Journal of Clinical and Nursing Research, 2024, Volume 8, Issue 10
http://ojs.bbwpublisher.com/index.php/JCNR
Online ISSN: 2208-3693
Print ISSN: 2208-3685

Clinical Study on the Treatment of Senile Alzheimer's Dementia with Sodium Oligomannate Combined with Memantine Hydrochloride

Jian Zhao*, Xi Li, Xuelian Jia, Ganke Gao

Comprehensive Internal Medicine Outpatient Department, Second People's Hospital of Fujian University of Traditional Chinese Medicine, Fuzhou 350000, Fujian Province, China

Corresponding author: Jian Zhao, 979838691@qq.com

Abstract: *Objective:* To analyze the clinical effects of sodium oligomannate combined with memantine hydrochloride in the treatment of senile Alzheimer's dementia. *Methods:* Sixty-eight cases of Alzheimer's dementia treated at the Second People's Hospital of Fujian University of Traditional Chinese Medicine from March 2020 to March 2022 were selected as the study subjects. The patients were divided into two groups based on different treatment methods: the control group (treated with memantine hydrochloride, 34 cases) and the treatment group (treated with sodium oligomannate + memantine hydrochloride, 34 cases). Cognitive function, activities of daily living, neurotransmitters, serum intestinal flora metabolic markers, inflammatory factors, neurotrophic factors, and adverse reactions were compared between the two groups. *Results:* The treatment group showed better cognitive function, quality of life scores, and levels of relevant metabolic markers in the body compared to the control group, with statistically significant differences ($P < 0.05$). The incidence of adverse reactions between the two groups (treatment group: 2%; control group: 4%) was not statistically significant ($\chi^2 = 0.731$, $P = 0.393$). *Conclusion:* Sodium oligomannate combined with memantine hydrochloride has better efficacy than the control group for treating senile Alzheimer's dementia. It significantly improves and restores cognitive function and daily living abilities, benefits neurotransmitter secretion and internal regulation, upregulates the expression of neurotrophic factors, and has fewer adverse reactions, making it a treatment worthy of further clinical promotion and application.

Keywords: Senile Alzheimer's dementia; Sodium oligomannate; Memantine hydrochloride; Cognitive function; Treatment

Online publication: October 28, 2024

1. Introduction

Alzheimer's dementia (AD) is a neurodegenerative disease, commonly seen in the elderly, clinically characterized by memory loss, aphasia, and in severe cases, behavioral abnormalities, sleep disorders, and personality changes, which significantly impact daily life [1]. For elderly patients with Alzheimer's dementia,

drug therapy is the first-line clinical approach. Memantine hydrochloride is often recommended by doctors as it can prevent the influx of calcium ions through the N-methyl-D-aspartate (NMDA) channel and inhibit the excitotoxicity of glutamate, thereby improving psychiatric symptoms [2]. However, the efficacy of single-drug treatment is limited, and adverse reactions are common, making combination therapy a focal point of clinical research [3,4]. Sodium oligomannate is a commonly used drug for regulating brain-gut axis function, capable of modulating the intestinal flora, reducing inflammation in the brain, and improving cognitive function, making it a novel treatment for Alzheimer's dementia [5]. Studies have found that sodium oligomannate has the same efficacy as donepezil and shows good safety [6]. However, there are currently no studies reporting on the combination of sodium oligomannate and memantine hydrochloride for Alzheimer's dementia, and the clinical value of their combined use remains unclear. Therefore, this study aims to investigate the effects of sodium oligomannate combined with memantine hydrochloride on 68 elderly patients with Alzheimer's dementia treated at our hospital between March 2020 and March 2022, providing a potential alternative or upgraded therapy for the clinical treatment of AD patients.

2. Materials and methods

2.1. Baseline comparison of demographic and imaging characteristics between the two groups

A total of 68 elderly patients with Alzheimer's dementia who were treated at the Second People's Hospital of Fujian University of Traditional Chinese Medicine from March 2020 to March 2022 were selected as study subjects. According to the different treatment methods, they were divided into a control group (treated with memantine hydrochloride, 34 cases) and a treatment group (treated with sodium oligomannate + memantine hydrochloride, 34 cases).

Demographic data of the included samples were collected, and all patients underwent MRI (Magnetic Resonance Imaging) to assist in diagnosing the disease. The baseline demographic and imaging characteristics are shown in **Table 1**. There were no statistically significant differences between the two groups in terms of gender ratio, age, and other basic demographic information ($P > 0.05$), indicating comparability between the two groups. Additionally, there were no statistically significant differences in MRI-related indicators between the two groups ($P > 0.05$).

This study was approved by the Ethics Committee of the Second People's Hospital of Fujian University of Traditional Chinese Medicine (Approval No.: SPHFJP-S2023067-1).

Table 1. Baseline demographic and imaging characteristics of the two groups

	Baseline demographic			
Characteristics	**Age (range/ mean)**	**Gender distribution (male/female)**	**Severity (mild/ moderate)**	**Disease duration (range/ mean, years)**
Treatment group	60–80 / 70.24 ± 5.32	18 / 16	16 / 18	0.5–4.5 / 2.34 ± 0.12
Control group	60–80 / 70.36 ± 5.43	19 / 15	17 / 19	0.5–4.0 / 2.32 ± 0.11
t / χ^2 value	$t = 0.283$	$\chi^2 = 0.0593$	$\chi^2 = 0.0002$	$t = 0.271$
P value	$P = 0.833$	$P = 0.808$	$P = 0.988$	$P = 0.933$

Imaging characteristics					
Baseline MRI diagnostic characteristics	**Lateral fissure width (mm)**	**Longitudinal fissure width (mm)**	**Third ventricle width (mm)**	**Frontal horn index (%)**	**Caudate nucleus head diameter (mm)**
Treatment group	4.87 ± 1.59	6.61 ± 1.92	6.45 ± 1.23	35.67 ± 6.74	36.64 ± 8.09
Control group	4.90 ± 1.32	6.18 ± 1.77	6.34 ± 1.16	34.79 ± 4.75	35.77 ± 6.42
t	0.296	0.534	0.322	0.646	0.532
P	0.954	0.466	0.910	0.356	0.597
Local MRI diagnostic characteristics	**Cortical atrophy (%)**	**Sulcus widening (%)**	**Medial hippocampal CSF pool widening (%)**	**Hippocampal atrophy (%)**	**Temporal-parietal atrophy (%)**
Treatment group	21 (61.7)	21 (61.7)	13 (38.2)	12 (35.3)	16 (47.1)
Control group	18 (52.9)	19 (55.9)	15 (44.1)	14 (41.1)	17 (50.0)
χ^2	1.2308	0.6000	0.3429	0.3357	0.0970
P	0.267	0.439	0.558	0.562	0.755

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) Diagnosed with Alzheimer's dementia following the diagnostic criteria in the "Chinese Alzheimer's Disease Dementia Diagnosis and Treatment Guidelines (2020 Edition)" [4]; (2) Aged ≥ 60 years; (3) No antipsychotic medication use for at least one month prior to enrollment; (4) No allergic reaction to the study drugs; (5) Voluntary participation in the study.

Exclusion criteria: (1) Patients with tumor diseases or blood system diseases; (2) Dementia caused by bipolar disorder or schizophrenia; (3) History of drug addiction, substance abuse, or alcohol abuse; (4) Presence of malignant lesions in organs such as the liver or kidneys.

2.3. Drug treatment methods

The control group received treatment with memantine hydrochloride tablets (manufacturer: CSPC Ouyi Pharmaceutical Co., Ltd.; batch number: 1240005; approval number: H20203320; specification: 5 mg). The treatment regimen was as follows: (1) Initial dose of 5 mg once daily before bedtime for 1 week; (2) Week 2 with 10 mg once daily; (3) Week 3 with 15 mg daily (10 mg in the morning, 5 mg in the afternoon); (4) Week 4 with 20 mg daily (10 mg twice a day); (5) Subsequent weeks following the same dose as week 4 and continue the treatment for 6 months.

The treatment group received sodium oligomannate capsules (manufacturer: Shanghai Green Valley Pharmaceuticals Co., Ltd.; batch number: 211205; approval number: H20190031; specification: 150 mg) in addition to memantine hydrochloride, with the same dosage regimen for memantine as in the control group. Sodium oligomannate was administered at a dosage of 450 mg twice daily with warm water, for 6 months of continuous treatment.

2.4. Observation indicators

The following observation indicators were selected, with specific procedures based on the measurement guidelines from the People's Medical Publishing House [7]. Adverse reaction evaluations were based on the

"Chinese Classification and Diagnostic Criteria for Mental Disorders" (CCMD) [8].

(1) Cognitive function: This included orientation, language, concept usage, memory, attention, calculation ability, and language ability to assess the severity and degree of cognitive impairment. The Alzheimer's Disease Assessment Scale-Cognitive Section (ADAS-Cog) [9] and the Mini-Mental State Examination (MMSE) [10] were used as evaluation tools. ADAS-Cog has a total score of 75, with higher scores indicating worse cognitive function; MMSE has a total score of 30, with higher scores indicating better cognitive function. The Montreal Cognitive Assessment (MoCA) was also used for rapid screening of cognitive function abnormalities.

(2) Activities of daily living: This assessed the individual's ability to perform basic and instrumental activities of daily living. The Activity of Daily Living Scale (ADL) [11] was used as the evaluation tool, with a total score of 100; higher scores indicated better daily living abilities. The Functional Comprehensive Assessment (FCA) was also used to evaluate physical, cognitive, emotional, and social functions comprehensively.

(3) Neurotransmitters: Blood samples (8 mL) were taken before and after 6 months of treatment, centrifuged for 10 minutes at 3,500 r/min with an effective centrifuge radius of 15 cm, and the separated serum was stored at -20°C for later use. Enzyme-linked immunosorbent assay (ELISA) was used to detect 5-hydroxytryptamine (5-HT), acetylcholine (Ach), and glutamate (Glu).

(4) Serum intestinal flora metabolic markers: Phenylalanine (Phe), gamma-aminobutyric acid (GABA), and short-chain fatty acids (SCFA) were measured using an automatic biochemical analyzer before and after 6 months of treatment.

(5) Inflammatory factors: Serum levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were measured by ELISA before and after 6 months of treatment.

(6) Neurotrophic factors: Serum brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) were measured by radioimmunoassay before and after 6 months of treatment.

(7) Adverse reactions: Including nausea, diarrhea, and dizziness.

2.5. Statistical analysis

Statistical analysis was performed using SPSS version 22.0. All data underwent normality testing. Normally distributed data are expressed as mean ± standard deviation (SD), and comparisons between the two groups were conducted using the *t*-test. Categorical data are expressed as percentages, with group comparisons performed using the χ^2 test. A P-value < 0.05 was considered statistically significant.

3. Results

3.1. Comparison of cognitive function and activities of daily living between the two groups

As shown in **Table 2**, after treatment, the MoCA, MMSE, and ADL scores in the treatment group were significantly higher than those in the control group, and the differences were statistically significant ($P < 0.05$). For daily living abilities, the ADAS-Cog and FAQ scores in the treatment group were higher than those in the control group, with the difference in ADAS-Cog scores between the two groups being statistically significant ($P < 0.05$).

Table 2. Comparison of evaluation scale scores between the two groups before and after treatment (mean ± SD)

Group	MoCA		ADAS-Cog		MMSE		ADL		FAQ	
	Before	After	Before	After	Before	After	Before	After	Before	After
Treatment group (n = 34)	20.27 ± 1.84	22.31 ± 2.24*	37.35 ± 6.78	30.14 ± 3.57*	20.29 ± 3.18	24.39 ± 2.33*	65.34 ± 4.18	72.59 ± 8.32*	10.32 ± 2.46	8.43 ± 2.06
Control group (n = 34)	20.32 ± 2.31	20.67 ± 1.92*	36.52 ± 6.41	32.95 ± 6.82*	20.56 ± 3.24	22.37 ± 3.52*	65.89 ± 4.27	68.14 ± 6.13*	9.98 ± 2.19	9.52 ± 2.37
t	0.441	2.266	0.519	2.129	0.347	2.790	0.537	2.511	0.382	1.788
P	0.621	0.027*	0.606	0.037*	0.730	0.007*	0.593	0.015*	0.704	0.119

Note: Compared to before treatment in the same group, *P < 0.05. Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive; ADL, Activities of Daily Living Scale; FAQ, Functional Activities Questionnaire; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

3.2. Comparison of neurotransmitter levels between the two groups

After treatment, the levels of 5-HT, Ach, and Glu increased in both groups, with the treatment group showing significantly higher levels than the control group, and the differences were statistically significant (P < 0.05), as shown in **Table 3**.

Table 3. Comparison of neurotransmitter levels between the two groups before and after treatment (mean ± SD)

Group	5-HT (ng/mL)		Ach (nmol/L)		Glu (μmol/L)	
	Before	After	Before	After	Before	After
Treatment group (n = 34)	40.37 ± 6.23	51.68 ± 8.34*	23.59 ± 2.47	30.58 ± 5.33*	63.25 ± 7.12	72.98 ± 10.36*
Control group (n = 34)	40.85 ± 6.74	47.53 ± 7.62*	23.86 ± 2.53	27.52 ± 4.72*	63.57 ± 7.28	67.34 ± 8.15*
t	0.305	2.142	0.445	2.506	0.183	2.495
P	0.761	0.036*	0.658	0.015*	0.855	0.015*

Note: Compared with before treatment, *P < 0.05. Abbreviations: 5-HT, 5-hydroxytryptamine; Ach, acetylcholine; Glu, glutamic acid.

3.3. Comparison of serum intestinal flora metabolism markers between the two groups

After treatment, the Phe level in the treatment group was significantly lower than that in the control group, and the differences were statistically significant (P < 0.05). The GABA and SCFA levels in the treatment group were significantly higher than those in the control group, with statistically significant differences (P < 0.05), as shown in **Table 4**.

3.4. Comparison of inflammatory factor levels between the two groups

As shown in **Table 5**, after treatment, the IL-6 and TNF-α levels decreased in both groups, with a more significant reduction in the treatment group than in the control group, and the differences were statistically significant (P < 0.05).

Table 4. Comparison of serum intestinal flora metabolism markers between the two groups before and after treatment (mean ± SD)

Group	Phe (μmol/L)		GABA (μmol/L)		SCFA (μmol/L)	
	Before	After	Before	After	Before	After
Treatment group (n = 34)	126.38 ± 10.47	99.47 ± 5.24*	30.27 ± 4.16	38.61 ± 7.34*	65.34 ± 5.32	72.43 ± 7.29*
Control group (n = 34)	125.76 ± 10.32	105.38 ± 10.12*	30.85 ± 4.29	34.25 ± 4.86*	65.97 ± 5.48	68.36 ± 6.21*
t	0.246	3.024	0.566	2.888	0.481	2.478
P	0.807	0.004*	0.573	0.005*	0.632	0.016*

Note: Compared with before treatment, *P < 0.05. Abbreviations: GABA, Gamma-aminobutyric acid; Phe, Phenylalanine; SCFA, Short-chain fatty acids.

Table 5. Comparison of inflammatory factor levels between the two groups before and after treatment (mean ± SD)

Group	IL-6 (ng/L)		TNF-α (ng/L)	
	Before	After	Before	After
Treatment group (n = 34)	41.38 ± 7.23	33.45 ± 3.16*	156.49 ± 15.24	133.85 ± 10.31*
Control group (n = 34)	40.85 ± 7.11	36.93 ± 6.22*	155.78 ± 15.03	140.79 ± 14.28*
t	0.305	2.909	0.193	2.298
P	0.762	0.005*	0.847	0.025*

Note: Compared with before treatment, *P < 0.05. Abbreviations: IL-6, Interleukin-6; TNF-α, Tumor necrosis factor-alpha.

3.5. Comparison of neurotrophic factors between the two groups

After treatment, the levels of BDNF and NGF in the treatment group were significantly higher than those in the control group, and the differences were statistically significant (P < 0.05), as shown in **Table 6**.

Table 6. Comparison of neurotrophic factor levels between the two groups before and after treatment (mean ± SD)

Group	BDNF (ng/L)		NGF (ng/L)	
	Before	After	Before	After
Treatment group (n = 34)	26.35 ± 3.18	36.59 ± 6.32*	20.85 ± 1.34	26.92 ± 4.29*
Control group (n = 34)	27.42 ± 3.26	32.68 ± 3.47*	21.36 ± 1.42	24.15 ± 2.03*
t	1.370	3.162	1.523	3.403
P	0.175	0.002*	0.133	0.001*

Note: Compared with before treatment, *P < 0.05. Abbreviations: BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor.

3.6. Comparison of adverse reactions between the two groups

As shown in **Table 7**, the incidence of adverse reactions in the treatment group was slightly lower than that in the control group, but the difference was not statistically significant (P > 0.05).

Table 7. Comparison of adverse reactions between the two groups of patients [*n* (%)]

Group	Nausea (*n*)	Diarrhea (*n*)	Dizziness (*n*)	Total incidence (%)
Treatment group (*n* = 34)	1	0	1	5.9
Control group (*n* = 34)	2	1	1	11.8
χ^2-value	-	-	-	0.731
P-value	-	-	-	0.393

4. Discussion

Alzheimer's disease (AD) is relatively common in clinical practice, and its etiology may be related to genetic factors, β-amyloid, and apolipoprotein E gene, among others. Long-term smoking, poor dietary habits, and vascular factors are triggers for the disease [9]. AD patients are prone to symptoms such as memory loss, abnormal behavior, and emotional disturbances. If not treated in time, AD can lead to serious complications like pneumonia, organ failure, and urinary system infections, with severe cases resulting in a loss of daily living abilities. Thus, early diagnosis and treatment of AD are of great importance for improving prognosis [10].

At present, there is no treatment that can completely cure AD. Current clinical approaches mainly involve pharmacotherapy to slow disease progression, improve symptoms, and enhance prognosis [11]. Memantine hydrochloride, a commonly used non-competitive NMDA receptor antagonist, inhibits the pathological elevation of glutamate, and reduces intracellular calcium ion levels in neurons, thereby mitigating neuronal damage, restoring cognitive function, and alleviating dementia symptoms. However, long-term use can lead to side effects such as nausea, dizziness, and diarrhea, and monotherapy often falls short of expectations. Thus, combining memantine with other drugs has become a popular topic in clinical research [12–15].

This study showed that the treatment group, after receiving a combination of sodium oligomannate and memantine hydrochloride, had better ADAS-Cog, MMSE, ADL, and neurotransmitter scores compared to the control group ($P < 0.05$), with no significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$). The reason for this could be that memantine hydrochloride effectively regulates NMDA receptors, preventing excitotoxicity and neuronal damage. Sodium oligomannate, as a mixture of acidic and linear oligosaccharides, has an inhibitory effect on the differentiation and proliferation of pro-inflammatory cells. It can effectively suppress microglial activation, alleviate inflammation, reduce β-amyloid deposition, partially restore cognitive function, and regulate neurotransmitters [16–19]. The distinct mechanisms of action of memantine hydrochloride and sodium oligomannate allow for synergistic effects, enhancing therapeutic outcomes by restoring cognitive function, daily living abilities, and neurotransmitter levels without increasing adverse reactions.

Clinical research has found that gut microbiota imbalances and their metabolites can increase gut permeability and trigger systemic inflammation, affecting central nervous system function and worsening cognitive impairment in AD patients [20]. Among common gut microbiota metabolic markers, Phe, a sulfur-containing amino acid, increases neurotoxicity and worsens cognitive impairment; SCFA helps protect the gut barrier, and a reduction in SCFA damages intestinal epithelial integrity, causing neuroinflammation; GABA, an inhibitory neurotransmitter, when reduced, disrupts neurons and induces cognitive dysfunction. IL-6 and TNF-α are pro-inflammatory factors that are abnormally elevated in AD patients. This study found that SCFA

and GABA levels were higher, while Phe, IL-6, and TNF-α levels were lower in the treatment group compared to the control group ($P < 0.05$), which is consistent with findings by Taro *et al.* [11]. Sodium oligomannate, as a brain-gut axis regulator, when combined with memantine hydrochloride, prevents abnormal expression of gut microbiota metabolic markers, promotes gut microbiota balance, reduces central nervous system inflammation, and improves cognitive function [21].

Clinical research suggests that neurotrophic factors are associated with the onset of AD. BDNF and NGF are commonly used neurotrophic factors, and abnormal secretion of these factors can induce AD [22]. The results of this study showed that BDNF and NGF levels were higher in the treatment group than in the control group ($P < 0.05$), which is consistent with previous studies [23], suggesting that the combination of sodium oligomannate and memantine hydrochloride can inhibit neurotoxicity, upregulate neurotrophic factor levels and expression, and restore patients' cognitive function.

5. Conclusion

In conclusion, the combination of sodium oligomannate and memantine hydrochloride can improve cognitive function, neurotransmitter levels, neurotrophic factor expression, regulate gut microbiota, reduce inflammation, enhance daily living abilities in elderly AD patients, and is associated with few adverse reactions, making it a safe and effective treatment.

Funding

Clinical Special Project of Fujian University of Traditional Chinese Medicine (Project Number: XB2023027)

Disclosure statement

The authors declare no conflict of interest.

References

[1] GBD 2021 Diseases and Injuries Collaborators, 2024, Global Incidence, Prevalence, Years Lived with Disability (YLDs), Disability-Adjusted Life-Years (DALYs), and Healthy Life Expectancy (HALE) for 371 Diseases and Injuries in 204 Countries and Territories and 811 Subnational Locations, 1990–2021: A Systematic Analysis for the Global Burden of Disease Study 2021. Lancet, 403(10440): 2133–2161. https://doi.org/10.1016/S0140-6736(24)00757-8

[2] Topal F, Ertas B, Guler E, et al., 2022, A Novel Multi-Target Strategy for Alzheimer's Disease Treatment Via Sublingual Route: Donepezil/Memantine/Curcumin-Loaded Nanofibers. Biomater Adv, 138: 212870. https://doi.org/10.1016/j.bioadv.2022.212870

[3] Knorz AL, Quante A, 2022, Alzheimer's Disease: Efficacy of Mono- and Combination Therapy. A Systematic Review. J Geriatr Psychiatry Neurol, 35(4): 475–486. https://doi.org/10.1177/08919887211044746

[4] Morató X, Pytel V, Jofresa S, et al., 2022, Symptomatic and Disease-Modifying Therapy Pipeline for Alzheimer's Disease: Towards a Personalized Polypharmacology Patient-Centered Approach. Int J Mol Sci, 23(16): 9305. https://doi.org/10.3390/ijms23169305

[5] Syed YY, 2020, Sodium Oligomannate: First Approval. Drugs, 80(4): 441–444. https://doi.org/10.1007/s40265-020-01268-1. Erratum in Drugs, 80(4): 445–446. https://doi.org/10.1007/s40265-020-01274-3

[6] Zhang LF, Zhang YP, Lin PX, et al., 2022, Efficacy and Safety of Sodium Oligomannate in the Treatment of Alzheimer's Disease. Pak J Pharm Sci, 35(3): 741–745.

[7] Peng D, Zhang Z, 2015, Guidelines for the Operation of Neuropsychological Cognitive Scales. People's Medical Publishing House, Beijing.

[8] Chinese Society of Psychiatry, 2001, The Third Edition of the Chinese Classification and Diagnostic Criteria of Mental Disorders (CCMD-3). Chinese Journal of Psychiatry, 34(3): 184–188.

[9] Zhang X, Sun J, Xiao W, et al., 2024, Analysis of the Application Effect of Five Cognitive Function Screening Scales in the Elderly. Nursing Research, 38(7): 1162–1167.

[10] He M, Wang M, Gao J, et al., 2024, Reliability, Validity, and Clinical Application of the Chinese Version of the Cognitive Assessment Scale for Stroke Patients (C-CASP) in Non-Aphasic Stroke Patients. Chinese Journal of Rehabilitation Medicine, preprint, 1–7.

[11] Dong Q, Guo Q, Luo B, et al., 2017, Expert Consensus on the Management of Post-Stroke Cognitive Impairment. Chinese Journal of Stroke, 12(6): 519–531.

[12] Scheltens P, De Strooper B, Kivipelto M, et al., 2021, Alzheimer's Disease. Lancet, 397(10284): 1577–1590. https://doi.org/10.1016/S0140-6736(20)32205-4

[13] Long JM, Holtzman DM, 2019, Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. Cell, 179(2): 312–339. https://doi.org/10.1016/j.cell.2019.09.001

[14] Cummings JL, Tong G, Ballard C, 2019, Treatment Combinations for Alzheimer's Disease: Current and Future Pharmacotherapy Options. J Alzheimers Dis, 67(3): 779–794. https://doi.org/10.3233/JAD-180766

[15] Yaghmaei E, Lu H, Ehwerhemuepha L, et al., 2024, Combined Use of Donepezil and Memantine Increases the Probability of Five-Year Survival of Alzheimer's Disease Patients. Commun Med (Lond), 4(1): 99. https://doi.org/10.1038/s43856-024-00527-6

[16] Kabir MT, Uddin MS, Mamun AA, et al., 2020, Combination Drug Therapy for the Management of Alzheimer's Disease. Int J Mol Sci, 21(9): 3272. https://doi.org/10.3390/ijms21093272

[17] Xiao S, Chan P, Wang T, et al., 2021, A 36-Week Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Clinical Trial of Sodium Oligomannate for Mild-to-Moderate Alzheimer's Dementia. Alzheimers Res Ther, 13(1): 62. https://doi.org/10.1186/s13195-021-00795-7

[18] Jia L, Quan M, Fu Y, et al., 2020, Dementia in China: Epidemiology, Clinical Management, and Research Advances. Lancet Neurol, 19(1): 81–92. https://doi.org/10.1016/S1474-4422(19)30290-X

[19] Gao J, Wang W, 2021, A Case of Sodium Oligomannate Improving Cognitive Function, Behavioral and Psychological Symptoms, and Daily Function in Post-Ovarian Cancer Surgery Alzheimer's Disease Patients. Chinese Journal of New Drugs and Clinical Remedies, 40(11): 797–800.

[20] Wang X, Sun G, Feng T, et al., 2019, Sodium Oligomannate Therapeutically Remodels Gut Microbiota and Suppresses Gut Bacterial Amino Acids-Shaped Neuroinflammation to Inhibit Alzheimer's Disease Progression. Cell Res, 29(10): 787–803. https://doi.org/10.1038/s41422-019-0216-x

[21] Gupta HV, Beach TG, Mehta SH, et al., 2021, Clinicopathological Correlation: Dopamine and Amyloid PET Imaging with Neuropathology in Three Subjects Clinically Diagnosed with Alzheimer's Disease or Dementia with Lewy Bodies. J Alzheimers Dis, 80(4): 1603–1612. https://doi.org/10.3233/JAD-200323

[22] Ettcheto M, Busquets O, Cano A, et al., 2021, Pharmacological Strategies to Improve Dendritic Spines in Alzheimer's

Disease. J Alzheimers Dis, 82(S1): S91–S107. https://doi.org/10.3233/JAD-201106

[23] Angelucci F, Cechova K, Amlerova J, et al., 2019, Antibiotics, Gut Microbiota, and Alzheimer's Disease. J Neuroinflammation, 16(1): 108. https://doi.org/10.1186/s12974-019-1494-4