

Original Article



Clinical Practice Guidelines for Dementia: Recommendations for Cholinesterase Inhibitors and Memantine

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Conflict of Interest

The Steering and Working Committee members of the Clinical Practice Guideline Implementation Committee were checked for

ABSTRACT

Background and Purpose: This clinical practice guideline provides evidence-based recommendations for treatment of dementia, focusing on cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists for Alzheimer's disease (AD) and other types of dementia.

Methods: Using the Population, Intervention, Comparison, Outcomes (PICO) framework, we developed key clinical questions and conducted systematic literature reviews. A multidisciplinary panel of experts, organized by the Korean Dementia Association, evaluated randomized controlled trials and observational studies. Recommendations were graded for evidence quality and strength using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology.

Results: Three main recommendations are presented: (1) For AD, cholinesterase inhibitors (donepezil, rivastigmine, galantamine) are strongly recommended for improving cognition and daily function based on moderate evidence; (2) Cholinesterase inhibitors are conditionally recommended for vascular dementia and Parkinson's disease dementia, with a strong recommendation for Lewy body dementia; (3) For moderate to severe AD, NMDA receptor antagonist (memantine) is strongly recommended, demonstrating significant cognitive and functional improvements. Both drug classes showed favorable safety profiles with manageable side effects.

Conclusions: This guideline offers standardized, evidence-based pharmacologic recommendations for dementia management, with specific guidance on cholinesterase inhibitors and NMDA receptor antagonists. It aims to support clinical decision-making and improve patient outcomes in dementia care. Further updates will address emerging treatments, including amyloid-targeting therapies, to reflect advances in dementia management.

Keywords: Dementia; Alzheimer Disease; Cholinesterase Inhibitors; Memantine; Practice Guidelines

INTRODUCTION

Dementia refers to a condition where individuals who previously had no cognitive impairments experience progressive cognitive decline, leading to difficulties in daily activities.¹ The most common cause of dementia is Alzheimer's disease (AD), characterized by the abnormal accumulation and reduced clearance of beta-amyloid protein, leading to amyloid plaque buildup and hyperphosphorylation of tau protein. This process results in neurodegeneration and ultimately in cognitive and functional impairment.^{2,3} Other forms of dementia include vascular dementia, Lewy body dementia, Parkinson's disease dementia, and frontotemporal dementia.¹

Since AD was first described by Alois Alzheimer in 1906,⁴ pharmacological treatments have continued to evolve, especially following the introduction of the amyloid hypothesis in 1984. The first cholinesterase inhibitor, donepezil, was developed in 1993, followed by rivastigmine and galantamine in 2000 and 2001, respectively. In 2003, the N-methyl-D-aspartate (NMDA) receptor antagonist memantine was introduced and remains in use to this day.⁵ In 2024, with the anticipated introduction of amyloid antibody therapies, significant advancements in AD treatment are expected. Cholinesterase inhibitors and

any consultancy or employment relationships with commercially related organizations, commercial equity holdings, research grants, honoraria, ownership of intellectual property rights related to the content of the guideline, or similar relationships involving their family or family-affiliated companies during the development or approval process of the guideline. All participating members confirmed that there were no conflicts of interest that could influence the development or approval process of this guideline.

Author Contributions

Investigation: Kim Y, Kang DW, Kim GH, Kim KW, Kim HJ, Na S, Park KH, Park YH, Byeon G, Suh J, Shin JH, Shim Y, Yang Y, Um YH, Oh SI, Wang SM, Yoon B, Lee SM, Lee J, Lee JS, Lim JS, Jung YH, Chin J, Jang H, Choi M, Hong YJ, Rhee HY, Jang JW; Methodology: Kim Y, Kang DW, Kim GH, Kim KW, Kim HJ, Na S, Park KH, Park YH, Byeon G, Suh J, Shin JH, Shim Y, Yang Y, Um YH, Oh SI, Wang SM, Yoon B, Lee SM, Lee J, Lee JS, Lim JS, Jung YH, Chin J, Jang H, Choi M, Hong YJ, Rhee HY, Jang JW; Writing - original draft: Kim Y, Kim GH, Park YH, Shim Y, Oh SI, Yoon B, Lee JS, Lim JS, Hong YJ; Writing - review & editing: Kim Y, Kang DW, Kim GH, Kim KW, Kim HJ, Na S, Park KH, Park YH, Byeon G, Suh J, Shin JH, Shim Y, Yang Y, Um YH, Oh SI, Wang SM, Yoon B, Lee SM, Lee J, Lee JS, Lim JS, Jung YH, Chin J, Jang H, Choi M, Hong YJ, Rhee HY, Jang JW.

NMDA receptor antagonists have been used for patients with AD as well as for those with other types of dementia. It is expected that these medications will continue to be used even after the introduction of antibody therapies. However, there are currently no evidence-based treatment guidelines established in South Korea.

The Korean Dementia Association published the “Clinical Guidelines for Dementia: Part 1 – Diagnosis and Assessment” in 2010,⁶ and in 2021 released a revised version covering the diagnosis and assessment of dementia.⁷ The aim of these clinical guidelines is to develop new core recommendations related to treatment, including previously unaddressed topics. This revision seeks to evaluate and provide recommendations on the efficacy of pharmacological treatments, especially choline esterase inhibitors and NMDA receptor antagonist, not only for AD but also for other forms of dementia. The Korean version of the revision guideline is provided as **Supplementary Data 1**.

METHODS

Target population, scope, purpose, and users of the clinical practice guideline

The target population of this clinical practice guideline is patients with dementia. The scope of the guideline covers pharmacological treatment and was determined by the Quality Management Committee of the Korean Dementia Association through the development of key questions based on the Population, Intervention, Comparison, Outcomes (PICO) format. Specific details are provided for each key question. The purpose of this clinical practice guideline is to establish an evidence-based, objective standard for the treatment of dementia, thereby supporting clinical decision-making in diagnosis and treatment. The users of this guideline include neurologists and psychiatrists diagnosing and treating dementia, as well as internists, family medicine specialists, and primary care physicians, who can use it for decision-making related to dementia treatment.

Clinical practice guideline Implementation Committee composition

Major decisions throughout the entire process of developing the clinical practice guideline were made by the Steering Committee, and the budget related to the project was reviewed and approved by the Board of Directors of the Korean Dementia Association. The entire budget for this guideline was provided by the Korean Dementia Association, but the association did not influence the development of the clinical practice guideline beyond providing financial support. The Implementation Committee, mainly composed of members from the Quality Management Committee of the Korean Dementia Association, was responsible for drafting the guideline and recommendations. The Implementation Committee consisted primarily of neurologists, with the inclusion of psychiatrists, and was composed of Chairman Dongwon Yang, 9 Steering Committee members, 18 Working Committee members, three advisors, and one literature search expert (**Table 1**). The final recommendations were completed through defining key questions, evaluating the quality of the literature, collecting and selecting evidence, and assessing strength of recommendation. The literature search was conducted by One's Global Co., Ltd., and methodological advice on guideline development was provided by Team Leader Miyoung Choi of National Evidence-based Healthcare Collaborating Agency (NECA). Workshops were held for literature search, literature quality assessment, meta-analysis, and establishing evidence and strength of recommendation.

Table 1. Committee structure for the clinical practice guidelines development

Position	Affiliation	Name
Steering committee members	Catholic University Seoul St. Mary's Hospital, Neurology	Dong-Won Yang (Chairperson)
	Kangwon National University Hospital, Neurology	Yeshin Kim
	Hanyang University Hospital, Neurology	Hee-jin Kim
	Catholic University Incheon St. Mary's Hospital, Neurology	Seunghee Na
	Gil Medical Center, Neurology	Kee Hyung Park
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	Kangwon National University Hospital, Neurology	Jae-won Jang
	Catholic University Uijeongbu St. Mary's Hospital, Neurology	Yun Jeong Hong
Working committee members	Catholic University Seoul St. Mary's Hospital, Psychiatry	Dong Woo Kang
	Ewha Womans University Mokdong Hospital, Neurology	Geon Ha Kim
	Jeonbuk National University Hospital, Neurology	Ko Woon Kim
	Seoul National University Bundang Hospital, Neurology	Young Ho Park
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	Asan Medical Center, Neurology	Jae-Sung Lim
	Hallym Sacred Heart Hospital, Neurology	Young Hee Jung
	Hallym University, Psychology	Juhee Chin
	Seoul National University Hospital, Neurology	Hyemin Jang
Advisory committee	Asan Medical Center, Psychiatry	Sung Yoon Kim
	Chung-Ang University Hospital, Neurology	Young Chul Yoon
	National Evidence-based Healthcare Collaborating Agency (NECA)	Miyoung Choi
Literature review specialist	One's Global Co., Ltd	Kyungha Park

Internal and external review and consultation of the clinical practice guideline draft

The drafted guideline underwent an internal review by the Quality Management Committee of the Korean Dementia Association, which led to the development of the first revised version. Subsequently, external reviews were conducted with experts from related associations, including the Korean Neurological Association, the Korean Association for Geriatric Psychiatry, the Korean Neuropsychiatric Association, and the Korean Academy of Neurology, as well as other internal and external experts. The final version was prepared after reflecting the feedback received during this review process.

Dissemination and distribution of the clinical practice guideline

This guideline and its supplementary data have been published in the Journal of the Korean Dementia Association (<https://www.dnd.or.kr>) and are available for review on the website of the Korean Dementia Association (<https://www.dementia.or.kr/>).

Update plan for the clinical practice guideline

With the anticipated introduction of new therapies, such as antibody treatments for beta-amyloid, it is deemed necessary to add new recommendations or revise and complement existing ones based on domestic healthcare conditions. The guideline will be revised at intervals of approximately 3 years, and the revision process will be carried out by the Quality Management Committee of the Korean Dementia Association.

Guideline development methods

This clinical practice guideline was developed using a de novo approach, deriving recommendations based on key questions that were not included in the existing clinical practice guideline published in 2021.

Derivation of key questions (KQs)

KQs were derived through meetings of the Implementation Committee, during which major topics related to diagnosis and treatment that were not covered in existing clinical practice guidelines were selected. Subsequently, sub-key questions for each topic were chosen. Working committee members were assigned to each topic, and after defining PICO for each topic in meetings and through discussions, a final selection of 3 key questions was made. The three questions are as follows.

- KQ1: Are cholinesterase inhibitors effective in improving cognitive function/activities of daily living (ADLs) for AD dementia?
- KQ2: Are acetylcholinesterase inhibitors effective in improving cognitive function/ ADL for dementias other than AD?
- KQ3: Is the NMDA receptor antagonist (memantine) effective in improving cognition and ADL living in dementia?

Literature search and quality assessment

To identify literature that serves as the basis for the recommendations, a systematic review of the literature was conducted for each topic. One's Global Co., Ltd. and the working committee selected appropriate search terms for each topic, and searches were conducted using PubMed, Embase, Cochrane Library, KMBASE, and RISS. The retrieved literature was screened by the working committee according to inclusion and exclusion criteria. The inclusion criteria were: 1) randomized controlled trials (RCTs), and 2) studies that reported appropriate outcomes. The common exclusion criteria were: 1) studies conducted with inappropriate study designs, 2) studies not performed using appropriate PICO, 3) literature published in languages other than English or Korean, 4) duplicate publications, and 5) cases where the full text was unavailable. The decision on whether to include literature was made by pairs of committee members, and if inclusion was unclear, the decision was discussed in topic-specific working committee meetings. The search strategy is provided in **Supplementary Table 1**. The literature selection process for each topic was summarized and presented using a flowchart, as recommended by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (**Supplementary Fig. 1**).

To assess the quality of the final selected literature, randomized controlled trials related to treatment topics were evaluated using Cochrane Risk of Bias (<https://www.riskofbias.info/welcome/rob-2-0-tool>). Two implementation committee members independently assessed the quality of each piece of literature, and if their assessments did not match, the two members discussed the discrepancies to arrive at a final evaluation. If discrepancies remained unresolved, they were discussed with the chairman of the respective working group to derive a final quality assessment outcome.

Derivation of recommendations: determination of evidence level and recommendation strength

The final selected literature was reviewed and summarized in evidence tables, and where feasible, meta-analyses were conducted. The level of evidence and the strength of

Table 2. Definition and presentation of the quality levels of evidence in the GRADE method

Evidence level	Definition
High	Very confident in the estimated effect's closeness to reality.
Moderate	Reasonably confident in the estimate, though it may vary somewhat.
Low	Limited confidence, with the estimate potentially differing from the true effect.
Very Low	Very little confidence, with the estimate likely to differ significantly.

GRADE: Grading of Recommendations, Assessment, Development, and Evaluation.

Table 3. Strengths of recommendation and phrasing of recommendations

Strength of recommendation	Definition
Strongly Recommend (A)	Strongly supports use across most clinical settings, considering benefits, risks, evidence level, patient preferences, and resources.
Conditional Recommend (B)	Suggests use based on clinical context or patient preferences.
Conditional Against (C)	Recommends against use in certain cases where risks may outweigh benefits.
Strongly Against (D)	Generally advises against use, as risks outweigh benefits.
Inconclusive (I)	Lacks sufficient evidence to support or oppose use; relies on clinical judgment.
Expert Consensus	Based on clinical experience and expert opinion where evidence is lacking.

recommendations were evaluated using The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology (**Tables 2 and 3**).

RESULTS

KQ1: Are cholinesterase inhibitors effective for AD dementia?

PICO elements

- Population: Patients with AD dementia
- Intervention: Cholinesterase inhibitors
- Control: Placebo treatment
- Outcomes: Cognitive function/ADL/Dementia severity
- Study design: RCTs

Recommendation

Recommendation: For AD dementia, the use of cholinesterase inhibitors is effective in improving cognitive function, ADL, and dementia severity (*Level of evidence: Moderate, Strength of recommendation: Strongly Recommend [A]*).

Clinical considerations: It is necessary to confirm and consider potential side effects resulting from the use of cholinesterase inhibitors. Since dementia can be caused by various underlying conditions, additional biomarker testing and an expert evaluation are recommended to conduct a precise diagnosis for AD, which may help predict the efficacy of the treatment.

Evidence summary

To collect evidence for the above question, a total of 62,214 papers published up to 2023 were searched through PubMed, Embase, Cochrane Library, KMBase, and RISS. An additional 29 papers were manually retrieved. RCTs and large-scale observational studies were selected. Studies with fewer than 20 participants per group were excluded, as were those using comparators other than placebo. Through this process, a total of 40 studies on pharmacological interventions for dementia patients were selected. Among them, 26 studies

used cholinesterase inhibitors as the intervention, with 16 of these specifically targeting AD patients.⁸⁻²³ The intervention drugs included donepezil (9 studies),^{8,46} rivastigmine (3 studies),^{17,19} and galantamine (4 studies).²⁰⁻²³ All comparator groups used placebos. Efficacy variables included the Mini-Mental State Examination (MMSE; 6 studies),^{13,14,16,49} the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog; 6 studies),¹⁷⁻²² the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL; 4 studies),^{13,15,18} and the Clinician's Interview-Based Impression of Change Plus Caregiver Input/Clinical Global Impression of Change (CIBIC-Plus/CGI-C; 6 studies).^{13,14,16,49} A total of 16 studies⁸⁻²³ reported adverse events along with efficacy evaluation. The results of the synthesized evidence are as follows. A total of 16 studies were used for meta-analysis,⁸⁻²³ and the outcome measures included changes in MMSE, ADAS-Cog, ADCS-ADL, Clinical Dementia Rating–Sum of Boxes (CDR-SB), and CIBIC-Plus/CGI-C scores. The outcome measures are described in **Supplementary Data 2**, and the results of each study are summarized in **Supplementary Table 2** and **Supplementary Fig. 2**.

Based on 6 studies that used MMSE as an outcome measure,^{13,14,16,49} the use of donepezil or rivastigmine showed significant effects compared to the control group (**Fig. 1**).

Based on 6 studies that used ADAS-Cog as an outcome measure,¹⁷⁻²² the use of rivastigmine or galantamine showed significant effects compared to the control group (**Fig. 2**).

Based on 4 studies that used ADCS-ADL as an outcome measure,^{13,15,18} the use of donepezil or rivastigmine showed significant effects compared to the control group (**Fig. 3**).

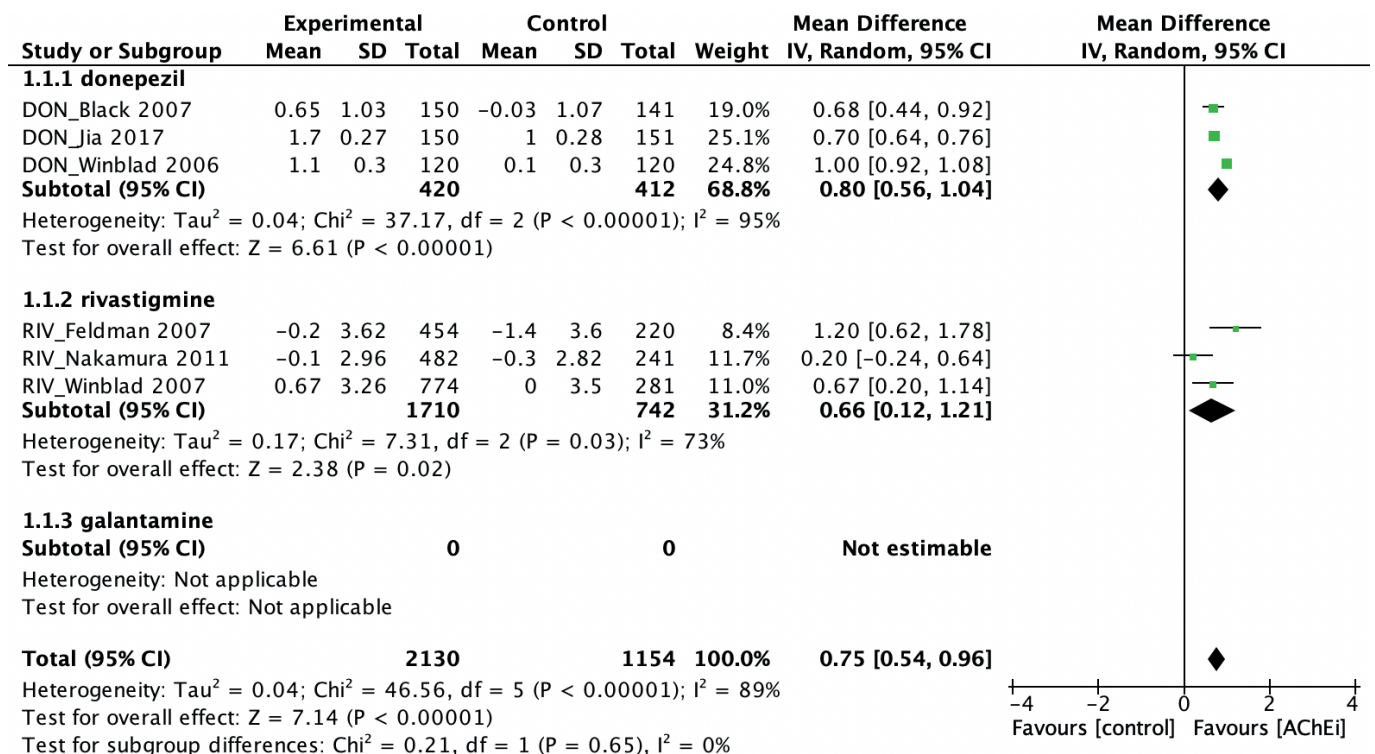


Fig. 1. Comparison of the effects of cholinesterase inhibitors and placebo on changes in MMSE.

MMSE: Mini-Mental State Examination, SD: standard deviation, IV: interval variable, CI: confidence interval, AChEi: acetylcholinesterase inhibitor.

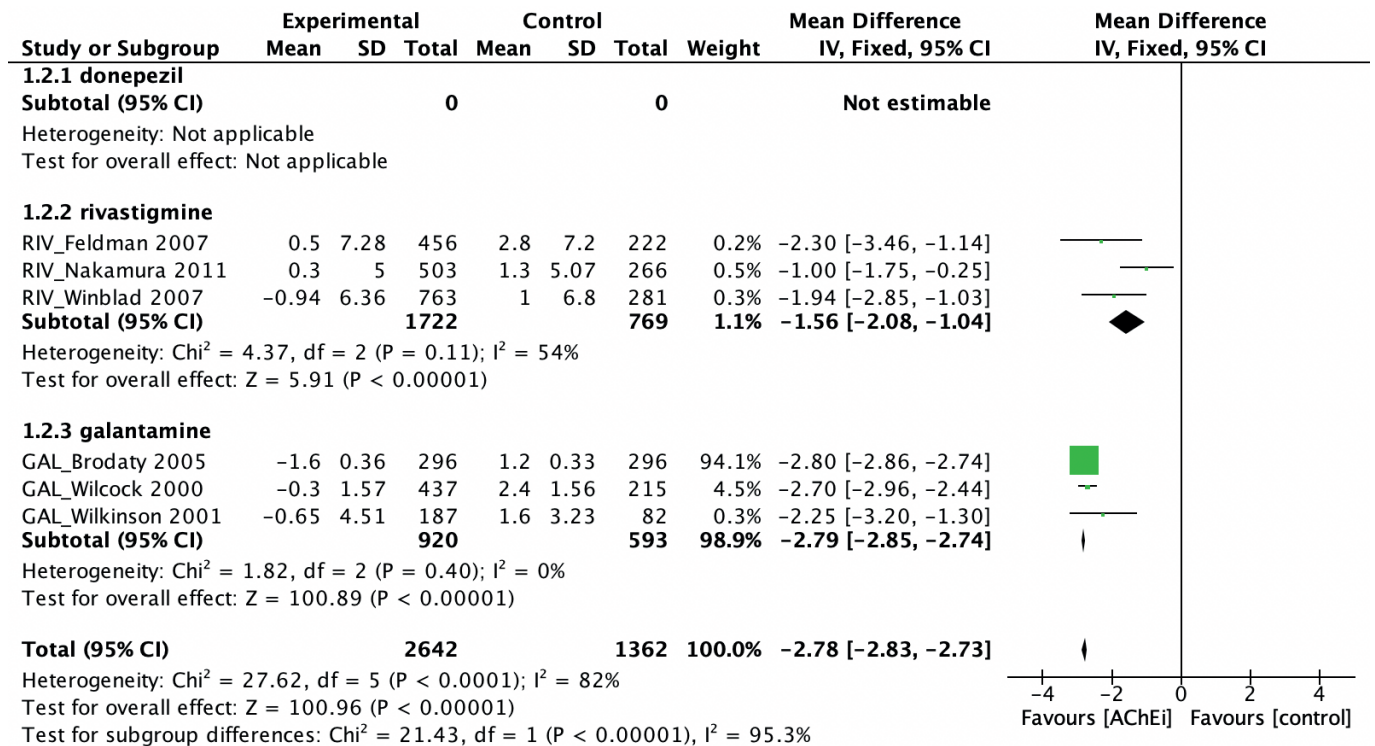


Fig. 2. Comparison of the effects of cholinesterase inhibitors and placebo on changes in ADAS-Cog.
ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale, SD: standard deviation, IV: interval variable, CI: confidence interval, AChEi: acetylcholinesterase inhibitor.

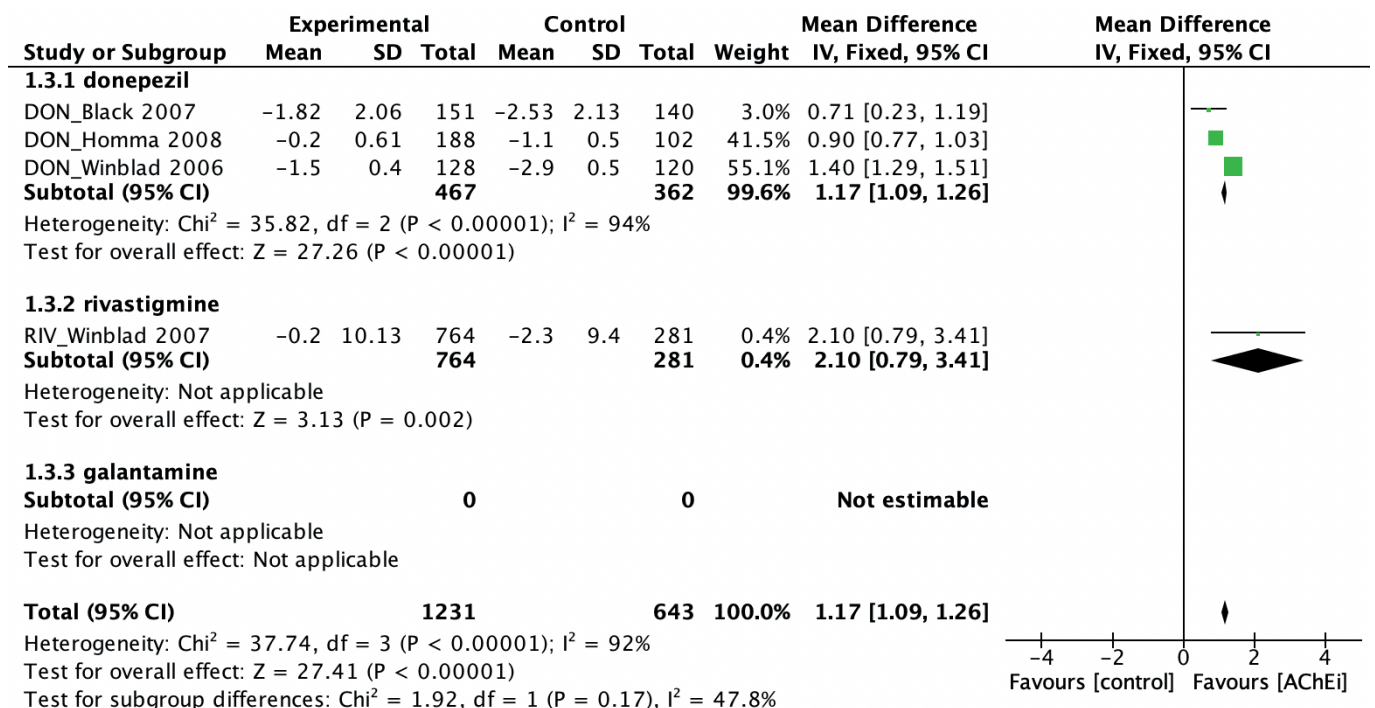


Fig. 3. Comparison of the Effects of Cholinesterase Inhibitors and Placebo on Changes in ADCS-ADL.
ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living, SD: standard deviation, IV: interval variable, CI: confidence interval, AChEi: acetylcholinesterase inhibitor.

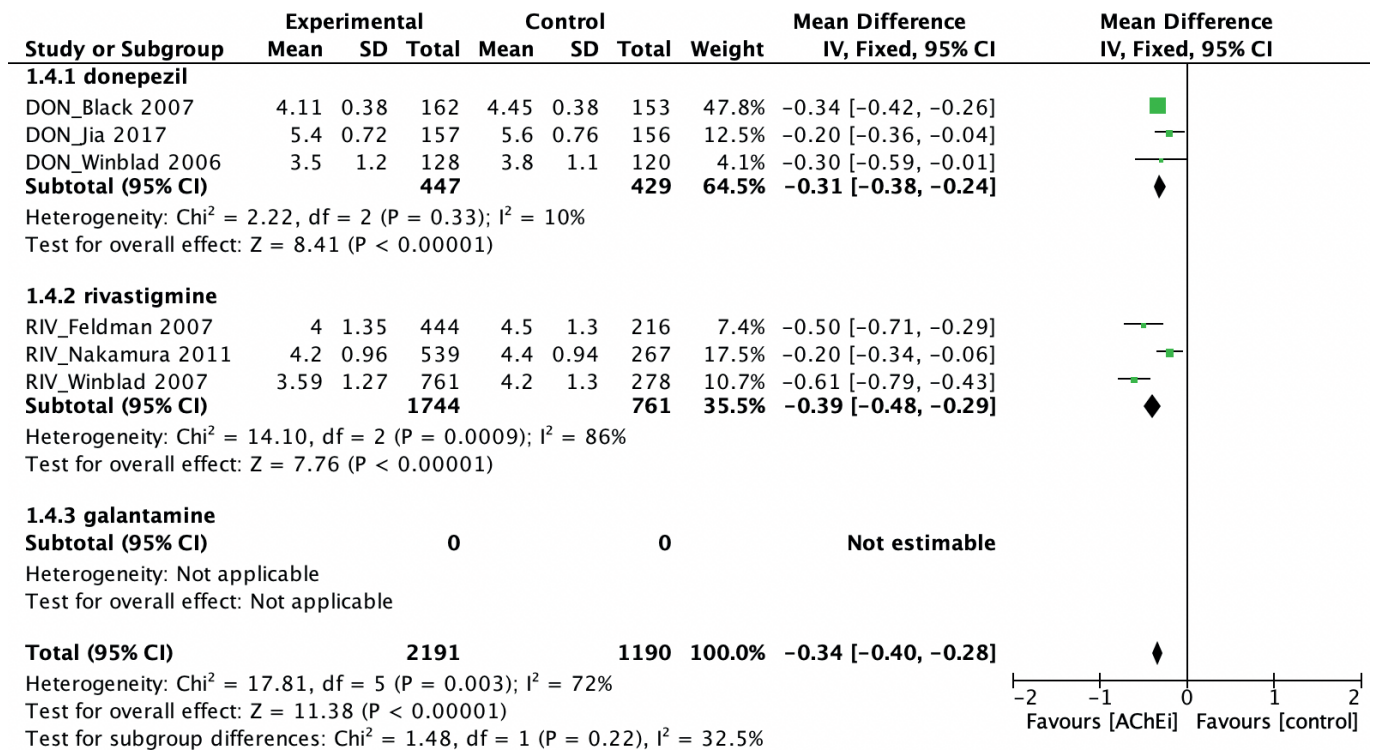


Fig. 4. Comparison of the Effects of Cholinesterase Inhibitors and Placebo on Changes in CIBIC-Plus/CGI-C.

CIBIC-Plus/CGI-C: Clinician's Interview-Based Impression of Change Plus Caregiver Input/Clinical Global Impression of Change, SD: standard deviation, IV: interval variable, CI: confidence interval, AChEi: acetylcholinesterase inhibitor.

Meta-analysis using studies that employed CDR-SB as an outcome measure could not be performed due to insufficient data. Based on 6 studies that used CIBIC-Plus/CGI-C^{13,14,16,49} as an outcome measure, the use of donepezil or rivastigmine showed significant effects compared to the control group (**Fig. 4**).

Various adverse effects were reported regarding safety, with cholinergic side effects such as diarrhea, nausea, loss of appetite, and vomiting being the most common. Most of these adverse effects were mild to moderate in severity, and the overall tolerability was generally good. The group treated with cholinesterase inhibitors showed significantly more adverse effects compared to the placebo group (odds ratio [OR], 1.42; 95% confidence interval [CI], 1.21 to 1.67; **Fig. 5**). Moderate or severe adverse effects occurred more frequently in the cholinesterase inhibitor group than in the placebo group (OR, 1.56; 95% CI, 1.07 to 2.28; **Fig. 6**). In many cases, these adverse effects were considered unrelated to the drug. The adverse effects thought to be related to the drug included bradycardia, QT interval prolongation, dizziness, and syncope. Discontinuation due to adverse effects occurred in 2%–44% of the cholinesterase inhibitor-treated group (donepezil: 7%–16%, rivastigmine: 2%–5.5%, galantamine: 6.1%–44%), compared to 0%–19% in the placebo group.

The above results are summarized in **Table 4**.

Level of evidence (GRADE application)

All 16 studies were RCTs conducted on large cohorts of at least 100 participants. Based on critical outcome measures such as MMSE, ADAS-Cog, and ADCS-ADL, the final level of evidence was determined to be “Moderate.” The level was downgraded by one grade due

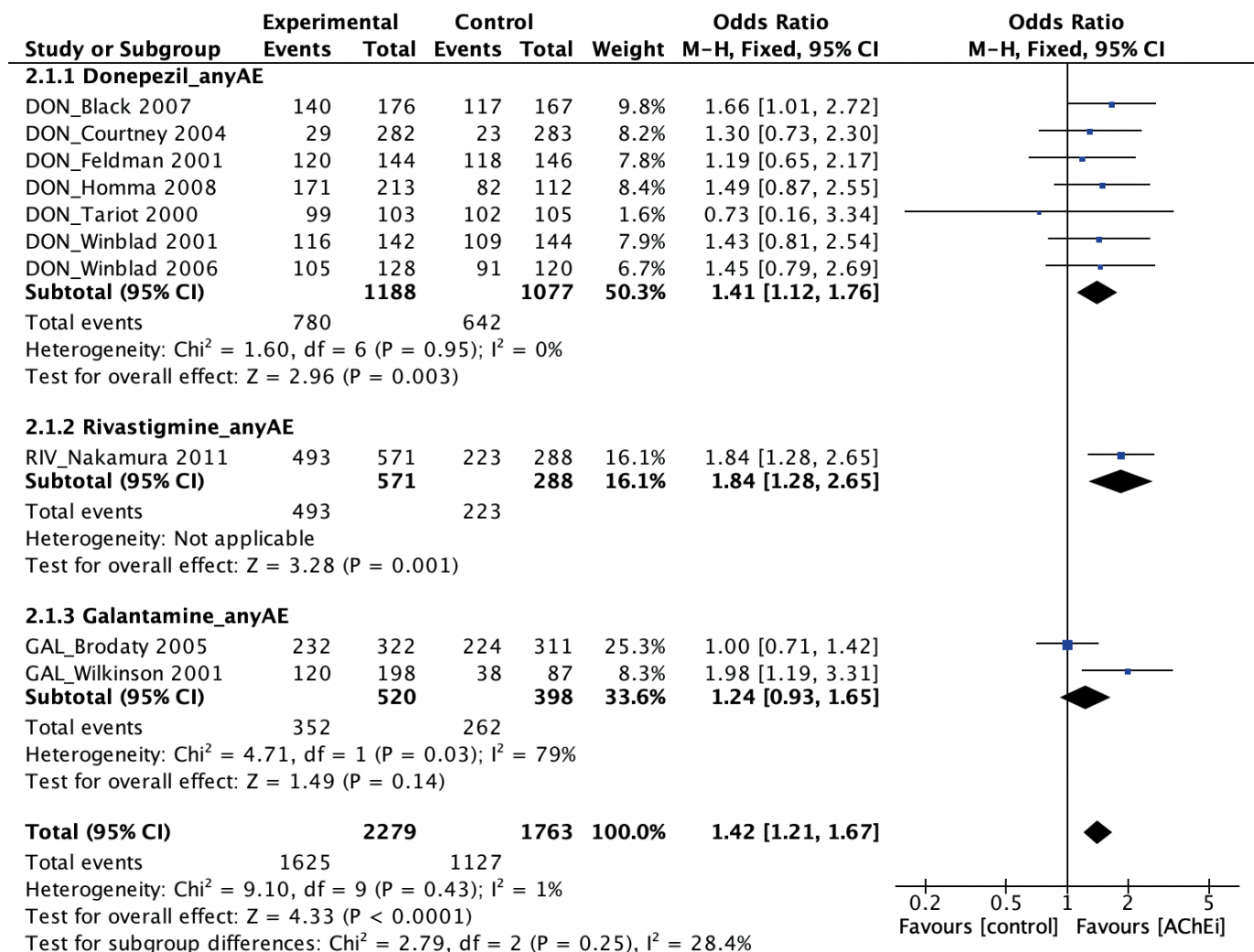


Fig. 5. Comparison of the risk of all adverse effects between cholinesterase inhibitors and placebo.
M-H: Mantel-Haenszel, CI: confidence interval, AChEi: acetylcholinesterase inhibitor.

to the risk of bias in the literature. The risk was considered lower compared to the benefits and given the high quality of evidence and the feasibility of applying the drug within the reimbursement range in actual clinical practice, it was assessed that the benefits outweighed the additional treatment and drug costs. Therefore, the strength of recommendation was “Strongly Recommend.”

Benefits and harms

1) Comprehensive evaluation of benefits

For patients diagnosed with AD dementia, the use of cholinesterase inhibitors demonstrated significant improvements in cognitive function, ADL, and dementia severity compared to the control group after approximately six months. By dementia severity, there were nine studies^{9,10,12,17,22} involving early-to-mid-stage AD dementia patients, six studies^{8,13,16,23} involving mid-to-late-stage AD dementia patients, and one study¹¹ that included participants across all stages or where the severity was unclear. Although differences in outcome measures existed depending on the stage, the overall effects showed relatively consistent results.

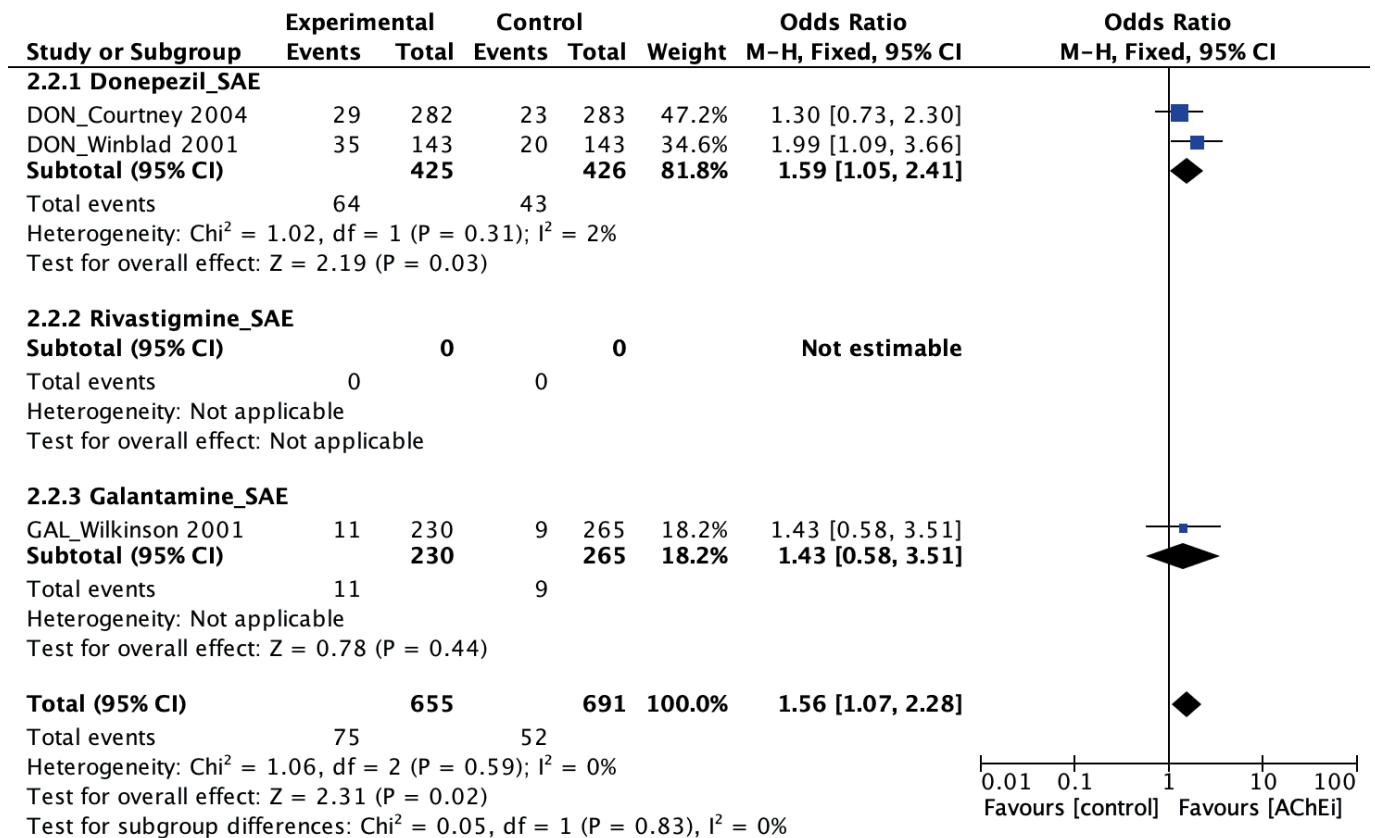


Fig. 6. Comparison of the risk of moderate to severe adverse effects between cholinesterase inhibitors and placebo.
M-H: Mantel-Haenszel, CI: confidence interval, AChEi: acetylcholinesterase inhibitor.

Table 4. GRADE summary of findings for cholinesterase inhibitors AD dementia (KQ1)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with AChEi			
MMSE (Critical)	The mean MMSE was 0	MD 0.81 higher (0.76 higher to 0.86 higher)	-	3,284 (6 RCTs)	⊕⊕⊕⊕ High
ADAS-Cog (Critical)	The mean ADAS-Cog was 0	MD 2.78 lower (2.83 lower to 2.73 lower)	-	4,004 (6 RCTs)	⊕⊕⊕○ Moderate ^a
ADCS-ADL (Critical)	The mean ADCS-ADL was 0	MD 1.17 higher (1.09 higher to 1.26 higher)	-	1,874 (4 RCTs)	⊕⊕⊕⊕ High
CDR-SB - not reported (Important)	-	-	-	-	-
CIBIC-Plus/CGI-C (Important)	The mean CIBIC-Plus/CGI-C was 0	MD 0.34 lower (0.4 lower to 0.28 lower)	-	3,381 (6 RCTs)	⊕⊕⊕⊕ High
AChEi - Any AE (Important)	639 per 1,000	716 per 1,000 (682 to 747)	OR 1.42 (1.21 to 1.67)	4,042 (10 RCTs)	⊕⊕⊕⊕ High
AChEi - Moderate to Severe AE (Important)	75 per 1,000	113 per 1,000 (80 to 157)	OR 1.56 (1.07 to 2.28)	1,346 (3 RCTs)	⊕⊕⊕⊕ High

Explanations: Risk of bias in blinding and incomplete outcome.

GRADE: Grading of Recommendations, Assessment, Development, and Evaluation, KQ: key question, CI: confidence interval; AChEi: acetylcholinesterase inhibitor, MMSE: Mini-Mental State Examination, MD: mean difference, RCT: randomized controlled trial, ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale, ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living, CDR-SB: Clinical Dementia Rating-Sum of Boxes, CIBIC-Plus/CGI-C: Clinician's Interview-Based Impression of Change Plus Caregiver Input/Clinical Global Impression of Change, AE: adverse event, OR: odds ratio.

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

2) Evaluation of harms

The group treated with cholinesterase inhibitors experienced significantly more occurrences of all adverse effects and moderate to severe adverse effects compared to the placebo group. The main adverse effects were cholinergic, including diarrhea, nausea, loss of appetite, and vomiting. Moderate to severe adverse effects were, in many cases, considered unrelated to the drug. However, adverse effects thought to be related to the drug included bradycardia, QT interval prolongation, dizziness, and syncope. Overall, the tolerability was good, but potential adverse effects need to be considered when using the drug.

3) Values and preferences

This recommendation does not address research results comparing patient preferences or the effects of different cholinesterase inhibitor components.

4) Resources (including costs)

Cholinesterase inhibitors are covered by insurance for patients diagnosed with AD dementia in South Korea, which means there are no major barriers to applying these drugs. Additionally, considering that patients and caregivers are generally well informed about the use of cholinesterase inhibitors and have little resistance to their use, it is believed that there are no obstacles to applying these drugs clinically.

5) Other considerations

Most of the studies used in this recommendation were based on outcome measurements taken at 6 months (24 weeks), so there is insufficient evidence to evaluate the benefits of longer-term drug use. All of the studies included in this recommendation were conducted based on clinical diagnosis rather than brain imaging or biomarker results to confirm AD. Therefore, it is likely that some patients with dementia due to causes other than AD were included. Since dementia can result from various underlying conditions, additional biomarker testing and expert consultation are recommended to perform a more precise diagnosis of AD, which could help predict the efficacy of the drug.

KQ2: Are acetylcholinesterase inhibitors effective in improving cognitive function/ADL for dementias other than AD?

PICO elements

- Population: Patients with Parkinson's disease dementia, Lewy body dementia, or vascular dementia
- Intervention: Cholinesterase inhibitors
- Control: Placebo treatment
- Outcomes: Cognitive function/ADL/Dementia severity
- Study design: RCTs

Recommendation

Recommendation:

- 1) Vascular dementia: The use of cholinesterase inhibitors in vascular dementia is effective in improving cognitive function, ADL, and reducing dementia severity (*Level of evidence: Moderate, Strength of recommendation: Conditional/Weak Recommend [B]*).

- 2) Lewy body dementia: The use of cholinesterase inhibitors in Lewy body dementia is effective in improving cognitive function, ADL, and reducing dementia severity (*Level of evidence: Moderate, Strength of recommendation: Strongly Recommend [A]*).
- 3) Parkinson's disease dementia: The use of cholinesterase inhibitors in Parkinson's disease dementia can be expected to improve cognitive function, ADL, and reduce dementia severity (*Level of evidence: Moderate, Strength of recommendation: Conditional/Weak Recommend [B]*).

Clinical considerations: It is necessary to check and consider potential side effects associated with the use of cholinesterase inhibitors

Evidence summary

To collect evidence for the above question, a total of 62,214 papers published up to 2023 were searched through PubMed, Embase, Cochrane Library, KMBase, and RISS. Additionally, 29 papers were added through hand searching. RCTs and large-scale observational studies were selected. Studies with fewer than 20 participants per group were excluded, as were those using comparators other than placebo. Through this process, a total of 40 studies on pharmacological interventions for dementia patients were selected. Of these, 26 studies focused on cholinesterase inhibitors, with 10 studies involving non-AD dementia patients: 5 on vascular dementia,²⁴⁻³³ 3 on Lewy body dementia,³⁰⁻³² and 2 on Parkinson's disease dementia.^{33,34} Outcome measures included MMSE (7 studies),^{25,27,29,31-34} ADAS-Cog (6 studies),^{25,26,28,29,33,34} ADCS-ADL (3 studies),^{28,29,33} and CIBIC-Plus/CGI-C (5 studies).^{25,29,31,33,34} Ten studies reported adverse effects.²⁵⁻³⁴

Regarding the efficacy and tolerability of cholinesterase inhibitors in dementias other than AD, the following findings were noted: First, in vascular dementia, Wilkinson et al.'s study (2003)²⁵ involved patients aged 40 and older with vascular dementia, meeting the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria and scoring 10–26 on the MMSE. The group treated with donepezil (5–10 mg) showed significant improvement compared to the placebo group in ADAS-Cog and CIBIC-Plus scores. Moretti et al.'s study (2003)²⁷ involved subcortical vascular dementia patients treated with rivastigmine (3–6 mg) for 12 months. Compared to the aspirin-treated group, there were significant improvements in MMSE scores. In Erkinjuntti et al.'s study (2002),²⁶ probable vascular dementia patients or AD patients with cerebrovascular disease (scoring 10–24 on MMSE) treated with galantamine (24 mg for 6 months) showed significant improvements in ADAS-Cog, CIBIC-Plus, and ADL compared to the placebo group. In Auchus et al.'s study (2007),²⁸ probable vascular dementia patients (MMSE score of 10–26) treated with galantamine for 26 weeks showed improvements in ADAS-Cog, except for those with dementia due to strategic infarctions; however, there were no significant effects on CIBIC-Plus or ADCS-ADL. Ballard et al.'s study (2008)²⁹ involved mild to moderate vascular dementia patients treated with rivastigmine for 24 weeks, which demonstrated significant effects in Vascular Dementia Assessment Scale, MMSE, and ADAS-Cog, but no significant effects in ADCS-Clinicians' Global Impression of Change Scale (CGIC) or ADCS-ADL, indicating an improvement in cognitive function but not in ADL or behavioral measures. All studies on vascular dementia consistently showed good safety and tolerability.

Considerations for recommendation

1) Level of evidence (applying GRADE)

All ten references were RCTs involving large-scale studies with at least 100 participants. Based on key outcome indicators, including MMSE, ADAS-Cog, CIBIC, and ADCS-ADL, the level of evidence was ultimately determined to be moderate. The evidence level was downgraded by one level due to inconsistency in the literature.

For Lewy body dementia, although the evidence is limited, the quality is high, suggesting that there will be benefits, with the risk being lower compared to the benefits, thus leading to a “Strongly Recommend.” For Parkinson’s disease dementia, benefits are expected, and the risks are lower compared to the benefits; however, the quality of evidence is insufficient, resulting in a “Conditional/Weak Recommendation.” In the case of vascular dementia, although benefits are expected, and the risks are lower compared to the benefits, heterogeneity was observed in the study populations, and the likelihood of drug coverage in actual clinical settings is low. Therefore, use is recommended when the benefit outweighs the cost of care and medication, leading to a “Conditional/Weak Recommendation.”

2) Evaluation of harms

In all studies involving vascular dementia, Lewy body dementia, and Parkinson’s disease dementia (excluding AD), most adverse effects were mild to moderate, and tolerability between treatment groups was generally favorable. The rate of treatment discontinuation due to adverse effects was higher in the galantamine (13%–20%) and rivastigmine (5.5%–20%) groups compared to the placebo group (0.9%–8%), with gastrointestinal-related adverse effects (nausea, vomiting) being the most common cause. Cardiovascular adverse effects and Parkinsonian symptoms were reported in some studies, but most were mild. The incidence of serious adverse effects was similar or slightly higher in the treatment groups (5.7%–20%) compared to the placebo groups (5.9%–18%), with no significant clinical differences. For donepezil and rivastigmine, the incidence of adverse effects increased at higher doses, but most patients continued treatment. Adverse effects leading to death were rare, and the safety profiles of donepezil, galantamine, and rivastigmine were consistent with previous findings in most studies (**Supplementary Table 3** and **Supplementary Fig. 3**).

3) Values and preferences

This recommendation statement does not include studies comparing patients’ preferences or the effects of individual cholinesterase inhibitors.

4) Resources (including costs)

The use of cholinesterase inhibitors is restricted within the insurance coverage scope in South Korea, except for AD dementia. Rivastigmine has been approved for dementia related to Parkinson’s disease, whereas donepezil and galantamine have only been approved for AD dementia. None of the three drugs have been approved for vascular dementia. Therefore, off-label use may present a barrier.

5) Other considerations

Most of the studies used in this recommendation statement were based on outcomes measured at 6 months (week 24). Therefore, there is insufficient evidence to evaluate the benefits of using these drugs beyond this period. Additionally, the small number of studies and their inconsistency require careful interpretation of the findings.

KQ3: Is the NMDA receptor antagonist (memantine) effective in improving cognition and ADL for dementia?

PICO elements

- Population: Patients with dementia
- Intervention: NMDA receptor antagonist (memantine)
- Control: Placebo treatment
- Outcomes: Cognitive function/ADL/Dementia severity
- Study design: RCTs

Recommendation

Recommendation: For AD dementia, the use of NMDA receptor antagonists is effective in improving cognitive function, ADL, and dementia severity (*Level of evidence: Moderate, Strength of recommendation: Strongly Recommend [A]*).

Clinical considerations:

- It is necessary to monitor and consider potential adverse effects resulting from the use of NMDA receptor antagonists.
- Since NMDA receptor antagonists are covered under the national insurance system for moderate to severe AD dementia, initial assessment and follow-up of the dementia stage are needed to confirm treatment eligibility.
- NMDA receptor antagonists can be considered for patients diagnosed with moderate to severe AD dementia. They have also shown effectiveness in patients already taking cholinesterase inhibitors; however, caution is needed regarding potential adverse reactions.
- NMDA receptor antagonists can be considered for mild to moderate Lewy body dementia.
- NMDA receptor antagonists are not beneficial for patients with frontotemporal dementia.
- NMDA receptor antagonists are not beneficial for patients with vascular dementia.

Evidence summary

To collect evidence for the above question, a total of 62,214 papers published up to 2023 were searched through PubMed, Embase, Cochrane Library, KMBase, and RISS. An additional 29 papers were added through hand searching. RCTs and large-scale observational studies were selected. Studies with fewer than 20 participants per group were excluded, as were those using comparators other than placebo. Through this process, a total of 40 studies on pharmacological interventions for dementia patients were selected. Fourteen of these studies involved NMDA receptor antagonists (**Supplementary Fig. 1**).³⁵⁻⁴⁸ The control group used a placebo. The target populations were dementia patients, with 10 studies focusing on AD dementia,^{35-43,48} 2 on vascular dementia,^{44,45} 1 on Lewy body dementia or Parkinson's disease dementia,⁴⁶ and 1 on frontotemporal dementia.⁴⁷ Outcome measures included MMSE (4 studies),^{35,37,39,45} ADAS-Cog (4 studies),^{36,37,44,45} the Severe Impairment Battery (SIB; 7 studies),^{35,38,41-43,48} ADCS-ADL (7 studies),^{35-38,41,46,48} and CIBIC-Plus/CGI-C (9 studies).^{35-38,41,43,45,47,48} Seven studies^{35,36,38,40,44,47,48} reported adverse effects. The characteristics and results of the studies are presented in the evidence table (**Supplementary Table 4** and **Supplementary Fig. 4**). The summary of the results is as follows.

Efficacy and safety of NMDA receptor antagonists in AD dementia

1) NMDA receptor antagonist monotherapy

In AD dementia, the efficacy and tolerability of NMDA receptor antagonists were evaluated in several studies. First, in Tariot et al.'s study (2004),⁴⁸ severe AD dementia patients treated with an NMDA receptor antagonist (5–10 mg) showed significant improvements in SIB and ADCS-ADL scores compared to the placebo group at 24 weeks, with no issues in tolerability. In Herrmann et al.'s study (2013),⁴² which involved moderate to severe AD dementia patients with severe behavioral disturbances (Neuropsychiatric Inventory [NPI] score ≥ 13 , NPI agitation/aggression score ≥ 1), treatment with an NMDA receptor antagonist (5–20 mg) showed no significant effects on NPI or total SIB scores compared to placebo at 24 weeks. However, safety and tolerability were good. Due to issues with subject recruitment, the clinical trial was terminated early, and caution is needed in interpreting the results.

2) Combination of acetylcholinesterase inhibitors and NMDA receptor antagonists

In Grossberg et al.'s study (2013),⁴¹ moderate to severe AD dementia patients already taking cholinesterase inhibitors were treated with an NMDA receptor antagonist (28 mg). At 24 weeks, the NMDA receptor antagonist group showed significant improvements in SIB and CIBIC-Plus scores compared to the placebo group. The rate of discontinuation due to adverse events was 9.9% in the NMDA receptor antagonist group and 6.3% in the placebo group, but there were no major issues in tolerability.

Dementias other than AD dementia

Regarding the efficacy and tolerability of NMDA receptor antagonists in dementias other than AD, several studies were reviewed. First, for Parkinson's disease dementia and Lewy body dementia, Emre et al.'s study (2010)⁴⁶ compared NMDA receptor antagonists (5–20 mg) to placebo in patients with Parkinson's disease dementia and Lewy body dementia, with MMSE scores ranging from 10 to 24. After 24 weeks, no significant improvement was observed in ADCS-CGIC, NPI, ADCS-ADL23, Unified Parkinson's Disease Rating Scale (UPDRS) Part III, or Zarit burden interview scores for Parkinson's disease dementia. In Lewy body dementia, no significant improvements were seen in NPI, ADCS-ADL23, UPDRS Part III, or Zarit burden interview scores, with significant improvement only in ADCS-CGIC scores. Most adverse effects were mild, and there were no issues with tolerability.

Second, for frontotemporal dementia, Boxer et al.'s study (2013)⁴⁷ compared NMDA receptor antagonists (10 mg) to placebo, finding no significant improvement in NPI or CGI-C scores. While there were no major issues with overall tolerability, cognitive adverse events were more frequently observed in the NMDA receptor antagonist group compared to the placebo group.

Third, for vascular dementia, Wilcock et al.⁴⁵ and Orgogozo et al.⁴⁴ compared NMDA receptor antagonists (20 mg) to placebo. In mild to moderate vascular dementia patients, there were positive effects on cognitive improvement.

Results of evidence synthesis on the efficacy and safety of NMDA receptor antagonists in AD. The synthesized evidence is summarized as follows. A total of 7 studies were included in the meta-analysis, and the outcome measures included changes in MMSE, ADCS-ADL, SIB, and CIBIC-Plus/CGI-C scores.

In the three studies that used MMSE as an outcome measure, NMDA receptor antagonists showed no significant effect compared to the control group (**Fig. 7**).

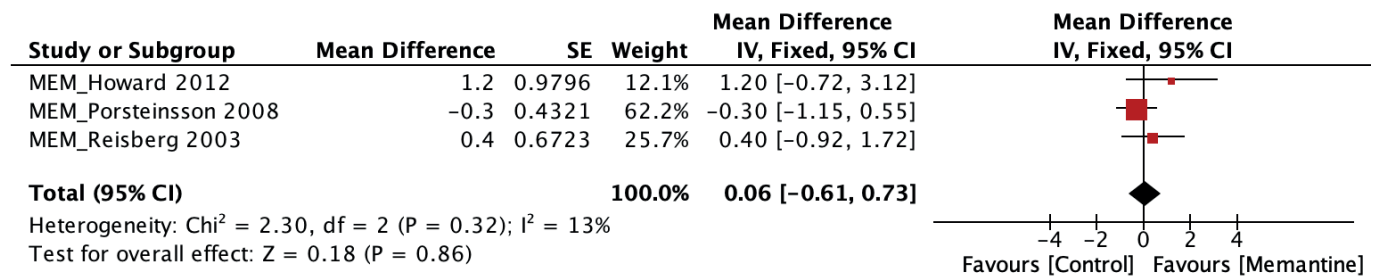


Fig. 7. Comparison of the effects of NMDA receptor antagonists and placebo on changes in MMSE.
 NMDA: N-methyl-D-aspartate, MMSE: Mini-Mental State Examination, SE: standard error, IV: interval variable, CI: confidence interval.

The use of NMDA receptor antagonists showed a significant effect compared to the control group. In a study involving 1,002 participants in the experimental group and 978 in the control group, the NMDA receptor antagonist group had an average ADCS-ADL score 1.14 points higher (95% CI, 1.06 to 1.22) than the control group, demonstrating a significant difference and indicating a positive effect on improving ADL ($p < 0.001$; **Fig. 8**).

In studies using the SIB score, the use of NMDA receptor antagonists showed a significant improvement in cognitive function compared to the control group. In a study involving 993 participants in the experimental group and 971 in the control group, the NMDA receptor antagonist group had an average SIB score 1.53 points higher (95% CI, 1.44 to 1.62) than the control group, showing a statistically significant difference ($p < 0.001$; **Fig. 9**).

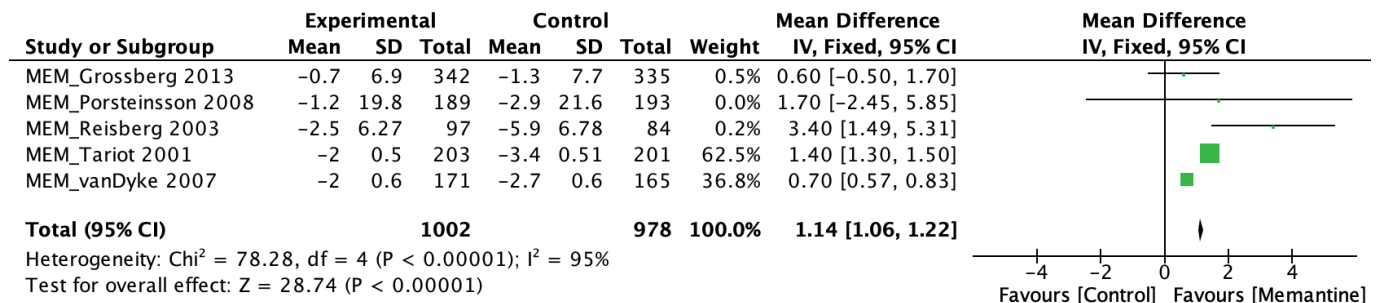


Fig. 8. Comparison of the effects of NMDA receptor antagonists and placebo on changes in ADCS-ADL.
 NMDA: N-methyl-D-aspartate, ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living, SD: standard deviation, IV: interval variable, CI: confidence interval.

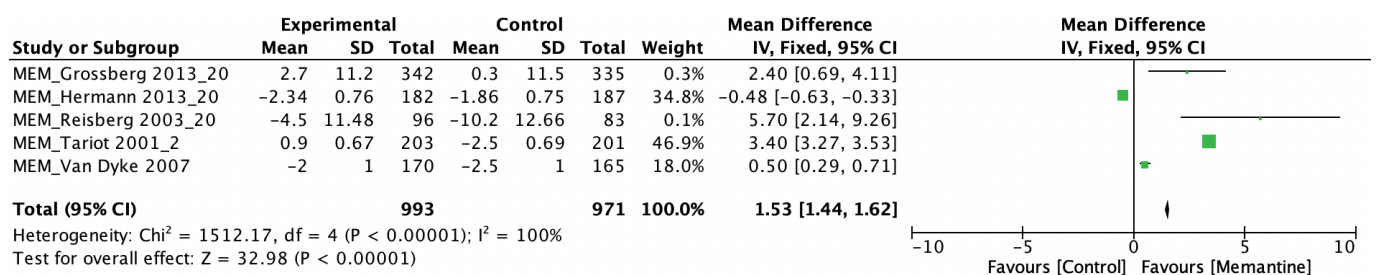


Fig. 9. Comparison of the effects of NMDA receptor antagonists and placebo on changes in SIB.
 NMDA: N-methyl-D-aspartate, SIB: Severe Impairment Battery, SD: standard deviation, IV: interval variable, CI: confidence interval.

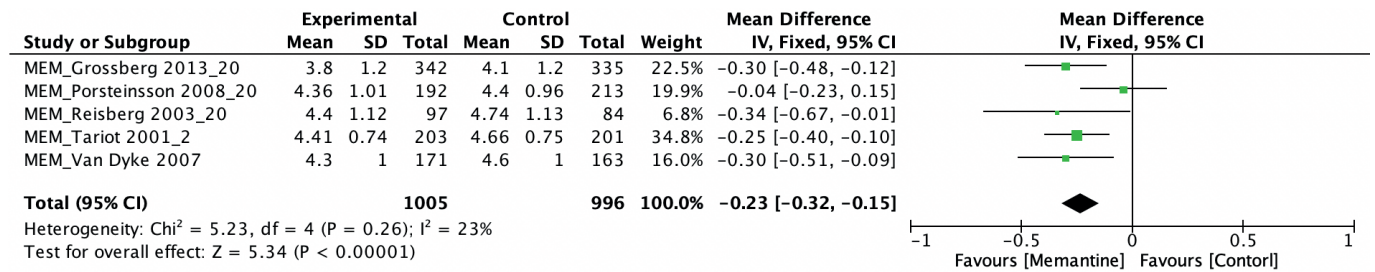


Fig. 10. Comparison of the effects of NMDA receptor antagonists and placebo on changes in CIBIC-Plus/CGI-C.

NMDA: N-methyl-D-aspartate, CIBIC-Plus/CGI-C: Clinician's Interview-Based Impression of Change Plus Caregiver Input/Clinical Global Impression of Change, SD: standard deviation, IV: interval variable, CI: confidence interval.

In studies using the CIBIC-Plus/CGI-C score as an assessment variable, the use of NMDA receptor antagonists showed a positive effect on the overall improvement of cognitive function and ADL compared to the control group. In a study involving 1,005 participants in the experimental group and 996 in the control group, the memantine group had an average CIBIC-Plus/CGI-C score 0.23 points lower (95% CI, -0.32 to -0.15) than the control group, indicating a statistically significant difference ($p < 0.001$; **Fig. 10**).

The results are summarized in the following **Table 5**.

Level of evidence (applying GRADE)

All 14 studies were RCTs, with at least 100 participants in each study, except for one. The level of evidence was ultimately determined as moderate based on the results of critical outcome measures such as MMSE, ADAS-Cog, ADCS-ADL, SIB, and CIBIC-Plus. The precision of the literature was assessed, and one level was downgraded. The risk compared to the benefit was considered low, and the quality of evidence was high. The likelihood of drug application within the reimbursement range in actual clinical practice was also high, suggesting that the benefits outweigh the additional medical and drug costs. Therefore, a “Strong Recommendation” was given.

Table 5. GRADE summary of findings for NMDA receptor antagonists in AD dementia (KQ3)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	Risk with memantine			
MMSE (Critical)	The mean MMSE was 0	MD 0.06 higher (0.61 lower to 0.73 higher)	-	669 (3 RCT)	⊕⊕⊕○ Moderate ^a
ADAS-Cog - not reported (Critical)	-	-	-	-	-
ADCS-ADL (Critical)	The mean ADCS-ADL was 0	MD 1.14 higher (1.06 higher to 1.22 higher)	-	1,598 (4 RCTs)	⊕⊕⊕⊕ High
SIB (Important)	The mean SIB was 0	MD 1.53 higher (1.44 higher to 1.62 higher)	-	1,964 (5 RCTs)	⊕⊕⊕○ Moderate ^b
CIBIC-Plus (Important)	The mean CIBIC-Plus was 0	MD 0.23 lower (0.32 lower to 0.15 lower)	-	2,001 (5 RCTs)	⊕⊕⊕⊕ High

Explanations: Small sample size and wide confidence interval; Unknow reason of high heterogeneity.

GRADE: Grading of Recommendations, Assessment, Development, and Evaluation, NMDA: N-methyl-D-aspartate, AD: Alzheimer's disease, CI: confidence interval, MMSE: Mini-Mental State Examination, MD: mean difference, RCT: randomized controlled trial, ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale, ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living, SIB: Severe Impairment Battery, CIBIC-Plus: Clinician's Interview-Based Impression of Change Plus Caregiver Input.

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Benefit and risk

1) Comprehensive evaluation of benefits

The use of NMDA receptor antagonists in patients diagnosed with AD dementia has shown significant improvements in cognitive function, ADL, and the severity of dementia. These significant effects were also observed when used in combination with cholinesterase inhibitors. In other forms of dementia, NMDA receptor antagonists may have some efficacy in mild to moderate dementia with Lewy bodies, especially in overall function. However, no benefit has been confirmed for Parkinson's disease dementia or frontotemporal dementia. The limited number of studies on other forms of dementia calls for caution in interpretation.

2) Evaluation of risk

For AD dementia, the group receiving NMDA receptor antagonists showed no significant difference in adverse events compared to the placebo group. Major side effects included dizziness, confusion, headache, and gastrointestinal symptoms, most of which were mild or moderate. Serious side effects were rare and did not differ significantly from the placebo group. In other forms of dementia, similar side effects were observed without significant differences compared to placebo. Overall, NMDA receptor antagonists demonstrated good tolerability, though major side effects should be carefully monitored during use.

3) Value and preferences

This guideline does not cover research comparing patients' preferences.

4) Resources (including costs)

NMDA receptor antagonists are covered under the national insurance system for patients with moderate to severe AD dementia, thus posing no major obstacles for such patients in terms of drug access. Treatment requires initial assessment and follow-up evaluation of the stage of dementia to determine eligibility. However, for dementias other than AD dementia, insurance coverage is not provided, which may act as a barrier.

5) Other considerations

Most of the studies cited in this guideline are based on outcomes measured at 6 months (week 24), and therefore evidence on the benefits of longer-term use is limited.

DISCUSSION

This clinical practice guideline focuses on evidence-based recommendations for enhancing cognitive function in dementia patients through cholinesterase inhibitors and NMDA receptor antagonists. These recommendations were established based on RCTs, supported by systematic reviews and meta-analyses conducted using data from these trials. Using the GRADE methodology, the evidence was graded for its quality and strength, and the following key findings are summarized (**Table 6**).

There are some limitations. This guideline does not include long-term efficacy data, as most studies span 12–24 weeks. It also does not address patient preferences or the comparative effectiveness of different drug components. These limitations highlight the need for personalized treatment planning and ongoing research to refine therapeutic strategies.

Table 6. Summary of guideline

KQ	Key question	Recommendation	Evidence level	Strength of recommendation
1	Are cholinesterase inhibitors effective in improving cognitive function/ADL for AD dementia?	For AD dementia, the use of cholinesterase inhibitors is effective in improving cognitive function, ADL, and dementia severity.	Moderate	Strongly Recommend (A)
2	Are acetylcholinesterase inhibitors effective in improving cognitive function/ADL for dementias other than AD?	Vascular dementia: The use of cholinesterase inhibitors in vascular dementia is effective in improving cognitive function, ADL, and reducing dementia severity.	Moderate	Conditional/Weak Recommend (B)
		Lewy body dementia: The use of cholinesterase inhibitors in Lewy body dementia is effective in improving cognitive function, ADL, and reducing dementia severity.	Moderate	Strongly Recommend (A)
		Parkinson's disease dementia: The use of cholinesterase inhibitors in Parkinson's disease dementia can be expected to improve cognitive function, ADL, and reduce dementia severity.	Moderate	Conditional/Weak Recommend (B)
3	Is the NMDA receptor antagonist (memantine) effective in improving cognition and ADL for dementia?	For patients with AD dementia, the use of NMDA receptor antagonists is effective in improving cognition, ADL, and the severity of dementia.	Moderate	Strongly Recommend (A)

KQ: key question, ADL: activity of daily living, AD: Alzheimer's disease, NMDA: N-methyl-D-aspartate.

When implementing these recommendations, clinicians should weigh the benefits of these pharmacological treatments against their potential risks and costs. Discussions with patients and caregivers about treatment options, anticipated outcomes, and possible side effects are critical for shared decision-making.

This guideline represents the first systematic effort in South Korea to standardize pharmacological treatment recommendations for dementia based on rigorous evidence evaluation. It serves as a foundation for updating treatment strategies as new therapies emerge, aiming to optimize clinical outcomes and address unmet needs in dementia care.

SUPPLEMENTARY MATERIALS

Supplementary Data 1

Korean version of Clinical Practice Guideline for Dementia

Supplementary Data 2

Introducing the scales for assessment

Supplementary Table 1

Search query

Supplementary Table 2

Evidence table for the use of acetylcholinesterase inhibitors AD dementia

Supplementary Table 3

Evidence table for the use of acetylcholinesterase inhibitors in dementias other than Alzheimer's disease

Supplementary Table 4

Evidence table for the use of NMDA receptor antagonist (memantine)

Supplementary Fig. 1

Literature search flow chart (PRISMA flowchart).

Supplementary Fig. 2

Quality assessment results of the studies about use of acetylcholinesterase inhibitors AD dementia.

Supplementary Fig. 3

Quality assessment results of the studies about use of acetylcholinesterase inhibitors in dementias other than Alzheimer's disease.

Supplementary Fig. 4

Quality assessment results of the studies about NMDA receptor antagonists.

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