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Original Article



# Clinical Practice Guidelines for Dementia: Recommendations for the Pharmacological Treatment of Behavioral and Psychological Symptoms

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## ABSTRACT

**Background and Purpose:** Dementia often accompanies behavioral and psychological symptoms of dementia (BPSD), including agitation, aggression, depression, and psychosis, which impact patients' quality of life and caregiver burden. Effective management of BPSD

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**Conflict of Interest**

The authors have no financial conflicts of interest.

is essential to support patient and caregiver well-being. This study presents evidence-based clinical practice guidelines for pharmacological treatments of BPSD in dementia, focusing on antipsychotics, antidepressants, cognitive enhancers, and other medications.

**Methods:** This guideline was developed by the Korean Dementia Association's Quality Management Committee. Key questions were framed using the Population, Intervention, Comparison, Outcome methodology, followed by systematic literature searches. Randomized controlled trials were assessed for quality, and recommendations were graded based on evidence levels, employing the Grading of Recommendations, Assessment, Development and Evaluation system to establish strength and applicability.

**Results:** Recommendations vary by medication type and symptom severity. Antipsychotics, such as risperidone, are conditionally recommended for managing aggression and psychosis in dementia, while antidepressants, specifically citalopram, are advised for agitation in Alzheimer's disease. Cognitive enhancers, including cholinesterase inhibitors and memantine, showed moderate efficacy for general BPSD improvement and rapid eye movement sleep behavior disorder in Lewy body dementia. Specific drugs, like pimavanserin, demonstrated efficacy in addressing psychosis in Alzheimer's patients.

**Conclusions:** These guidelines provide a structured approach to pharmacological management of BPSD in dementia, addressing efficacy and safety profiles across drug categories. The recommendations emphasize personalized treatment plans to optimize therapeutic outcomes while minimizing risks, with a conditional approach suggested in cases with limited evidence.

**Keywords:** Dementia; Behavioral Symptoms; Drug Therapy; Guideline

## INTRODUCTION

Dementia refers to a condition where cognitive decline occurs in adults who previously exhibited normal development, typically in older adulthood or late middle age, leading to the loss of independent daily functioning. Causes of dementia include Alzheimer's disease, vascular dementia, Lewy body dementia, and frontotemporal dementia, each of which presents unique prognostic and therapeutic challenges.[1] In dementia, cognitive decline is often accompanied by behavioral and psychological symptoms of dementia (BPSD), which may emerge early and become more pronounced in the advanced stages. Key BPSD features include mood and anxiety symptoms, such as depression and anxiety, as well as insomnia, apathy, agitation, disinhibition, repetitive behaviors, and psychotic symptoms like hallucinations and delusions. These symptoms contribute significantly to caregiver stress and are a primary factor in early institutionalization. Consequently, managing BPSD effectively is essential to improving the quality of life for both patients and caregivers.[2]

These clinical practice guidelines evaluate the efficacy and potential adverse effects of pharmacologic treatments commonly employed in clinical settings for BPSD, particularly focusing on antipsychotics, antidepressants, cognitive enhancers, and other medications.

## METHODS

### Target population, scope, purpose, and users of the clinical practice guidelines

The target population of these clinical guidelines is patients with dementia. The scope of the guidelines covers pharmacological treatment, developed by the Korean Dementia

**Author Contributions**

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

Association Quality Management Committee through key questions (KQs) structured around the Population, Intervention, Comparison, and Outcomes (PICO) format. The purpose of these guidelines is to establish an evidence-based standard for dementia treatment, aimed at aiding clinical decision-making regarding diagnosis and therapy. Intended users of these guidelines include neurologists and psychiatrists diagnosing and treating dementia, as well as internists, family physicians, and primary care providers involved in dementia management and treatment planning. The Korean version of the revision guideline is provided as **Supplementary Data 1**.

## Clinical practice guideline development committee composition

Primary decisions throughout the guideline development process were made by the Steering Committee, with the project budget reviewed and approved by the Korean Dementia Association Board. Although the guidelines were fully funded by the Korean Dementia Association, there was no influence from the association on guideline development. The Executive Committee, composed primarily of members of the Korean Dementia Association's Quality Management Committee, was responsible for drafting these guidelines. Neurologists served as the core members, with additional input from psychiatrists, and the committee included Chairperson Dongwon Yang, nine steering committee members, 18 working committee members, three advisors, and a literature review specialist (**Table 1**). The committee finalized recommendations through the identification

**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 |
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of KQs, assessment of evidence quality, data collection, and grading of recommendations. Literature searches were performed by One's Global Co., Ltd, and methodology advice was provided by Ms. Miyoung Choi, from the National Evidence-based Healthcare Collaborating Agency. Workshops were held to guide literature review, meta-analysis, evidence assessment, and recommendation grading.

The initial draft of the guidelines was reviewed internally by the Korean Dementia Association Quality Management Committee to produce a first revision, followed by an external review involving related societies such as the Korean Neurological Association, Korean Association for Geriatric Psychiatry, Korean Neuropsychiatric Association, and other relevant groups. Feedback from this review process was incorporated into the final version.

## Dissemination and future revisions

The guidelines, along with supplementary materials, are available in the Korean Dementia Association journal (https://www.dnd.or.kr) and on the Korean Dementia Association website (https://www.dementia.or.kr). Considering the expected introduction of new therapeutic options, such as beta-amyloid antibodies, the guidelines will be reviewed and updated as necessary, with revisions planned at approximately 3-year intervals by the Quality Management Committee of the Korean Dementia Association.

## Guideline development methods

These clinical practice guidelines were developed *de novo*, building upon new KQs that were not addressed in the 2021 guidelines.

## KQ development

The Executive Committee identified major topics related to BPSD management not previously covered in existing guidelines and formulated four KQs through PICO-based discussion. The four questions are as follows.

- KQ1: For dementia patients with BPSD, do antipsychotics provide more benefit than harm compared to placebo or non-pharmacological interventions?
- KQ2: For dementia patients with BPSD, do antidepressants provide more benefit than harm compared to placebo or non- pharmacological interventions?
- KQ3: For dementia patients with BPSD, do cognitive enhancers provide more benefit than harm compared to placebo or non- pharmacological interventions?
- KQ4: For dementia patients with BPSD, do other medications provide more benefit than harm compared to placebo or non- pharmacological interventions?

## Literature search and quality assessment

Systematic reviews were conducted for each KQ. One's Global Co., Ltd selected keywords for each topic and searched PubMed, Embase, Cochrane Library, KMbase, and RISS databases. Studies were screened based on criteria including 1) randomized controlled trial (RCT) design and 2) relevant outcomes. Common exclusion criteria were 1) non-applicable study designs, 2) studies not conforming to PICO, 3) publications in languages other than English or Korean, 4) duplicate publications, and 5) inability to obtain full texts. Selected studies were reviewed using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines,[3] resulting in 33 studies (7 on antipsychotics, 9 on antidepressants, 11 on cognitive enhancers, and 6 on other medications) (**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) (**Supplementary Data 2**).

**Table 2.** Evidence levels in the GRADE system

| 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.** Recommendation strengths and expressions

| Recommendation strength | 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. |

### Evidence grading and recommendation development

After reviewing the selected studies, evidence tables were created and meta-analyses conducted where applicable. Levels of evidence and recommendation strengths were graded using the Grading of Recommendations, Assessment, Development and Evaluation 14 methodology (**Tables 2** and **3**).[4]

## RESULTS

### KQ1: For dementia patients with BPSD, do antipsychotic treatments provide more benefit than harm compared to placebo or non-pharmacological interventions?

*PICO elements*

- Population: patients with dementia
- Intervention: antipsychotics treatment
- Control: placebo or non-pharmacological interventions
- Outcomes:
  Primary outcome: scores on behavioral and psychological symptom scales (e.g., agitation, psychotic symptoms)
  Secondary outcome: adverse effects
- Study design: RCTs

*Recommendation*

- Antipsychotics may be used in dementia patients to improve agitation, aggression, and psychotic symptoms (Evidence level: moderate, Recommendation grade: conditional recommendation [weak]).
- Clinical considerations antipsychotic use should be carefully evaluated due to potential adverse effects, including extrapyramidal symptoms and sedation.

*Supporting evidence*

The expert review included seven studies, of which three involved only patients diagnosed with Alzheimer's disease, while others included mixed dementia populations (Alzheimer's,


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vascular, and other types). The primary outcome measures were the Cohen Mansfield Agitation Inventory (CMAI) in three studies, the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) scale in two studies, the Neuropsychiatric Inventory (NPI) in three studies, and the Brief Psychiatric Rating Scale (BPRS) in one study. These studies evaluated changes in outcome measures after 6 to 12 weeks of treatment and presented adverse event rates separately for intervention and placebo groups (**Supplementary Table 1**, **Supplementary Fig. 2**).

Agitation studies including non-Alzheimer's dementia patients showed that in the 2003 study by Brodaty et al.,[5] risperidone (0.5–2 mg/day) significantly improved agitation with or without aggression compared to placebo. In the 2006 study by Tariot et al.,[6] quetiapine (25–600 mg/day) improved agitation on the BPRS but not on the NPI-agitation scale. Haloperidol (0.5–12 mg/day) did not significantly improve agitation on either scale and increased symptoms of anergia on the BPRS-anergia scale.[6] However, this study included patients with mixed diagnoses (e.g., schizophrenia, bipolar disorder, alcohol-related dementia, and delusional disorder), which may limit its generalizability to dementia populations.

For studies focusing on Alzheimer's disease, two studies by Grossberg et al.[7] (2020) showed that brexpiprazole (2 mg/day) significantly improved CMAI scores compared to placebo. Notably, these studies targeted patients with pre-existing agitation symptoms (NPI-agitation score ≥4), making the findings relevant for this subgroup. As a result, in May 2023, the Food and Drug Administration approved brexpiprazole (brand name: Rexulti) for treating agitation in Alzheimer's patients. In another study by Paleacu et al.[8] (2008) on Alzheimer's patients, quetiapine (150–300 mg/day) did not show significant improvement in NPI domain scores for agitation, likely due to the small sample size (12 patients) and short observation period (6 weeks).

Studies including mixed dementia patients showed that risperidone (0.5–2 mg/day) significantly improved BEHAVE-AD psychosis subscale scores in a study by Brodaty et al.[5] (2003). In a 2005 study by Brodaty et al.,[9] only patients with a BEHAVE-AD psychosis subscale score of ≥2 were included, and risperidone again demonstrated significant improvement in psychotic symptoms compared to placebo. This study not only replicated previous findings but also used the BEHAVE-AD psychosis subscale as the primary outcome, reinforcing risperidone's efficacy. Conversely, in the 2005 study by Deberdt et al.,[10] neither olanzapine (2.5–10 mg/day) nor risperidone improved NPI hallucination/delusion scores significantly. Similarly, Tariot et al.[6] (2006) reported no significant effect of quetiapine (100–600 mg/day) or haloperidol on NPI-hallucination or delusion scores, although this study included patients with heterogeneous diagnoses.

*Benefits and risks*

1) Benefits

When dementia is diagnosed, it is clinically essential to evaluate underlying conditions through blood work, imaging, etc. Antipsychotics may be considered for Alzheimer's patients with prominent BPSD symptoms, particularly agitation and psychosis. However, existing studies generally observe treatment effects within a 3-month period, and evidence for longer-term use remains limited.

2) Risks

In studies including mixed dementia types, risperidone (0.5–2 mg/day) was associated with


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increased drowsiness and urinary tract infections compared to placebo in the 2003 study by Brodaty et al.[9] Risperidone-treated patients also showed an increase in extrapyramidal symptoms, measured by the Extrapyramidal Symptom Rating Scale.[9] In a 2020 study by Grossberg et al.,[7] brexpiprazole (0.5–2 mg/day) was associated with adverse event rates of 65.0% for 2 mg, 49.0% for 0.5–1 mg, and 45.9% for placebo over a 12-week period. Common side effects with brexpiprazole at 2 mg were headache, insomnia, dizziness, and urinary tract infection, with headache being the most common (7.6%) in the lower dose group. Most side effects were mild to moderate. Serious adverse event (SAE) rates were 9.3% in the 2 mg group, 10.2% in the 0.5–1 mg group, and 5.2% in the placebo group, with urinary tract infection and agitation reported as serious side effects. Five deaths occurred in the brexpiprazole group, though none were deemed related to the treatment. In a 2006 study by Tariot et al.[6] focusing on Alzheimer's patients, haloperidol was associated with a significant increase in Parkinsonian gait and bradykinesia compared to non-drug treatment.

Based on these findings, **Table 4** presents the evidence grade for the benefits of antipsychotic treatment in dementia patients, with "agitation" rated as high for Alzheimer's patients and moderate for non-Alzheimer's patients, and "psychotic symptoms" rated as moderate. **Table 5** outlines the primary adverse effects, with an evidence grade of moderate.

**Table 4.** Evidence level for the benefits of antipsychotic treatment

| Outcomes | Anticipated absolute effects (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with placebo | Risk with antipsychotic agents | | | |
| [Key findings] Agitation | | | | | |
| Alzheimer's dementia | In two large-scale studies on Alzheimer's patients treated with brexipiprazole,[7] the intervention group showed a significant improvement in agitation symptoms compared to the placebo group. However, risperidone showed no significant improvement in a separate study, which had a low evidence level due to its small sample size (12 participants). | | | 717 (3 RCTs) | ⊕⊕⊕⊕ High |
| Non-Alzheimer's dementia | Studies with heterogeneous dementia diagnoses generally showed a trend toward improvement in agitation symptoms with antipsychotic treatment. This was demonstrated in a large-scale study by Brodaty et al.[9] (2003), although findings varied across scales in the 2006 study by Tariot et al.[6] | | | 714 (2 RCTs) | ⊕⊕⊕○ Moderate* |
| [Key findings] Psychotic symptoms | In a study by Paleacu et al.[8] (2008), which included only Alzheimer's dementia patients, quetiapine showed no significant improvement in psychotic symptoms compared to placebo, though the study had a small sample size of 12 participants. In studies including heterogenous diagnostic groups, risperidone showed significant improvements in psychotic symptoms in two large-scale studies by Brodaty et al.[5,9] (2003 and 2005). However, in a study by Deberdt et al.[10] (2005), neither olanzapine nor risperidone demonstrated significant effects on psychotic symptoms compared to placebo. | | | 950 (5 RCTs) | ⊕⊕⊕○ Moderate* |

CI: confidence interval, GRADE: Grading of Recommendations, Assessment, Development and Evaluation, RCT: randomized controlled trial.
*Inconsistency in result direction.

**Table 5.** Evidence level for the risks of antipsychotic treatment

| Outcomes | Anticipated absolute effects (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with placebo | Risk with antipsychotic agents | | | |
| [Key findings] Adverse effect | Risperidone was associated with a significant increase in drowsiness, urinary tract infections, and scores on extrapyramidal symptom rating scales.<br>In patients receiving brexpiprazole, the incidence of adverse events was 65.0% in the 2 mg group, 49.0% in the 0.5–1 mg group, and 45.9% in the placebo group, with most side effects being mild to moderate.<br>In a 2006 study by Tariot et al.[6] focused on Alzheimer's disease, haloperidol was compared with non-drug interventions and was associated with a significant increase in extrapyramidal symptoms, including Parkinsonian gait and bradykinesia. | | | 892 (3 RCTs) | ⊕⊕⊕○ Moderate* |

CI: confidence interval, GRADE: Grading of Recommendations, Assessment, Development and Evaluation, RCT: randomized controlled trial.
*Imprecision due to small events.


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### KQ2: For dementia patients with BPSD, do antidepressants provide more benefit than harm compared to placebo or non-pharmacological interventions?

*PICO elements*

- For Alzheimer's dementia, antidepressants may be used to improve symptoms of depression, agitation, and aggression (Evidence level: moderate, Recommendation grade: conditional recommendation [weak]).
- For Alzheimer's dementia, the use of antidepressants is not recommended for the improvement of apathy or overall behavioral and psychological symptoms (Evidence level: moderate, Recommendation grade: conditional recommendation against [weak]).
- Clinical considerations: antipsychotic use should be carefully evaluated due to potential adverse effects, including gastrointestinal symptoms (decreased appetite, nausea, indigestion, diarrhea) and sedation.
- For non-Alzheimer's dementia, these effects have not been demonstrated.

*Recommendation*

- Population: patients with dementia
- Intervention: antidepressants treatment
- Control: placebo treatment
- Outcomes:
  Primary outcome: scores on behavioral and psychological symptom scales
  Secondary outcome: adverse effects
- Study design: RCT

*Supporting evidence*

Through expert review, a total of nine studies were selected. All studies were RCTs with antidepressant treatment as the intervention and placebo as the control. All 9 studies focused on patients with dementia due to Alzheimer's disease. Seven studies used the NINCDS-ADRDA criteria for diagnosis of Alzheimer's dementia, while two used the DSM-IV criteria. In terms of outcome variables, six studies focused on Alzheimer's dementia patients with comorbid depression, one study on patients with agitation/aggression, one on patients with apathy but no depression, and one study on Alzheimer's dementia patients with BPSD without specific symptom classification.

The Mini-Mental Status Examination (MMSE) score range in five studies was 10–26, while Porsteinsson et al.[11] (2014) and Finkel et al.[12] (2004) had wider or lower score distributions of 5–28 and 8–23, respectively. Two studies, Zuidersma et al.[13] (2019) and Banerjee et al.[14] (2013), did not report MMSE scores. Primary outcome measures included one study using the agitation subscale of the Neurobehavioral Rating Scale (NBRS), four studies using the Cornell Scale for Depression in Dementia (CSDD), one using the Apathy Evaluation Scale–Clinician Version (AES-C), and one using the NPI, with CSDD being the most commonly used scale (**Supplementary Table 2**, **Supplementary Fig. 3**).

*Benefits*

1) Depression

Among studies on Alzheimer's patients with comorbid depression, Banerjee et al.[14] (2013) and Zuidersma et al.[13] (2019) evaluated the effects of sertraline and mirtazapine on depression using the CSDD scale at 13 and 39 weeks of treatment. Both studies found no


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significant benefit of either sertraline or mirtazapine compared to placebo for depression. In Zuidersma et al.[13] (2019), patients with predominant symptoms of pessimism and low self-esteem showed a significant improvement in CSDD scores with mirtazapine at 13 weeks, but this effect was not observed at 39 weeks. In studies by Rosenberg et al.[15] (2010) and Weintraub et al.[16] (2010), sertraline was also evaluated for depression at 12 and 24 weeks using the CSDD scale, with neither study demonstrating significant treatment effects. For escitalopram, An et al.[17] (2017) assessed treatment effects on depression in Alzheimer's patients over 12 weeks with no significant improvement compared to placebo. Similarly, Jeong et al.[18] (2022) found no significant improvement with vortioxetine at three weeks using the CSDD scale. Overall, these studies suggest that mirtazapine may offer short-term benefits for certain depressive symptoms, such as pessimism and low self-esteem, but no significant benefit was found for other antidepressants compared to placebo.

2) Agitation, aggression, apathy, and overall BPSD

In a study by Porsteinsson et al.[11] (2014), citalopram significantly improved agitation and aggression symptoms compared to placebo in Alzheimer's patients with these symptoms, as assessed at nine weeks using the NBRS-A scale. The study found an estimated treatment effect of citalopram with an odds ratio of 2.13 compared to placebo for agitation and aggression and a significant reduction in caregiver distress scores. For apathy, which is a common BPSD in Alzheimer's patients, Maier et al.[19] (2020) evaluated the effect of bupropion on apathy in Alzheimer's patients without depression. Using the AES-C scale, they found no significant treatment effect compared to placebo at 12 weeks.[19] Lastly, Finkel et al.[12] (2004) evaluated sertraline for overall BPSD at 12 weeks using the NPI scale and found no significant treatment effect. In this study, patients in the intervention group received both donepezil and sertraline, while the control group received placebo plus donepezil. However, when analyzing specific subgroups with moderate to severe BPSD, sertraline showed significant effects on NPI subdomains, including dysphoria, irritability, anxiety, and agitation/aggression at 12 weeks.[12]

These results suggest that citalopram may be beneficial for agitation and aggression in Alzheimer's patients, and sertraline may have specific benefits in moderate to severe BPSD cases for certain symptom subdomains. However, no significant benefit of antidepressants was found for apathy or overall BPSD symptoms.

*Risks*

In the study by Porsteinsson et al.[11] (2014), adverse effects in the citalopram group included significantly higher rates of decreased appetite, diarrhea, and fever compared to placebo. Falls and upper respiratory infections were more common in the treatment group but did not reach statistical significance. The treatment group also had an average QTc interval increase of 18.1 ms compared to the control group. Rosenberg et al.[15] (2010) reported higher rates of diarrhea, dyspepsia, dry mouth, and dizziness in the sertraline group compared to placebo. In Jeong et al.[18] (2022), nausea (8.16% vs. 3.92%) and diarrhea (6.12% vs. 3.92%) were more common with vortioxetine compared to placebo. Maier et al.[19] (2020) reported significantly higher rates of gastrointestinal symptoms (17.2% vs. 6.1%) with bupropion compared to placebo, but no significant differences in sleep disturbances, falls, agitation, or confusion. An et al.[17] (2017) found no significant difference in adverse effects between the escitalopram and placebo groups. In Banerjee et al.[14] (2013), sertraline was associated with more gastrointestinal symptoms, such as nausea, compared to placebo, while mirtazapine was associated with sedation and drowsiness more often than placebo. In the study by Weintraub


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**Table 6.** Evidence level for the benefits of antidepressants treatment

| Outcomes | Anticipated absolute effects (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with placebo | Risk with anti-depressive agents | | | |
| [Key findings] Depression | In patients with Alzheimer's dementia accompanied by depression, short-term therapeutic effects of mirtazapine were observed in cases where prominent symptoms included pessimism and low self-esteem, which align with the diagnostic criteria for major depressive disorder.[13] However, four other studies failed to demonstrate significant therapeutic benefits of mirtazapine compared to placebo. | | | 1,098 (6 RCTs) | ⊕⊕⊕○ Moderate* |
| [Key findings] BPSD other than depression | | | | | |
| Agitation and aggression | In patients with Alzheimer's dementia accompanied by agitation and aggression, citalopram demonstrated significant therapeutic effects on agitation and aggression symptoms compared to placebo.[11] Additionally, in cases where the severity of behavioral and psychological symptoms was moderate to severe, sertraline showed significant therapeutic effects on specific subdomains of behavioral and psychological symptoms, including agitation and aggression.[12] | | | 413 (2 RCTs) | ⊕⊕⊕○ Moderate* |
| Apathy, overall BPSD | There is no significant therapeutic effect of antidepressants compared to placebo for apathy or overall BPSD. | | | 344 (2 RCTs) | ⊕⊕⊕○ Moderate* |

CI: confidence interval, GRADE: Grading of Recommendations, Assessment, Development and Evaluation, RCT: randomized controlled trial, BPSD: behavioral and psychological symptoms of dementia.
*Inconsistency between studies and outcomes direction.

**Table 7.** Evidence level for the risks of antidepressants treatment

| Outcomes | Anticipated absolute effects (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with placebo | Risk with antipsychotic agents | | | |
| [Key findings] Adverse effects | Gastrointestinal symptoms (decreased appetite, nausea, indigestion, diarrhea), dry mouth, dizziness, fever, QTc interval prolongation on ECG, drowsiness, and sedation may occur as side effects of antidepressants. However, the incidence of serious adverse effects is not significantly higher compared to placebo. | | | 1,066 (7 RCTs) | ⊕⊕⊕○ Moderate* |

CI: confidence interval, GRADE: Grading of Recommendations, Assessment, Development and Evaluation, RCT: randomized controlled trial, ECG: electrocardiogram.
*Imprecision due to small events.

et al.[16] (2010), sertraline was associated with higher rates of diarrhea, dizziness, and dry mouth compared to placebo.

Most studies did not report significant differences in SAEs between treatment and placebo groups. However, Weintraub et al.[16] (2010) found a significantly higher rate of SAEs in the sertraline group compared to placebo, particularly pulmonary-related SAEs, including infections, pneumothorax, and pulmonary embolism.

Based on these findings, the evidence level for the benefits of antidepressant treatment is presented in **Table 6**. For "depression," the evidence level is rated as "moderate"; for "agitation and aggression," it is also "moderate"; and for "apathy and overall BPSD," it is "moderate." **Table 7** provides the evidence level for the primary adverse effects, with an overall rating of "moderate."

### KQ3: For dementia patients with BPSD, do cognitive enhancers provide more benefit than harm compared to placebo or non-pharmacological interventions?

*PICO elements*

- Population: patients with dementia
- Intervention: cholinesterase inhibitors (ChEIs; donepezil, rivastigmine, and galantamine) and NMDA receptor antagonists (memantine)


https://doi.org/10.12779/dnd.2025.24.1.24

- Control: placebo treatment
- Outcomes:
  Primary outcome: overall behavioral and psychological symptoms (NPI score), sleep disturbance symptoms (rapid eye movement [REM] sleep, overall sleep)
  Secondary outcome: adverse effects
- Study design: RCT

*Recommendation*

- In patients with dementia, cognitive enhancers such as ChEIs and memantine can be used to improve overall behavioral and psychological symptoms.
- In cases of dementia with Lewy bodies and Parkinson's disease dementia, memantine may be used to improve REM sleep behavior symptoms (Evidence level: moderate, Recommendation grade: conditional recommendation [weak]).
- Clinical considerations: potential side effects of cognitive enhancers, including gastrointestinal symptoms, somnolence, falls, and worsening of cognitive function, should be carefully considered.

*Supporting evidence*

Following the same process as with antipsychotics, a total of 11 studies were selected. All 11 RCTs were double-blind, placebo-controlled studies. Six studies evaluated memantine monotherapy, an NMDA receptor antagonist, compared to placebo, while two studies assessed the combination of a ChEIs with memantine versus ChEIs with placebo. Of the six studies on memantine monotherapy, five evaluated treatment effects using the NPI. Among these five, three studies involved Alzheimer's patients,[20-22] one focused on frontotemporal dementia,[23] and another on Parkinson's disease dementia/Lewy body dementia.[24] The remaining study examined the effects of memantine on sleep symptoms in patients with Parkinson's disease dementia and Lewy body dementia.[25] The two studies on combination therapy of ChEIs and memantine evaluated BPSD using the NPI in Alzheimer's patients. One study combined memantine with donepezil,[26] and the other used one of three ChEIs: donepezil, galantamine, or rivastigmine.[27] Additionally, three studies compared changes in NPI scores with ChEI monotherapy (galantamine in two studies, donepezil in one) versus placebo (**Supplementary Tables 3**-**5**, **Supplementary Fig. 4**).[27-29]

*Benefits and risks*

1) Memantine monotherapy

All six studies on memantine monotherapy were double-blind, placebo-controlled trials. Among these, five studies used the NPI scale to evaluate the treatment effect. A meta-analysis including these 5 studies found that memantine monotherapy did not statistically significantly improve NPI scores compared to placebo (**Fig. 1**). Among the studies using the NPI scale, three were conducted in Alzheimer's patients, while the other two involved patients with frontotemporal dementia and Parkinson's disease dementia/Lewy body dementia.

In the first Alzheimer's study by Peskind et al.[20] (2006), 394 patients with mild-to-moderate Alzheimer's disease were randomized to receive memantine (20 mg/day) or placebo over 24 weeks. NPI scores at 12 weeks (mean difference, −2.4; 95% confidence interval [CI], −4.7, −0.2; $p$=0.035) and 24 weeks (mean difference, −3.5; 95% CI, −6.2, −0.8; $p$=0.011) were significantly better in the memantine group than in the placebo group. Treatment discontinuation due to adverse effects occurred in 19 patients (9.5%) in the memantine group


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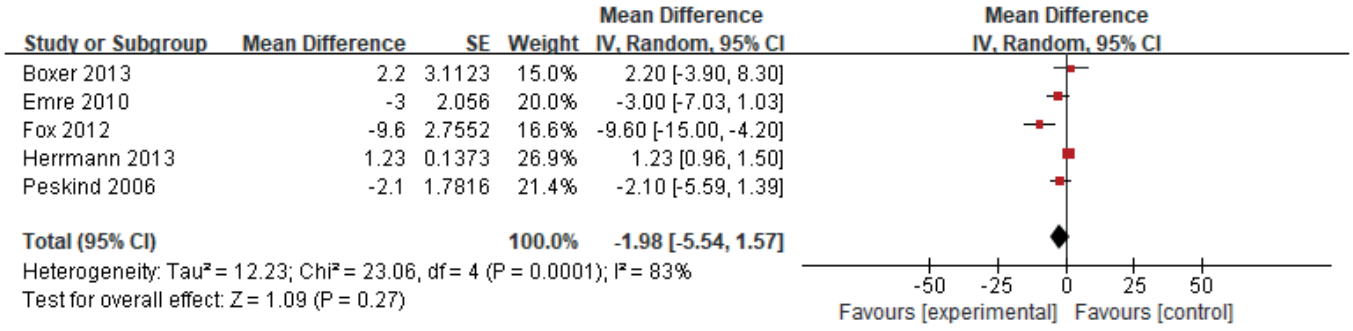


**Fig. 1.** Meta-analysis results of memantine monotherapy.
SE: standard error, CI: confidence interval.

versus 10 patients (5.0%) in the placebo group, with somnolence being significantly higher in the memantine group (7% vs. 1%).

In a second Alzheimer's study by Fox et al.[21] (2012), 149 Alzheimer's patients with high levels of agitation (CMAI score ≥45) were randomized to memantine or placebo. Memantine showed significant improvements in NPI scores at six weeks (mean difference, −6.9; 95% CI, −12.2, −1.6; $p$=0.012) and 12 weeks (mean difference, −9.6; 95% CI, −15.0, −4.3; $p$=0.0005) compared to placebo, but no significant differences in CMAI scores were observed at either time point. Adverse event rates were similar between groups.

Herrmann et al.[22] (2013) evaluated memantine in Alzheimer's patients with moderate-to-severe BPSD, where NPI total scores were ≥13 and NPI agitation/aggression scores ≥1. At 24 weeks, there was no statistically significant difference in NPI score changes between the memantine group (−3.90±1.24) and the placebo group (−5.13±1.23). Adverse event rates were 72.7% in the memantine group and 75.8% in the placebo group.

In Boxer et al.[23] (2013), memantine was evaluated in patients with frontotemporal dementia over 26 weeks, showing no significant difference in NPI score changes between the memantine and placebo groups (mean difference, 2.2; 95% CI, −3.9, 8.3; $p$=0.47). Although overall adverse event rates were similar, falls (11% vs. 4.3%) and cognitive adverse events were more frequent in the memantine group.

A meta-analysis of the five studies—three targeting Alzheimer's dementia and two focusing on non-Alzheimer's dementia—demonstrated a significant improvement in overall neuropsychiatric symptoms. The mean difference was 0.34 (**Fig. 1**).

Emre et al.[24] (2010) studied 192 patients with Parkinson's disease dementia or Lewy body dementia over 24 weeks. In the subgroup of Lewy body dementia patients, those on memantine had significantly greater NPI score improvements compared to placebo (mean difference, −5.9; 95% CI, −11.6, −0.2; $p$=0.041), but no significant differences were observed in the total sample or Parkinson's disease dementia subgroup. The most common SAEs included stroke (memantine group, n=3), falls (memantine, n=2; placebo, n=1), and dementia progression (memantine, n=2).

A study by Larsson et al.[25] (2010) used sleep-related scales instead of the NPI, assessing patients with mild-to-moderate Parkinson's disease dementia or Lewy body dementia. After


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24 weeks, the memantine group showed significant improvements in REM sleep behavior disorder symptoms on the Stavanger Sleep Questionnaire compared to placebo (mean difference, 0.5; 95% CI, 0.05, 0.90; $p$=0.006), although there were no significant differences in daytime sleepiness (Epworth Sleepiness Scale). No adverse events were reported.

2) Memantine combination therapy

Two studies assessed combination therapy with ChEIs and memantine, both double-blind, placebo-controlled trials using the NPI scale. A meta-analysis including these two studies showed that combination therapy significantly improved NPI scores compared to ChEIs with placebo (**Table 2**). In the study by Tariot et al.[26] (2004), moderate-to-severe Alzheimer's dementia patients received either donepezil plus memantine or donepezil plus placebo over 24 weeks. NPI scores were significantly lower in the combination group, indicating better outcomes in BPSD. Adverse event rates did not differ significantly (donepezil + placebo, 72%; donepezil + memantine, 78%), but treatment discontinuation due to adverse events was higher in the donepezil + placebo group (12.5% vs. 7.4%). Confusion was significantly more common in the donepezil + memantine group (7.7% vs. 2.0%, $p$=0.01).

In a study by Youn et al.[27] (2021), 148 patients aged 60 or older with MMSE scores of 10–20 and NPI scores ≥11 were assigned to ChEI + placebo or ChEI + memantine groups. At 12 weeks, NPI score changes were −5.45±11.26 in the ChEI + memantine group and −6.58±13.04 in the ChEI + placebo group, with no statistically significant differences. However, NPI-disinhibition scores were significantly lower in the combination group. Adverse events did not differ between groups. A meta-analysis including these two studies found that ChEI + memantine combination therapy significantly improved NPI scores compared to placebo (**Fig. 2**).

3) ChEI therapy

In a study by Auchus et al.[28] (2007), 786 patients with vascular dementia received galantamine for two weeks. No significant differences in NPI score changes were observed compared to placebo, although gastrointestinal adverse events were more common in the galantamine group (6% vs. 1%). Erkinjuntti et al.[29] (2008) administered galantamine for six months to 231 Alzheimer's patients with cerebrovascular disease. While there were no significant differences in NPI score changes between groups, a significantly greater proportion of the galantamine group showed improvement on the NPI (64.9% vs. 56.6%; $p$=0.02). The galantamine group also had higher rates of gastrointestinal side effects, including nausea and vomiting.

In a study by Holmes et al.[30] (2004), donepezil administered over 12 weeks resulted in significantly lower NPI and caregiver distress (NPI-D) scores compared to placebo (NPI: −2.9 vs. 3.3, $p$=0.02; NPI-D: −2.0 vs. 1.0, $p$=0.01). No adverse events were reported in this study.

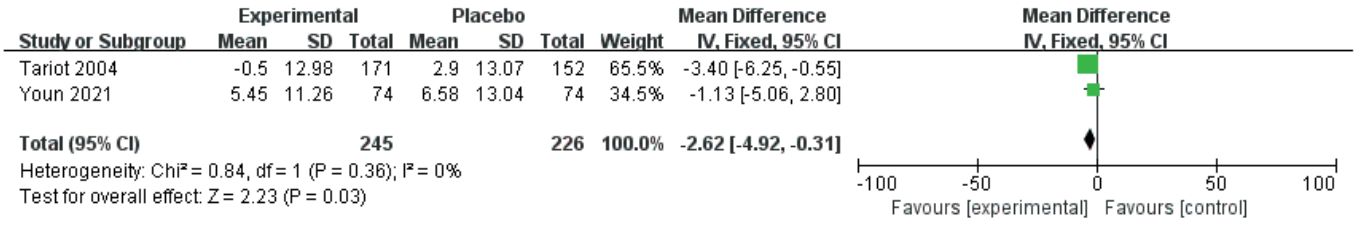


**Fig. 2.** Meta-analysis results of combination therapy (memantine + cholinesterase inhibitors).
SD: standard deviation, CI: confidence interval.


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**Table 8.** Evidence level for the benefits of cognitive enhancers treatment

| Outcomes | Anticipated absolute effects (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with placebo | Risk with antipsychotic agents | | | |
| [Key findings] Memantine: overall BPSD (NPI score) | A meta-analysis of five RCTs comparing memantine treatment and placebo groups (three studies on Alzheimer's dementia and two studies on non-Alzheimer's dementia) showed a significant improvement in overall neuropsychiatric symptoms (mean difference, 0.34 [0.09, 0.59]) (favoring memantine). | | | 1,030 (5 RCTs) | ⊕⊕⊕⊕ High |
| [Key findings] Memantine: REM sleep behavior disorder symptom (SSQ), overall sleep quality (ESS) | Studies in patients with dementia with Lewy bodies and Parkinson's disease dementia demonstrated that memantine significantly improved REM sleep behavior disorder symptom compared to placebo; however, its effect on overall sleep quality was not significant. | | | 42 (1 RCTs) | ⊕⊕⊕○ Moderate* |
| [Key findings] Cholinesterase inhibitors: overall BPSD (NPI score) | In patients with Alzheimer's dementia or Alzheimer's dementia with cerebrovascular disease, treatment with cholinesterase inhibitors improves overall BPSD symptoms. However, no significant effects have been observed in patients with vascular dementia. | | | 1,113 (3 RCTs) | ⊕⊕⊕⊕ High |

CI: confidence interval, GRADE: Grading of Recommendations, Assessment, Development and Evaluation, RCT: randomized controlled trial, REM: rapid eye movement, SSQ: Stavanger Sleep Questionnaire, ESS: Epworth Sleepiness Scale, BPSD: behavioral and psychological symptoms of dementia, NPI: Neuropsychiatric Inventory.
*Imprecision due to small sample size and confidence interval cross null effect.

**Table 9.** Evidence level for the risks of cognitive enhancers treatment

| Outcomes | Anticipated absolute effects (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with placebo | Risk with antipsychotic agents | | | |
| [Key findings] Cholinesterase inhibitors | Gastrointestinal side effects (nausea, vomiting): two studies reported a significantly higher incidence of gastrointestinal side effects in the galantamine treatment group. | | | 1,017 (2 RCTs) | ⊕⊕⊕○ Moderate* |
| [Key findings] Memantine | Somnolence, falls, cognitive adverse events: in the study by Peskind et al.[20] (2006), somnolence was reported significantly more frequently in the memantine group. Similarly, the study by Boxer et al.[23] observed a significantly higher incidence of falls and cognitive adverse events in the memantine group. However, three other studies[21,22,24] reported no significant differences in adverse events between the two groups. | | | 687 (5 RCTs) | ⊕⊕⊕○ Moderate* |

CI: confidence interval, GRADE: Grading of Recommendations, Assessment, Development and Evaluation, RCT: randomized controlled trial.
*Imprecision due to small events.

Based on these results, the evidence level for the benefits of cognitive enhancers is presented in **Table 8**. Memantine was rated as "high" for overall BPSD, "moderate" for REM sleep behavior disorder symptom and overall sleep quality improvement. ChEIs were rated as "high" for overall behavioral symptoms. The primary adverse effects are presented in **Table 9**, with the evidence grade for memantine and ChEI-related adverse effects rated as "moderate."

## KQ4: For dementia patients with BPSD, do other medications provide more benefit than harm compared to placebo or non-pharmacological interventions?

*PICO elements*

- Population: patients with dementia
- Intervention: sodium valproate, divalproex sodium, lithium, melatonin, modafinil, pimavaserine
- Control: placebo treatment
- Outcomes:
  Primary outcome: agitation/aggression, apathy, psychosis
  Secondary outcome: adverse effects
- Study design: RCT

*Recommendation*

- The use of other medications to improve agitation, aggression, and apathy in patients with dementia is not recommended (Evidence level: moderate; Recommendation grade: conditional recommendation against use [weak]).


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- Pimavanserin can be used to improve psychotic symptoms in patients with Alzheimer's dementia (Evidence level: moderate; Recommendation grade: conditional recommendation [weak]).
- Clinical considerations: when using valproate, potential side effects such as drowsiness, gait disturbances, tremors, diarrhea, constipation, and fatigue should be carefully considered.

*Supporting evidence*

1) Agitation/aggression

In the study by Sival et al.[31] (2002), sodium valproate was administered to 42 dementia patients for three weeks, with no effect on reducing aggression as measured by the Social Dysfunction and Aggression Scale-9. However, this study's evidence level is low due to the small dosage, short treatment duration, and insufficient statistical adjustments. In a study by Gehrman et al.[32] (2009) involving 41 dementia patients in nursing homes, a 10-day course of melatonin (8.5 mg immediate-release and 1.5 mg extended-release) showed no significant difference in agitation symptoms, as measured by the CAMI scale, between the treatment and placebo groups. In a 2011 study by Tariot et al.,[33] sodium valproate (10–12 mg/kg) was given to 313 Alzheimer's patients with moderate-to-severe symptoms without existing BPSD, comparing incident rates of delusions, hallucinations, and agitation/aggression (defined as an NPI score of ≥3). After two years, there was no significant difference in the occurrence of BPSD between the treatment and placebo groups. In the study by Devanand et al.[34] (2022), 12 weeks of lithium carbonate (150–600 mg) in Alzheimer's patients showed no significant reduction in NPI agitation/aggression scores compared to placebo.

2) Apathy

In the study by Frakey et al.[35] (2012), modafinil (200 mg) was administered to 23 Alzheimer's patients with mild-to-moderate symptoms for eight weeks. There was no significant improvement in apathy, as measured by the Frontal Systems Behavior Scale, compared to placebo.

3) Psychotic symptoms

In a 2019 study by Ballard et al.,[36] 181 Alzheimer's patients received pimavanserin (34 mg) for six weeks, showing a significant reduction in NPI psychosis scores (combined hallucination and delusion scores) compared to placebo (**Supplementary Table 6**, **Supplementary Fig. 5**).

*Benefits and risks*

Based on these studies, the evidence level for the benefits of various treatments is presented in **Table 10**, categorized by target symptoms due to the inclusion of multiple drug types. For agitation and aggression, sodium valproate, divalproex sodium, lithium, and melatonin showed no efficacy in improving agitation/aggression in dementia patients (Evidence grade: moderate). For apathy, modafinil showed no improvement in apathy symptoms in Alzheimer's patients (Evidence grade: low). For psychotic symptoms, the newly introduced drug pimavanserin demonstrated efficacy in improving psychosis symptoms in Alzheimer's patients (Evidence grade: moderate). The primary adverse effects associated with these other treatments are shown in **Table 11**. Pimavanserin and lithium had no significant difference in overall adverse effects compared to placebo (Evidence grade: low), while divalproex sodium was associated with a higher risk of somnolence, gait disturbance, tremor, diarrhea, constipation, weakness, and dyspnea (Evidence grade: moderate).


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**Table 10.** Evidence level for the benefits of other medication treatment

| Outcomes | Anticipated absolute effects (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with placebo | Risk with antipsychotic agents | | | |
| [Key findings] Agitation, aggression | Sodium valproate, divalproex sodium, lithium, and melatonin have no effect on improving agitation and aggression in patients with dementia. | | | Sodium valproate: 42, divalproex sodium: 313, lithium: 77, melatonin:41 (4 RCTs) | ⊕⊕⊕○ Moderate* |
| [Key findings] Apathy | Modafinil is not effective in improving apathy in patients with Alzheimer's dementia. | | | 22 (1 RCTs) | ⊕⊕○○ Low† |
| [Key findings] Psychosis | Pimavanserin is effective in improving psychotic symptoms in patients with Alzheimer's dementia. | | | 178 (1 RCTs) | ⊕⊕⊕○ Moderate* |

CI: confidence interval, GRADE: Grading of Recommendations, Assessment, Development and Evaluation, RCT: randomized controlled trial.
*Imprecision due to small sample size.
†Imprecision due to small sample size and confidence interval cross the null effect.

**Table 11.** Evidence level for the risks of other medication treatment

| Outcomes | Anticipated absolute effects (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with placebo | Risk with antipsychotic agents | | | |
| Pimavanserin | There is no difference in overall adverse effects compared to placebo. | | | 178 (1 RCTs) | ⊕⊕○○ Low* |
| Lithium | There is no difference in overall adverse effects compared to placebo. | | | 77 (1 RCTs) | ⊕⊕○○ Low* |
| Divalproex sodium | There is an increased risk of somnolence, gait disturbances, tremors, diarrhea, constipation, fatigue, weakness, and respiratory difficulty. | | | 313 (1 RCTs) | ⊕⊕⊕○ Moderate* |

CI: confidence interval, GRADE: Grading of Recommendations, Assessment, Development and Evaluation, RCT: randomized controlled trial.
*Imprecision due to small events

## DISCUSSION

In establishing these guidelines for the pharmacological treatment of BPSD, we identified well-designed prior RCTs. Systematic reviews of these studies allowed us to conclude with a moderate level of evidence. However, due to inconsistency in result direction among the study findings, the recommendation grades were determined as conditional recommendations for or against implementation. The summary of the findings from this guideline is as follows (**Table 12**).

**Table 12.** Summary of guideline

| KQ | Key Question | Recommendation | Evidence level | Recommendation grade |
|---|---|---|---|---|
| 1 | For dementia patients with BPSD, does antipsychotic treatment offer more benefit than placebo or non-drug interventions? | • Antipsychotics may be used to improve agitation, aggression, and psychotic symptoms in dementia patients. | Moderate | Conditional recommendation (weak) |
| 2 | For dementia patients with BPSD, does antidepressant treatment offer more benefit than placebo or non-drug interventions? | • For Alzheimer's dementia patients, antidepressants may be used to improve depression, agitation, and aggression symptoms. | Moderate | Conditional recommendation (weak) |
| | | • For Alzheimer's dementia patients, antidepressants are not recommended for the improvement of apathy or overall BPSD. | Moderate | Conditional recommendation against (weak) |
| 3 | For dementia patients with BPSD, do cognitive enhancers offer more benefit than placebo or non-drug interventions? | • In dementia patients, cognitive enhancers such as cholinesterase inhibitors and memantine may be used to improve overall BPSD. | Moderate | Conditional recommendation (weak) |
| | | • In Lewy body dementia and Parkinson's disease dementia, memantine may be used to improve REM sleep behavior disorder symptoms. | Moderate | Conditional recommendation (weak) |
| 4 | For dementia patients with BPSD, do other medications offer more benefit than placebo or non-drug interventions? | • Other medications are not recommended for improving agitation, aggression, or apathy symptoms in dementia patients. | Moderate | Conditional recommendation against (weak) |
| | | • Pimavanserin may be used to improve psychotic symptoms in Alzheimer's dementia patients. | Moderate | Conditional recommendation (weak) |

KQ: key question, BPSD: behavioral and psychological symptoms of dementia, REM: rapid eye movement.


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*KQ1: In patients with dementia, antipsychotics may be used to improve agitation, aggression, and psychotic symptoms.*

*KQ2: For Alzheimer's dementia patients, antidepressants may be used to improve symptoms of depression, agitation, and aggression.; For Alzheimer's dementia patients, the use of antidepressants is not recommended for improving apathy or overall behavioral and psychological symptoms.*

*KQ3: In patients with dementia, cognitive enhancers such as ChEIs and memantine may be used to improve overall behavioral and psychological symptoms.; For patients with Lewy body dementia and Parkinson's disease dementia, memantine may be used to improve symptoms of REM sleep behavior disorder.*

*KQ4: The use of other medications is not recommended for improving symptoms of agitation, aggression, or apathy in dementia patients; Pimavanserin may be used to improve psychotic symptoms in patients with Alzheimer's dementia.*

As limitations of this clinical practice guideline, this guideline does not address patient preferences or the comparative effectiveness of specific drug components. Additionally, most studies referenced in these recommendations evaluated outcomes over relatively short periods, ranging from 12 to 24 weeks; therefore, there is insufficient evidence to assess the long-term benefits of medication use.

From a resource and cost perspective, cognitive enhancers are covered by insurance in Korea for patients diagnosed with Alzheimer's dementia, while antipsychotic or antidepressant medications are not covered unless there is a concurrent diagnosis of psychosis or depression. Thus, careful consideration of these factors is warranted when prescribing these medications.

Moreover, the use of antipsychotics in dementia patients still remains a topic of debate, with some studies indicating potential risks such as an increased likelihood of stroke.[36] It is recommended to discuss these risks and benefits thoroughly with patients and their caregivers before initiating treatment.

In conclusion, this guideline represents the first systematic review by an expert panel in Korea to address pharmacological treatment for BPSD in dementia patients. We hope that this serves as a foundation for future updates as new medications are introduced and becomes a resource that addresses clinical demands not fully covered in this current edition.

## SUPPLEMENTARY MATERIALS

**Supplementary Data 1**
Korean clinical practice guideline

**Supplementary Data 2**
Scales used in the literature

**Supplementary Table 1**
Overview of antipsychotic medication studies included in the current guidelines


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**Supplementary Table 2**
Overview of antidepressant medication studies included in the current guidelines

**Supplementary Table 3**
Studies on memantine monotherapy included in the current guidelines

**Supplementary Table 4**
Studies on memantine + cholinesterase inhibitors combination therapy included in the current guidelines

**Supplementary Table 5**
Studies on cholinesterase inhibitors monotherapy included in the current guidelines

**Supplementary Table 6**
Summary table of other medication studies included in the current guidelines

**Supplementary Fig. 1**
PRISMA flow diagram: article selection process.

**Supplementary Fig. 2**
Evidence of articles: antipsychotics.

**Supplementary Fig. 3**
Evidence of articles: antidepressants.

**Supplementary Fig. 4**
Evidence of articles: cognitive enhancers.

**Supplementary Fig. 5**
Evidence of articles: other drugs.

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