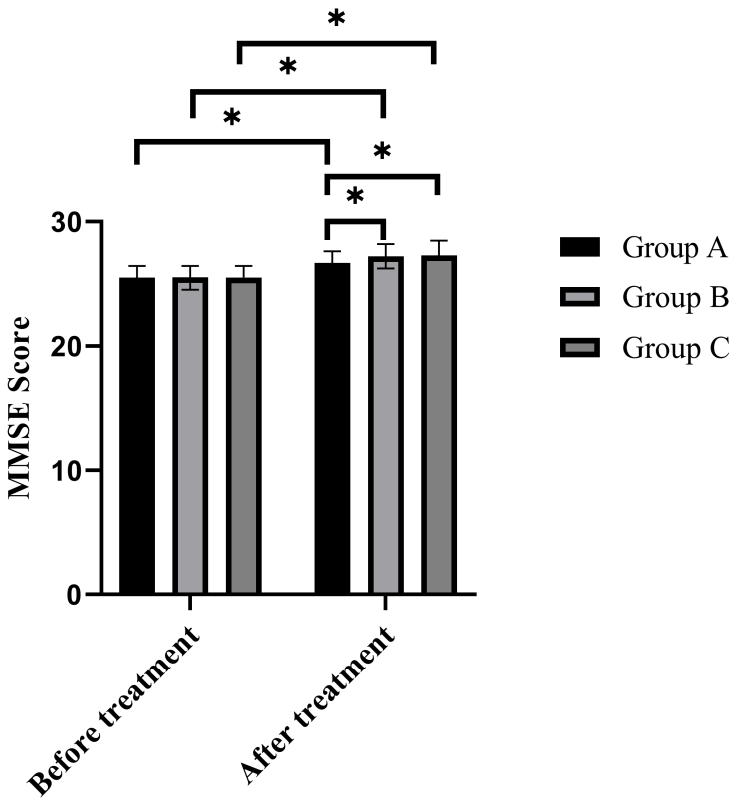

Fig. 2: Comparison of MMSE scores of patients. Note: $^{*}P<0.05$; MMSE: Mini-Mental State Examination Scale.

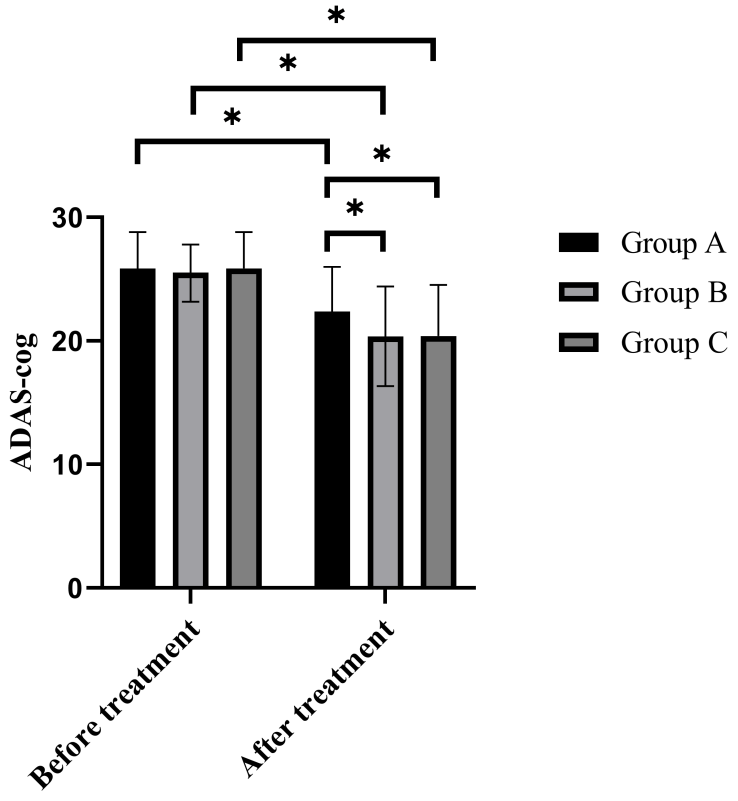

Fig. 3: Comparison of ADAS-cog scores of patients. Note: $^{*}P<0.05$; ADAS-cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale.

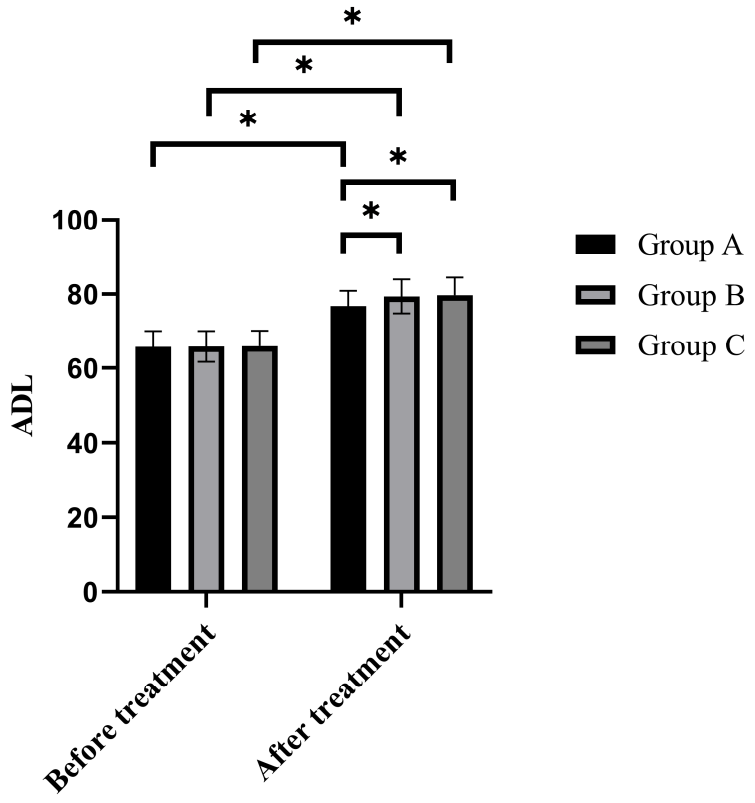

Fig. 4: Comparison of ADL scores of patients. Note: $^{*}P<0.05$; ADL: Activities of Daily Living Scale.

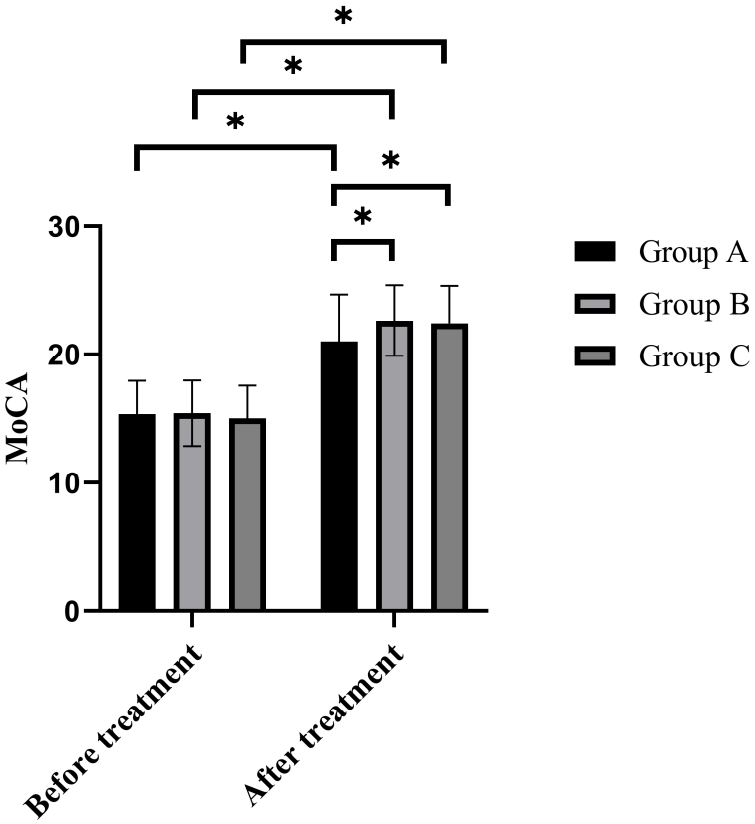

Fig. 5: Comparison of MoCA scores of patients. Note: $^{*}P<0.05$; MoCA: Montreal Cognitive Assessment Scale.

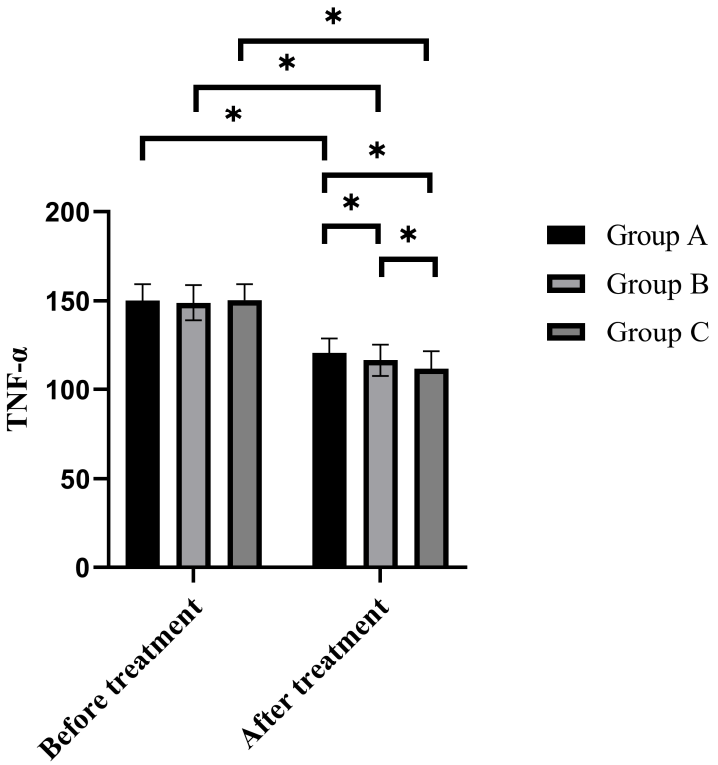

Fig. 6: Comparison of TNF- α of patients. Note: $^{*}P<0.05$; TNF-α: Tumor Necrosis Factor-α.

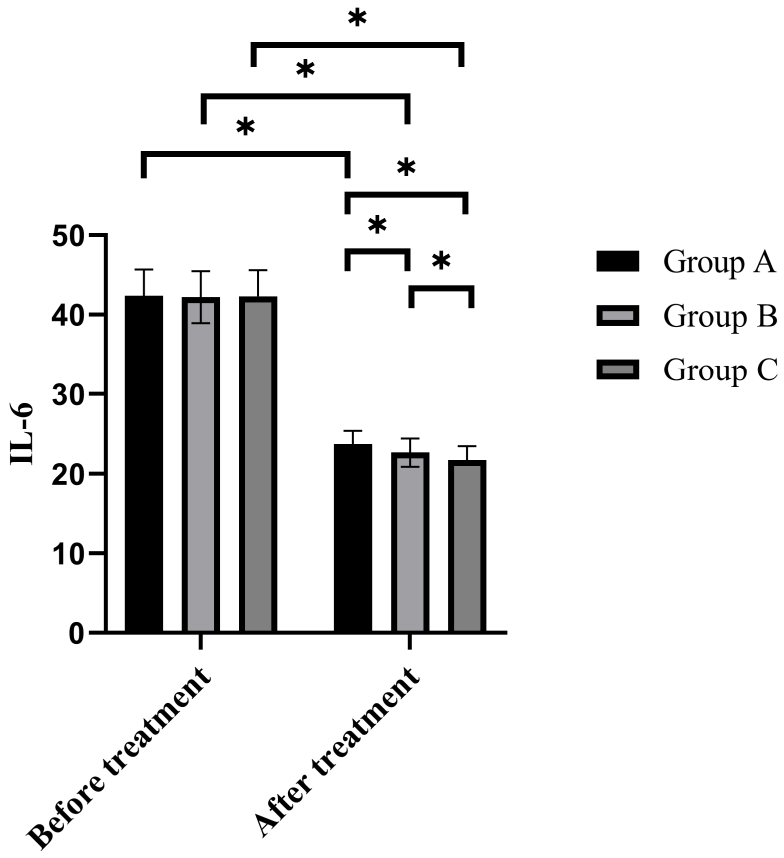

Fig. 7: Comparison of IL-6 of patients. Note: $^{*}P<0.05$; IL-6: Interleukin-6.

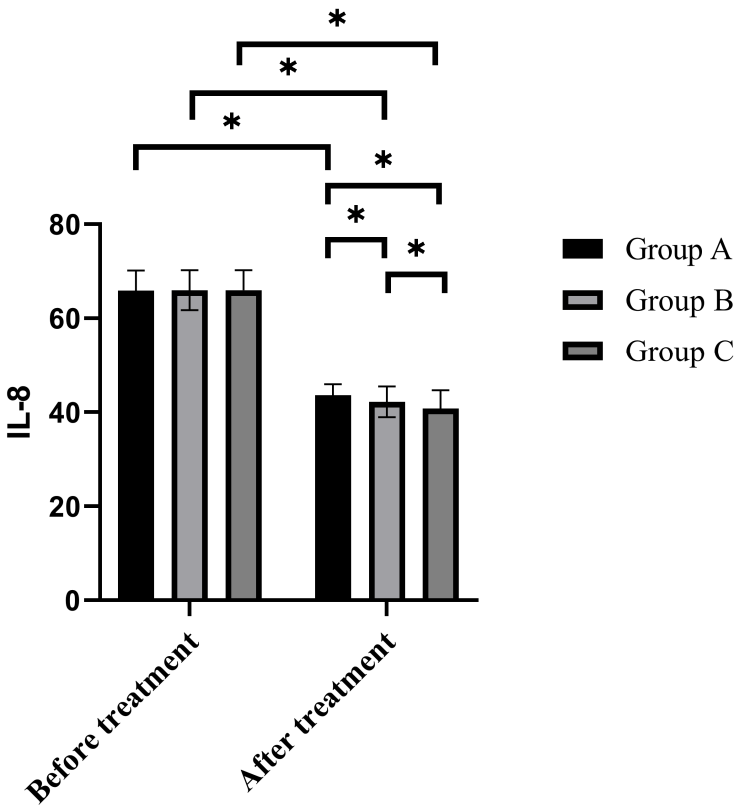

Fig. 8: Comparison of IL-8 of patients. Note: *P<0.05; IL-8: Interleukin-8.

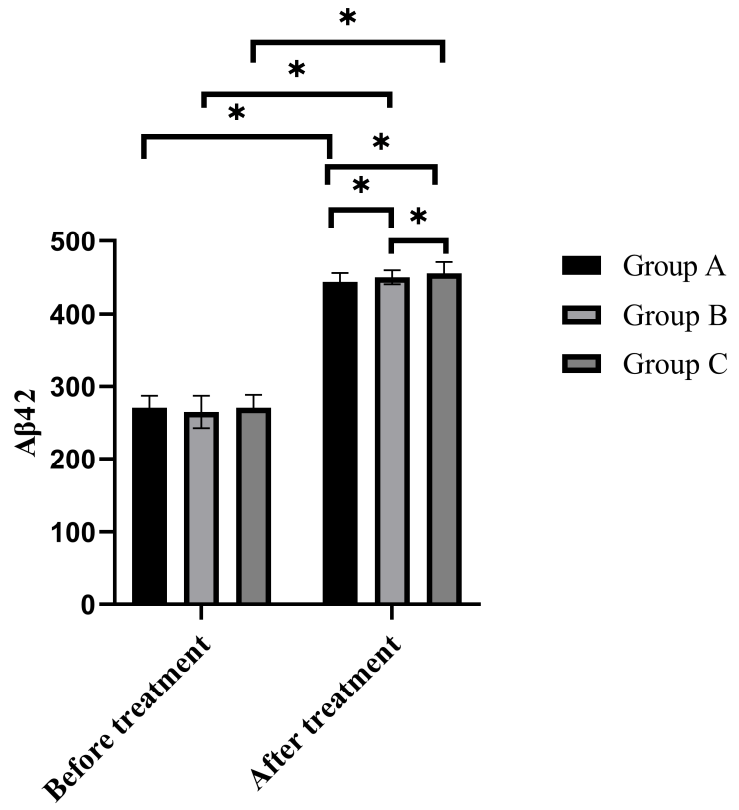

Fig. 9: Comparison of A β of patients. Note: *P<0.05; Aβ42: β-Amyloid (1-42).

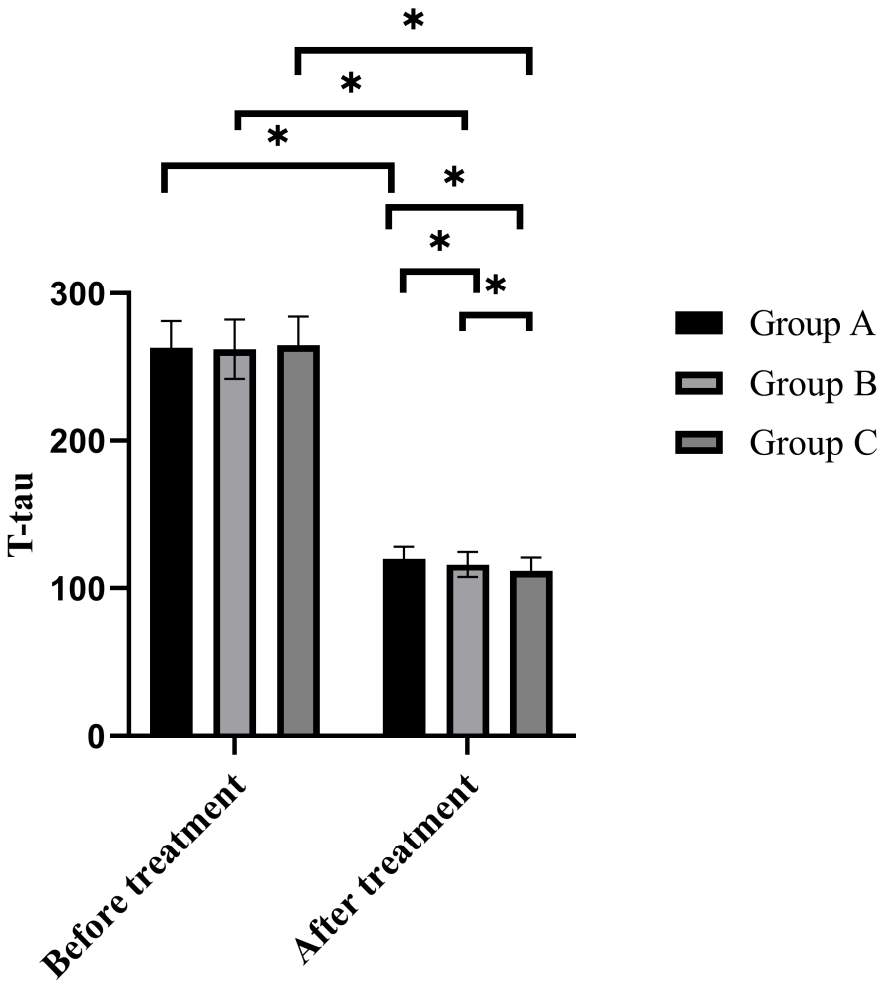

Fig. 10: Comparison of T-tau of patients. Note: $^{*}P<0.05$; T-tau: Total Tau Protein.

Table 2: Comparison of adverse reactions of patients [*n* (%)]

Variables	Adverse reactions [*n* (%)]				
	Nausea	Drowsiness	Headache	Diarrhea	Total
Group A (n=42)	0	2	0	1	3 (7.1)
Group B (n=42)	1	0	1	0	2 (4.8)
Group C (n=42)	0	0	2	0	2 (4.8)
P			0.86		
Effect size (Cramer' s V)			0.049		

The potent inhibitory effect of sodium oligomannate on all three factors implies that it can more comprehensively block inflammation-mediated pathological damage, providing a solid pathological basis for the improvement of cognitive function.

Neuroinflammation can accelerate the progression of core AD pathology by affecting Aβ metabolic clearance and tau protein phosphorylation (Chen and Yu, 2023). In this study, all three drugs significantly increased serum Aβ42 concentration and decreased T-tau concentration, but the magnitude of these changes in the sodium oligomannate group was significantly superior to that in the other two groups, suggesting that sodium oligomannate has unique advantages in regulating the core pathological processes of AD. The increase in Aβ42 levels may be related to the drugs promoting the clearance of Aβ deposits in the brain or reducing their abnormal aggregation. As noted by Skylynn (Thangwaritorn *et al*., 2024), sodium oligomannate can inhibit Aβ aggregation by disrupting histidine-mediated electrostatic interactions between Aβ molecules; donepezil has also been confirmed to reduce the formation of Aβ aggregates (Siddique *et al*., 2024). The decrease in T-tau levels directly reflects the alleviation of neuronal damage, preventing the loss of cytoskeletal function and reduced microtubule stability caused by

excessive tau phosphorylation. This effect complements sodium oligomannate's mechanism of inhibiting neuroinflammation through intestinal flora regulation (Kulkarni *et al*., 2025). From a clinical perspective, such in-depth improvements at the pathological level not only provide biological evidence for the cognitive improvement effects of the drugs but also indicate potential long-term benefits. For patients with early-stage AD, timely blocking of Aβ aggregation and abnormal tau phosphorylation is expected to slow the progression of neurofibrillary tangles and amyloid plaques, prolong the period of mild symptoms in patients and prevent them from rapidly entering the disabled stage. This holds significant practical value for reducing long-term care costs and maintaining patients' quality of life.

There was no significant difference in the incidence of adverse events among the three groups of patients, indicating that donepezil, memantine and sodium oligomannate all had good tolerability in patients with early-stage AD, with no serious safety risks observed. This result provides an important safety guarantee for clinical medication selection; particularly for patients with early-stage AD who have concurrent mild underlying diseases, all three drugs exhibit high feasibility for clinical use (Wei *et al*., 2023). It is worth emphasizing that while sodium oligomannate demonstrates superior efficacy in regulating neuroinflammation and improving pathological conditions, it does not increase the risk of adverse events. This further highlights its comprehensive advantages in the treatment of early-stage AD, offering a more ideal alternative for patients who have poor response to or intolerance of donepezil and also providing a scientific basis for the formulation of individualized clinical medication regimens (Sun *et al*., 2021).

Study limitations

This study is a retrospective clinical controlled study. Although the collection and analysis of research data were conducted by researchers who did not participate in the treatment of these patients, which ensured the objectivity of the study to a certain extent, retrospective studies themselves have inherent limitations; at the same time, there are many deficiencies in the study design and implementation process, specifically manifested as follows: the samples were only obtained from 126 patients admitted to this hospital—while this meets the basic statistical requirements, the sample size is relatively small and does not cover populations with different economic levels and cultural backgrounds, so selection bias may exist and the generalizability and representativeness of the study results will also be affected to a certain extent; the cognitive assessment scale has obvious potential biases, as its measurement tools and assessment methods are subjective, factors such as the assessor's experience and professional level will affect judgments and patients' self-reported data are easily interfered by the social desirability effect, leading to assessment results that cannot truly reflect patients' cognitive status; the study lacks a scientific randomized design and implementation of blinding—failure to randomly group patients may lead to unbalanced baseline characteristics among groups and both researchers and patients being aware of the treatment plan can easily introduce subjective factors to interfere, affecting the objectivity of judging treatment effects; in addition, the study did not conduct detailed adherence tracking, making it impossible to confirm whether patients strictly followed the doctor's advice for treatment and the potential variability of biochemical tests was not controlled, as factors such as the accuracy of testing instruments and sample processing conditions may all cause fluctuations in test results; in terms of the study cycle and effect, the observation period of this study was only 12 weeks and no long-term follow-up was carried out, which not only made it impossible to understand the long-term efficacy of the drugs and the disease progression of AD patients, but also failed to clarify the potential medication risks that may occur during the long-term medication of patients; moreover, as AD is a chronic neurodegenerative disease, its pathological changes and significant fluctuations in indicators require accumulation over a long course of the disease, making it difficult to observe strong effects in the short term, which is confirmed by the fact that the effect size of all observation indicators in this study is less than 0.2. Based on this, multicenter, large-sample prospective randomized controlled studies can be carried out in the future, expanding the study sample size and including patients from different regions and with different life backgrounds to improve the generalizability and reliability of the study results; at the same time, long-term follow-up should be conducted to explore the impact of different drugs on AD patients in different disease progression cycles and the effect of long-term medication and further in-depth research can also be carried out on the effect of combining two or three of the above three drugs to provide a more solid theoretical basis for clinical application.

CONCLUSION

In summary, this study may suggest that donepezil, memantine and sodium oligomannate can all improve cognitive decline and neuroinflammation in AD's early phases, with good efficacy and safety and promote the recovery of patients with significant significance. Sodium oligomannate exhibited superior effects in improving neuroinflammation, which provides scientific basis for the clinical optimisation of drug regimen.

Acknowledgment

Not applicable.

Authors' contributions

Xinbo Deng: Developed and planned the study, performed experiments and interpreted results. Edited and refined the manuscript with a focus on critical intellectual contributions.

Ying Zeng: Participated in collecting, assessing and interpreting the data. Made significant contributions to date interpretation and manuscript preparation.
Dan Ding: Provided substantial intellectual input during the drafting and revision of the manuscript.

Funding
There was no funding.

Data availability statement
All data generated or analysed during this study are included in this published article.

Ethic approval
The clinical study followed the Declaration of Helsinki (World Medical, 2025) and other relevant ethical regulations and was reviewed and approved by Yichun People's Hospital Ethics Committee (No. 2022(ky)-0065), which detailed the study's purpose, the process and the potential risks to the subjects or their proxies and obtained written informed consent.

Conflicts of interest
The authors declare that they have no conflicts of interest.

Consent to participate
We secured a signed informed consent form from every participant.

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