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REVIEW ARTICLE

# A 2025 update on treatment strategies for the Alzheimer's disease spectrum

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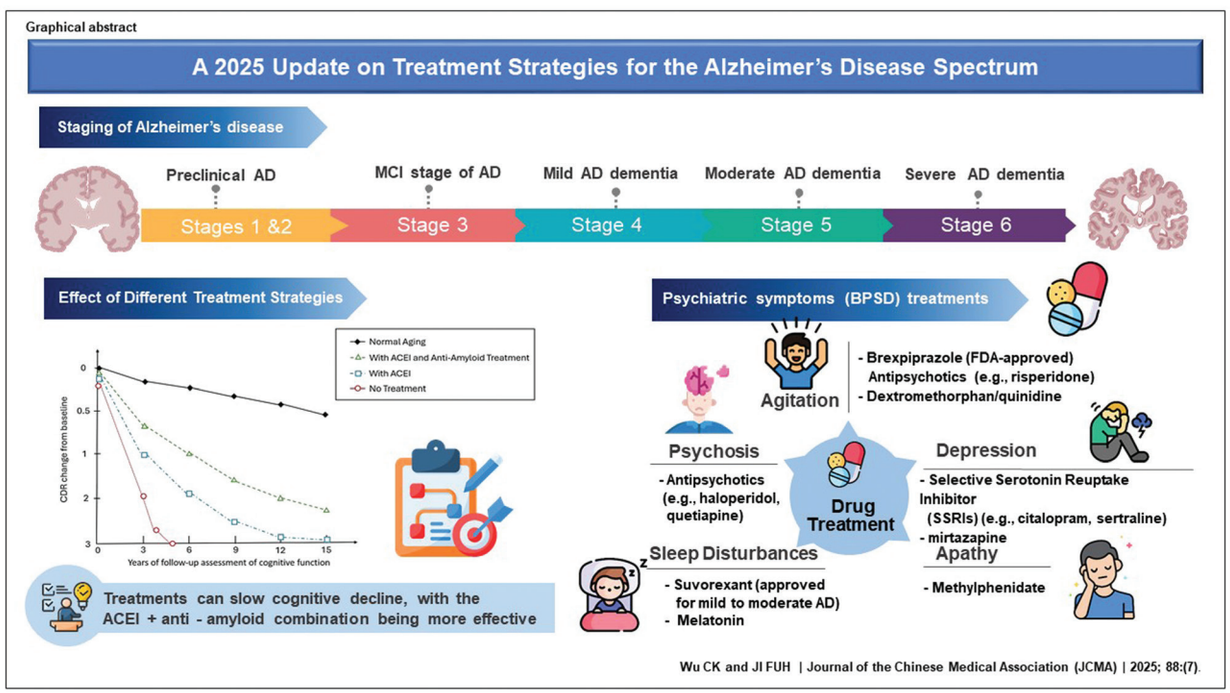
## Abstract

Alzheimer's disease (AD) is a complex and progressive neurodegenerative disorder with a continuum of stages ranging from preclinical/asymptomatic phase to severe dementia. Over the past decades, significant advances in diagnostic biomarkers and disease-modifying therapies have reshaped the treatment landscape. This review provides a comprehensive overview of the current treatment paradigm for AD in 2025, incorporating the latest developments in pharmacological and non-pharmacological interventions. The advent of anti-amyloid immunotherapy, including the US Food & Drug Administration (FDA)-approved monoclonal antibodies such as lecanemab and donanemab, has proven efficacy in slowing cognitive decline in early-stage AD. These therapies mark a change in thinking in AD management, emphasizing the importance of early diagnosis and intervention. Cholinesterase inhibitors and memantine remain the standard treatments for mild, moderate to severe dementia, providing symptomatic relief and functional stabilization. Additionally, emerging strategies targeting tau pathology and neuroinflammation are under investigation, offering hope for future breakthroughs. Beyond pharmacotherapy, this review highlights the importance of personalized, multimodal treatment approaches that integrate lifestyle modifications, cognitive training, and caregiver support. The updated diagnostic framework, incorporating fluid and imaging biomarkers, enables more precise staging and individualized treatment plans. Despite these advances, challenges still lie in refining patient selection, addressing treatment-related side effects, and ensuring accessibility to appropriate therapies. As the field moves forward, ongoing clinical trials and real-world evidence will further refine treatment strategies. A proactive approach, combining early detection with disease-modifying and symptomatic therapies, is essential for improving patient outcomes and quality of life. This article synthesizes current knowledge and provides a roadmap for clinicians and researchers navigating the evolving landscape of AD treatment.

**Keywords:** Alzheimer's disease; Amyloid immunotherapy; Cholinesterase inhibitors; Dementia treatment strategies; Disease-modifying therapy

Graphical abstract



**Lay Summary:** Treatment for Alzheimer's disease (AD) is evolving significantly in 2025, with new advances in both diagnosis and therapy. A major step forward is the FDA approval of anti-amyloid immunotherapies like lecanemab and donanemab. These drugs are used for early-stage AD, including mild cognitive impairment (MCI) and mild dementia, by targeting and reducing amyloid plaques in the brain. This highlights the importance of early detection and intervention. For patients with mild to severe dementia, established medications such as cholinesterase inhibitors and memantine continue to be crucial. They help manage symptoms and stabilize cognitive and functional abilities. The current approach emphasizes personalized care, combining these therapies with lifestyle modifications and cognitive support to improve patient outcomes.

## 1. INTRODUCTION

When the US organized experts to set goals for the national plan in Alzheimer's disease (AD), one main goal is to develop new effective treatments by the year 2025.[1] Anticipating the growing population of baby boomers into the age above 65 in the coming decades, the US congress signed in the law of the National Alzheimer's Project Act in 2011 to address the future care burden of age-related AD and associated dementias. This act mandates the US Department of Health Human Services to create budget and plan year by year to promote education, care-providing strategies, and research for prevention and effective treatments for AD and associated dementias.

In 2016, the National Institute of Neurological Disease and Stroke organized a reviewing committee and discussed the goals of future projects. In light of advanced technologies and accumulative knowledge of AD and associated dementias at the time, the committee was confident that a goal can be set up to develop effective treatments in 10 years based on expected progress in critical research on key topics.[2] Now in the year 2025, it is safe to say that we have reached this goal at last, only with some caveats.

Thus, in this article, we want to explain the background of how we achieve this aim and to highlight the research data that can be translated into clinical practice to treat AD in its full spectrum—so-called the Alzheimer's disease continuum—in the modern terminology.

## 2. EVOLUTION OF AD TREATMENT

In the 1980s, research on AD found the molecular components of senile plaques (SPs) and neurofibrillary tangles (NFTs), revealing their role in cognitive impairment. The first breakthrough came with the discovery of cholinergic deficits in the basal forebrain.[3] However, there were several requirements for the success of developing effective treatments in AD. First, the clinical diagnosis of AD was yet to be established for drug trials. Second, the measurable test scales remained to be developed to test the efficacies of new drugs. Third, to achieve statistical significance for treatment effectiveness, a collaborative study group must be formed to recruit an adequate sample size of subjects for drug trials.

In 1993, the US Food & Drug Administration (FDA) approved tacrine, the first AD treatment,[4] though its use ceased to exist recently due to hepatotoxicity. In this study, standardized diagnostic criteria of probable AD were applied to all participants recruited by 17 study sites/academic medical center/specialty clinics. The range of severity of AD was decided within the mild to moderate stage, ie, the score of mini-mental state examination ranging from 10 to 26 out of full score of 30. The primary outcome measures used 1> the Alzheimer's Disease Assessment Scale (ADAS) for cognitive decline; 2> the Clinical Global Impression of Change (CGIC) for functional decline. Because, based on the prior study of progression in AD in mild to moderate stage, data showed a decline of more than four points of ADAS in 6-month study period would be expected for subjects of placebo group. If the treatment group would score less than four points of ADAS in the same study period, the study compound can be declared as effective with statistical significance. In addition, the data also showed daily activity function did not decline in treatment group as compared with that of the placebo group. Taken together, these data implied moderate but meaningful benefits of the first cholinesterase inhibitor (ChEI) in AD treatment. This landmark study set the standard for later drug trials, leading to the development of three other ChEIs, which successfully obtained FDA approval from 1993 to 2003.

Since 2000, research has been focused on targeting SPs and NFTs to delay AD progression. Aβ-42, a key part of SPs, is linked to genetic mutations in amyloid precursor protein (APP), leading to excessive amyloid production. The neurotoxicity of aggregated Aβ-42 and its role in tau phosphorylation prompts investigation into disease-modifying therapies.[5] In 2023, the FDA approved the first anti-amyloid immunotherapy.

Advanced research on NFTs has also clarified the role of tau, a microtubule-associated protein, in neuronal function. In AD, abnormal tau phosphorylation disrupts intracellular transport, leading to filament aggregation and neuronal dysfunction. The spread of phosphorylated tau from limbic regions to the neocortex worsens neurodegeneration. Strategies targeting tau pathology are actively being explored for disease modification; yet no such therapy has been successfully developed so far. Although no tau-targeted therapies have received FDA approval to date, several agents such as semorinemab, zagotenemab, and BIIB080 are currently under investigation in clinical trials, reflecting growing interest in tau as a therapeutic target.

The distribution and burden of plagues and tangles correlate with AD's clinical presentation. Higher amyloid load and tau pathology levels in specific brain regions determine disease progression and cognitive decline. Additionally, cerebral amyloid angiopathy, often accompanying with plaques and tangles, affects disease severity and vascular alteration in AD.

A recent growing understanding of SPs, NFTs, and biomarker technologies enables us to target the molecular-level mechanisms of AD as critical therapeutic strategy, aiming to slow or prevent AD progression. However, initial clinical trials, applying methodologies of developing ChEI, failed to show efficacy over 2 to 3 years.[6] Recognizing the limitations of treating mild to moderate AD, the FDA issued new guidelines for drug development emphasizing "early-stage intervention." Since 2012, the arrival of particular amyloid tracers empowers us to detect AD pathology in its earliest stages, defining a therapeutic window for intervention.[7] This approach culminated in the FDA's approval of two anti-amyloid immunotherapy drugs in 2023 and 2024, marking a significant advancement in AD treatment. Table 1 summarizes the history and clinical trial data of AD treatments.

To explain the overall achievable goals in treating AD, Fig. 1 illustrates the effect of different treatment strategies on

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**Table 1**

**Alzheimer's disease drug history and clinical trial data**

| Drug name | Approval year | Mechanism of action | Target stage | Key clinical trial findings |
|---|---|---|---|---|
| Tacrine | 1993 | Cholinesterase inhibitor | Mild to moderate dementia | First FDA-approved; moderate efficacy but no longer used due to liver toxicity. |
| Donepezil | 1996 | Cholinesterase inhibitor | Mild to severe dementia | Most widely used, shows moderate cognitive improvement over 6-12 mo. |
| Rivastigmine | 2000 | Cholinesterase inhibitor | Mild to moderate dementia | Effective in delaying cognitive decline; gastrointestinal side effects common. |
| Galantamine | 2001 | Cholinesterase inhibitor | Mild to severe dementia | Improves cognitive function; long-term effectiveness like Donepezil. |
| Memantine | 2003 | NMDA receptor antagonist | Moderate to severe dementia | Delays functional decline in moderate to severe dementia; often used in combination. |
| Lecanemab | 2023 | Anti-amyloid immunotherapy | Early stage (MCI and mild dementia) | Reduces amyloid plaques; approved for MCI and mild dementia with positive biomarkers. |
| Donanemab | 2024 | Anti-amyloid immunotherapy | Early stage (MCI and mild dementia) | Reduces amyloid plaques; approved for MCI and mild dementia; requires biomarker confirmation. |

FDA = US Food & Drug Administration; MCI = mild cognitive impairment; NMDA = N-methyl-D-aspartic acid.

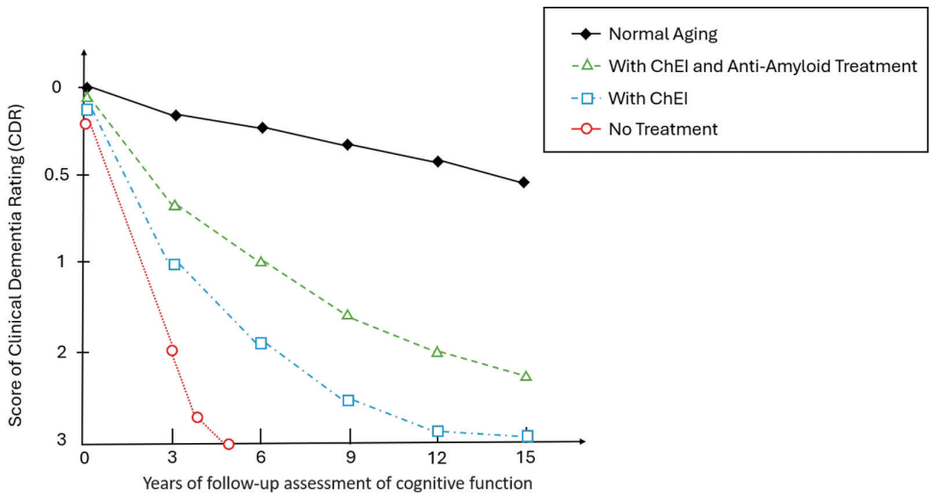


**Fig. 1** Effect of different treatment strategies on cognitive decline over time. This figure illustrates changes in CDR scores over a 15-y follow-up period among individuals with different treatment strategies for Alzheimer's disease. The y-axis stands for the change in CDR from baseline, with higher values showing greater cognitive decline. The x-axis stands for the years of follow-up assessment. CDR = clinical dementia rating; ChEI= cholinesterase inhibitors.

cognitive decline over time according to the published studies.[8–10] Ultimately, we want to maintain cognitive function as normal as we can as we age slowly over 20 years after age 65. Without any treatment, an individual with a diagnosis of mild dementia of AD would progressively worsen into severe dementia in about 3 years.[8] With ChEIs for treatment, patients with mild AD dementia can maintain relatively adequate cognitive function over more than five to eight years.[9] The decline slope is slower. Adding the anti-amyloid therapy to ChEI treatment in early-stage AD, the cognitive function can be maintained better and longer in the years to come (5-10 years).[10] Hopefully, as newer effective disease-modifying agents will be added in the near future, the asymptomatic individuals with AD pathology can have long-lasting normal cognitive function as those without AD pathology in normal aging conditions.

Although personalized treatment approaches in AD are gaining traction, their implementation faces significant barriers. Access to stratification tools such as amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) biomarkers is limited by cost and infrastructure, especially in low- and middle-income countries. Plasma biomarkers (eg, p-tau217, Aβ42/40) offer a promising, cost-effective alternative, though clinical integration is still evolving. Similarly, genetic profiling (eg, APOE ε4) may inform risk and treatment decisions but is not yet routine in practice. In resource-limited settings, optimizing conventional treatments like AChEI and memantine remains crucial. Expanding access to basic diagnostics and care training is essential to ensure that emerging AD therapies can benefit patients globally.

## 3. NEW DIAGNOSTIC CRITERIA FOR TREATMENT PLANNING

Recent advancements in research reveal that AD is a complex, slowly progressive neurodegenerative disease. New diagnostic tools can now detect AD-related pathological changes in the brain even before clinical symptoms manifest. The new diagnostic framework is developed as the foundation not only for the drug development of new disease-modifying treatments but also for application for clinical practice.[11]

This section describes the six stages of AD along its continuum, as defined by the latest research published in 2024 (Table 2).[11,12]

### 3.1. Stage 1

Senior individuals (age above 60), with no subjective memory or cognitive changes, do have biomarkers (brain PET and/or CSF/plasma biofluid data) positive results of AD pathology. This stage is considered as "asymptomatic Alzheimer's disease stage".

**Table 2**

**Alzheimer's disease stages and their corresponding treatments in 2025**

| Stage | Description | Treatment |
|---|---|---|
| Stage 1: Asymptomatic Alzheimer's disease | Age above 60 with positive biomarkers but no symptoms. | Experimental treatments targeting amyloid or tau pathology under investigation. |
| Stage 2: Subjective cognitive decline | Subtle memory changes with normal neuropsychological results and positive biomarkers. | Experimental treatments targeting amyloid or tau pathology under investigation. |
| Stage 3: Mild cognitive impairment | Objective cognitive impairment confirmed by tests can function independently. | FDA-approved anti-amyloid immunotherapy drugs (eg, Lecanemab, Donanemab). |
| Stage 4: Mild dementia due to Alzheimer's disease | Mild impairment in daily living activities; confirmed Alzheimer's pathology. | Cholinesterase inhibitors; add-on anti-amyloid immunotherapy drugs. |
| Stage 5: Moderate dementia | Requires assistance for independent activities of daily living. | Cholinesterase inhibitors; memantine; combination therapy recommended |
| Stage 6: Severe dementia | Severe cognitive impairment; needs full assistance for self-care tasks. | Cholinesterase inhibitors; memantine; focus on managing symptoms and quality of life. |

FDA = US Food & Drug Administration.

### 3.2. Stage 2

Senior individuals, who occasionally experience only subtle memory and cognitive changes and are tested with normal neuropsychological results, do have evidence of underlying AD pathology detected by biomarkers. This stage is often called as "subjective cognitive complaints (SCC)" stage or "subjective cognitive decline (SCD)" stage.

### 3.3.Stage 3

Senior individuals, who not only have subjective cognitive changes but also demonstrate a mild degree of cognitive impairment confirmed by neuropsychological assessment, can still function independently for daily living. Diagnostic biomarkers, particularly amyloid tracer brain PET and/or CSF assays of Aβ42 and tau, show evidence of underlying AD pathology. This stage is traditionally called "mild cognitive impairment (MCI)" stage.

### 3.4. Stage 4

Senior individuals, who have objectively confirmed cognitive dysfunction resulting in a mild degree of impairment in independent activities of daily living (iADLs), have positive results of AD pathology shown by PET or/and CSF data. This stage is traditionally considered as "mild dementia stage" of AD or "mild AD."

### 3.5. Stage 5

Senior individuals, who are cognitively impaired and have objective evidence of AD pathology and need assistance for inability to do iADLs, are considered as in the moderate stage of AD.

### 3.6. Stage 6

Senior individuals with have severely impaired cognitive function and objectively confirmed AD pathology and cannot perform iADLs and basic ADLs for self-care tasks, are deemed as in the severe stage of AD.

Currently, there are FDA-approved drugs for treating stages 3 to 6 of AD. The treatments are under development for stages 1 and 2.

## 4. TREATMENT FOR AD STAGE 1 AND STAGE 2

No FDA-approved drugs exist for asymptomatic or SCC stage of AD, but ongoing trials explore anti-amyloid and anti-tau therapies for prevention. The rationale of such drug studies is twofold. On one hand, more advanced diagnostic tools ensure that AD's pathology can be detected in preclinical stage/SCC stage (stages 1 and 2). On the other hand, research study found drugs approved for stages 3 and 4 cannot prevent further progression of stages 1 and 2 AD. Lifestyle interventions, including exercise, cognitive training, and vascular risk management, remain essential in delaying symptom onset.[13]

The A4 (**A**nti-**A**myloid treatment in **A**symptomatic **A**lzheimer's disease) study, a 5-year clinical trial examining the effects of solanezumab in asymptomatic individuals with amyloid accumulation, failed to show significant cognitive benefits.[14] Despite a well-defined study population and an extended treatment period, results indicated no substantial difference in cognitive decline between the treatment and placebo groups. While solanezumab demonstrated a favorable safety profile, amyloid levels remained elevated over the study period of about 4 years, and approximately 30% of participants in either group progressed to symptomatic AD (stage 3 or stage 4 of AD). Most importantly, the participants who eventually progressed, in fact, had higher levels of accumulated Aβ42 levels measured in post-treatment PET. These findings underscore the challenges of preventing disease progression at preclinical stages and highlight the need for more effective early interventions.

Although stage 1 and stage 2 of AD can be conceptually and objectively recognized in research, targeting at these 2 stages for drug development remains to be investigated. One main reason is that there is no simple set of criteria to separate stage 1 from stage 2 despite persistent efforts. Two drug studies (AHEAD study and TRAILBRAZER-ALZ 3 study), employing recently FDA-approved anti-amyloid drugs (lecanemab and donanemab), have completed the recruitment phase of preventive treatment for stage 1 and 2 AD.[15,16] With clinically proved effectiveness in Aβ clearance for AD stages 3 and 4, hopefully after a study period of 4 years these drugs can be applicable to stage 1 or stage 2 of AD.

## 5. TREATMENT FOR AD STAGE 3 (MCI STAGE)

Since the establishment of diagnostic criteria in 2001 by the American Academy of Neurology, treatment strategies for MCI due to AD have evolved over two decades. Advances in diagnostic tools now allow for definition and identification of cognitive impairment in stage 3, improving the reliability of recent drug trials.

Extensive research has been conducted on ChEIs and memantine for the treatment of MCI due to AD over the past decade. All clinical trials lasting between 12 and 48 months consistently failed to demonstrate any significant benefits. Consequently,

**Table 3**

**AD BPSD treatments**

| Symptom | Description | Primary treatment | Non-pharmacological interventions |
|---|---|---|---|
| Agitation | Excessive restlessness, aggression, irritability. | Brexpiprazole (FDA-approved); antipsychotics (eg, risperidone); dextromethorphan/quinidine | Music therapy, physical activities, caregiver training. |
| Depression | Mood disturbances, withdrawal, lack of energy. | SSRIs (eg, citalopram, sertraline); mirtazapine | CBT |
| Apathy | Lack of motivation, diminished initiative, emotional indifference | Methylphenidate | Behavioral activation; structured daily activities |
| Psychosis | Delusions, hallucinations | Antipsychotics (eg, haloperidol, quetiapine) | Cognitive therapy; environmental modifications |
| Sleep disturbances | Disrupted sleep patterns, insomnia, nighttime awakenings | Suvorexant (approved for mild to moderate AD); melatonin; | CBT-I; light therapy. Sleep hygiene education, managing underlying anxiety or depression |

AD = Alzheimer's disease; BPSD = behavioral and psychiatric symptoms of dementia; CBT = cognitive behavioral therapy; FDA = US Food & Drug Administration; SSRI = selective serotonin reuptake inhibitors.

none of these drugs received FDA approval for indication of treating MCI stage of AD. Among them, donepezil study found a tiny degree of cognitive improvement during the first 12 months of a 36-month study, but the effect was not sustained.[16] Based on these findings, the American Academy of Neurology's published guidelines do not recommend ChEIs for MCI treatment.[17]

The treatment of MCI due to AD advanced significantly with two landmark studies published in 2023.[10,18] The FDA approved two anti-amyloid immunotherapies, lecanemab and donanemab, for "early-stage" AD, encompassing both stage 3 (MCI) and stage 4 (mild dementia). Confirmation of AD pathology provided by amyloid PET imaging or CSF assays of Aβ42/total tau/P-tau levels is required for eligibility of these therapies.

The lecanemab trial included approximately 80% stage 3 participants, while the donanemab trial had about 65%. These drugs differ in their immunotherapeutic mechanisms, targeting accumulated Aβ42, and in their risk profiles, particularly about the potential for brain edema or hemorrhage. While both are practical treatment options for stage 3 or MCI due to AD, FDA warnings highlight safety concerns, especially for individuals at high risk of severe complications, including fatal outcomes.

While the approval of anti-amyloid therapies such as lecanemab and donanemab represents a major milestone in AD treatment, several important limitations must be acknowledged. First, their clinical efficacy, while statistically significant, remains modest—translating to a delay in cognitive decline of approximately 6 to 12 months in early-stage patients. Second, safety concerns are considerable, particularly the risk of amyloid-related imaging abnormalities (ARIA), which is notably higher in APOE ε4 carriers. Additionally, these therapies require intravenous infusions every two to four weeks, along with intensive MRI monitoring, posing logistical and financial barriers in many healthcare settings. Real-world implementation is further limited by access to amyloid PET or CSF biomarker confirmation, which is required for diagnosis and treatment eligibility. Although post-marketing surveillance is ongoing, long-term safety and cost-effectiveness remain to be fully determined. As such, clinicians must carefully weigh benefits, risks, and system readiness before broad adoption of these therapies.

## 6. TREATMENT FOR AD STAGE 4 (MILD DEMENTIA STAGE DUE TO AD)

Initially, most clinical trials for AD treatments focused on patients in the mild dementia stage. Over time, the cognitive criteria for mild dementia have evolved, with mini-mental state examination (MMSE) scores shifting from an average of 18 of 30 in the 1990s to 22 of 30 in the 2020s in a variety of drug studies in mild AD.

ChEIs are still the primary treatment for mild AD, enhancing acetylcholine levels to support cognitive and functional abilities.[9,19] Common side effects include nausea, vomiting, and diarrhea but are generally tolerable in long run. Anti-amyloid immunotherapy with lecanemab or donanemab is now considered as an add-on therapy.[10,20]

Clinical trials of donepezil, rivastigmine, and galantamine of participants with the average MMSE score–19 for AD in mild dementia stage demonstrated moderate reduction in cognitive decline over 6 months (or 26 weeks) using the ADAS-cog scale.[21–23] Extended studies up to 1 year (52 weeks) confirmed continued benefit in delaying progression from stage 4 to stage 5.

Anti-amyloid immunotherapy trials showed efficacy for mild dementia (stage 4) due to AD; the data were included and analyzed with stage 3 AD subjects. Approximately 20% of Lecanemab trial participants and 30% of Donanemab trial participants were in stage 4 according to the CDR global score (0.5—stage 3; 1—stage 4).[10,20] The FDA classifies both stages under the label of "early-stage" AD, permitting their use as the add-on therapy, though further research is needed to assess their long-term functional benefit particularly in stage 4.

## 7. TREATMENT FOR AD STAGE 5 AND STAGE 6 (MODERATE TO SEVERE DEMENTIA DUE TO AD)

There is compelling evidence supporting ChEIs for mild and moderate dementia due to AD, showing these drugs delay cognitive and functional decline and reduce abnormal behaviors.[24–26] Systematic reviews, in addition, show donepezil, rivastigmine, and memantine have better outcomes even in severe AD dementia (Stage 6) compared to placebo.[27]

Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, helps regulate glutamate and is beneficial in moderate to severe AD, improving global functioning, cognition, and daily activities.[28,29] Combined use with ChEIs, memantine shows slight cognitive and functional benefits in moderate to severe AD.[29,30] European Federation of Neurological Societies (EFNS) – European Neurological Society (ENS) /European Academy of Neurology (EAN) guidelines recommend these drugs as standard treatments, with combination therapy potentially preferred in moderate to severe stages.[31] Long-term use is associated with delayed functional decline and mortality, although more evidence is needed regarding cognitive stability.

A study using UK NHS electronic health records found both ChEIs and memantine temporarily stabilize cognitive decline for about 4 months post-initiation, particularly in moderate to severe cases.[32] Response rates were higher in real-world settings (68%) compared to trials (40%), likely due to additional

support and care provided particularly to patients who received medicines in the community.[32] Antipsychotics were linked to worse cognitive outcomes and reduced effectiveness of these medications.[32]

Adjunctive treatments like Gingko biloba or idalopirdine show limited benefits. More evidence is needed to support the use of antioxidants, anti-inflammatory drugs, and neuroprotective agents.

## 8. TREATMENT FOR BEHAVIORAL AND PSYCHIATRIC SYMPTOMS OF DEMENTIA IN AD

Behavioral and psychiatric symptoms of dementia (BPSD; another term: neuropsychiatric symptoms [NPS]), are prevalent in AD and include agitation, depression, apathy, psychosis, anxiety, aggression, disinhibition, and sleep disturbances.[33,34] These symptoms greatly impact patients' quality of life and burden of caregivers. Pharmacotherapy for BPSD is unpredictable, and most clinical trials have yielded negative results. Here, we focus on treating agitation, depression, apathy, psychosis, and sleep disturbances in AD (Table 3).

### 8.1. Agitation in AD

Agitation is prevalent in AD, characterized by restlessness, aggression, and irritability.[35] Both typical (eg, haloperidol) and atypical (eg, risperidone, quetiapine) antipsychotics are used but they both come with significant risks such as sedation and increased mortality.[36] In 2023, brexpiprazole was approved by the FDA for AD-related agitation, showing moderate efficacy at 2 mg/d.[37,38] Dextromethorphan/quinidine and escitalopram may also reduce agitation.[38,39] Escitalopram, an antidepressant, may reduce agitation but requires further validation.[38,40] Nonpharmacological interventions like music therapy and physical activities are preferred first-line approaches.[41]

### 8.2. Depression in AD

Depression co-occurs frequently with AD, manifesting as mood disturbances and social withdrawal. Selective serotonin reuptake inhibitors (SSRIs) like citalopram and sertraline have shown modest efficacy,[42,43] and mirtazapine can alleviate depressive symptoms and aid sleep.[44] Cognitive behavioral therapy (CBT) and mindfulness practices are effective complementary approaches.[43]

### 8.3. Apathy in AD

Apathy, marked by lack of motivation and emotional indifference, is common in AD.[45] Methylphenidate significantly improves apathy without major adverse events for a period of 3 months according to a research study.[46] Behavioral activation and structured daily activities are effective nonpharmacological alternatives.

### 8.4. Psychosis in AD

Psychosis involves delusions and hallucinations, often in moderate to severe AD stages. Antipsychotics are prescribed but pose risks like cardiovascular events. Cognitive therapy and environmental modifications can reduce psychotic symptoms without medication.[47]

### 8.5. Sleep disturbances in AD

Sleep disturbances are prevalent and worsen with AD progression, impairing amyloid-beta clearance.[47] Melatonin's efficacy is debated; some trials show improvement in sleep measures, while others do not.[47] Suvorexant, approved for adding the indication of insomnia in mild and moderate AD in 2020 by the US FDA, increases sleep time and reduces awakenings.[48] However, suvorexant is regulated as a Schedule IV controlled substance due to its potential addiction in the US so that suvorexant are not widely prescribed for AD patients. Cognitive behavioral therapy for insomnia (CBT-I) and light therapy effectively improve sleep quality.[49] Addressing anxiety, depression, and agitation can also enhance sleep.

In conclusion, BPSD in AD requires a multidisciplinary approach, prioritizing nonpharmacological strategies. Pharmacological interventions are reserved for severe cases, with tailored care plans of incorporating caregiver support and monitoring adverse effects to ensure better patient outcomes.

## 9. TREATMENT ISSUES ON ATYPICAL VARIANTS OF AD AND MIXED-TYPE DEMENTIA

Atypical variants of AD present unique diagnostic and management challenges due to their distinct clinical presentations, which differ from the classical amnestic form. These include dysexecutive AD, behavioral variant AD, posterior cortical atrophy (PCA), the logopenic variant of primary progressive aphasia (lvPPA), and corticobasal syndrome due to AD.[50] Pharmacological management largely mirrors that of typical AD, with ChEIs commonly prescribed despite limited clinical trials for atypical variants. A retrospective study suggested that ChEIs may help stabilize cognitive and functional decline in lvPPA, similar to their effects in amnestic AD.[51] For PCA, rehabilitation focusing on visuospatial deficits and compensatory strategies may be beneficial.[52] Emerging therapies, such as transcranial direct current stimulation (tDCS) combined with language therapy, show some promise for improving word retrieval in lvPPA.[53] Antipsychotics and antidepressants may be considered for severe neuropsychiatric/behavioral symptoms but these drugs need to be used cautiously due to potentially serious side effects.

Mixed dementia, characterized by the coexistence of AD pathology with other dementias—commonly vascular dementia—requires a multifaceted treatment approach.[54] Therapies targeting both AD and vascular pathophysiology are essential. ChEIs may provide benefits in patients with concurrent vascular pathology. Additionally, lipid-lowering treatments, particularly Simvastatin, have been associated with slower cognitive decline as measured by MMSE scores.[55] Managing vascular risk factors, such as hypertension, diabetes, and hyperlipidemia, is essential for slowing disease progression. Antihypertensive medications, including ChEI inhibitors, angiotensin receptor blockers, and calcium channel blockers, may help prevent cerebrovascular damage. Low-dose aspirin or other antiplatelets may be prescribed for secondary prevention. Lifestyle modifications, such as aerobic and strength training exercises, smoking cessation, a Mediterranean diet, and weight management, also play a critical role in disease management.[54]

In conclusion, advances in biomarker-guided diagnosis and anti-amyloid immunotherapies have shifted the management of early-stage AD. However, these treatments offer only modest clinical benefits and face significant safety and access challenges. We also acknowledge the limited long-term data and highlight ongoing trials (e.g., AHEAD, TRAILBLAZER-ALZ 3) as critical for future guidance, especially regarding preventive use. In parallel, the management of BPSD remains essential to improve quality of life. A practical, stage-specific approach that combines disease-modifying therapies, symptomatic care, and BPSD management will be vital to optimizing outcomes across diverse clinical settings.

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