Drug treatments in Alzheimer's disease

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Abstract. Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, impaired reasoning, and difficulty in daily activities. Current treatment strategies can be split into three major categories. Symptomatic pharmacologic treatments aim to improve cognition and daily behavior, providing short-term relief without altering the disease progression. Disease-modifying therapies (DMTs) focus on addressing the underlying pathology, including amyloid plaques, tau tangles, neuroinflammation, and synaptic dysfunction, which represent a promising approach to slow disease progression. Adjunct therapies are used to manage psychiatric and behavioral symptoms such as depression, anxiety, and agitation, which contribute significantly to patient burden. This review summarizes recent progress across these therapeutic categories, including symptomatic treatments that remain the mainstay of care, DMTs are emerging as potential breakthroughs, and adjunct therapies are essential for holistic management. In summary, an integrated strategy is ultimately required to address both the biological and clinical complexity of AD.

Keywords: Alzheimer's disease, Symptomatic pharmacologic treatments, Disease-modifying therapies, Adjunct therapies.

1. Introduction

AD is the main cause of dementia in the elderly, resulting in memory loss, impaired reasoning, and difficulties in daily functioning. As the disease progresses, the patient may gradually become confused and even lose the ability to care for themselves completely, which causes significant emotional stress and economic burden for the patient and their family. According to Alzheimer's Disease International, about 50 million people globally are likely to have dementia in 2018. By 2050, that number is expected to triple, with two-thirds of those affected residing in low-income and middle-income countries [1]. Clinically defined by the buildup of beta-amyloid (Aβ) plaques, tau neurofibrillary tangles, synaptic loss, and neuroinflammation. These processes contribute to progressive neuronal loss and brain atrophy, particularly in regions responsible for memory and executive function. While the amyloid cascade hypothesis has dominated the research field for decades, emerging evidence suggests that tau pathology, neuroinflammation, mitochondrial dysfunction, and vascular factors also play significant roles in disease progression.

Currently, treatment for AD falls into two broad primary categories: symptomatic therapies and DMTs (Figure 1). Symptomatic treatments, including cholinesterase inhibitors and NMDA receptor antagonists, provide modest improvements in cognition and daily functioning but do not alter disease progression. In contrast, DMTs aim to slow or halt neurodegeneration by targeting underlying pathological processes. The recent approvals of aducanumab and lecanemab, monoclonal antibodies directed against Aβ aggregates, represent a landmark in AD therapy. Beyond these primary categories, adjunctive approaches and supportive treatments remain important. Adjunct therapies (Figure 1), including psychiatric medications (e.g., antidepressants, antipsychotics, and sedatives) and non-pharmacological interventions (e.g., cognitive behavioral therapy and sleep hygiene protocols), addressing psychiatric, behavioral, and sleep-related comorbidities in AD, improving patient outcomes and alleviating caregiver burden. The combination therapy of donepezil and memantine is FDA-approved for patients with moderate to severe AD to enhance cognitive and functional symptom relief. For example, a retrospective study estimated that this therapy increased the five-year survival probability by 6.4%, potentially benefiting around 303,000 AD patients in the US [2]. Combination therapy with donepezil and memantine may offer additional benefits for functional measures in more advanced cases.

This review aims to provide a comprehensive and up-to-date synthesis of pharmacologic treatments for AD by focusing on three key therapeutic domains. First, it will summarize current symptomatic treatments, including cholinesterase inhibitors, NMDA receptor antagonists, and combination regimens, emphasizing their mechanisms, clinical efficacy, and limitations in improving cognition, daily functioning, and behavioral symptoms. Second, it will critically evaluate emerging DMTs that target core pathological processes such as Aβ aggregation, tau hyperphosphorylation, neuroinflammation, and synaptic dysfunction, with particular attention to recent monoclonal antibodies, enzyme inhibitors, and neuroprotective strategies, along with their therapeutic potential and safety concerns. Third, it will discuss adjunctive and supportive pharmacotherapies for the treatment of mental and behavioral symptoms of AD while considering the quality of evidence, risk–benefit profiles, and clinical applicability.

Table 1. Classification of Drug Therapies in AD

Category	Objective	Examples
Symptomatic Treatments	Improve cognition, function, and behavior.	Cholinesterase inhibitors; NMDA receptor antagonists
Disease-Modifying Therapies	Target underlying pathology to slow or halt disease progression.	Anti-amyloid antibodies; Anti-tau antibodies; Targeting neuroinflammation; Synaptic and neuroprotective agents
Adjunct Therapies	Manage psychiatric and behavioral symptoms.	Antidepressants; Antipsychotics; Anxiolytics

2. Symptomatic Pharmacologic Treatments

2.1. Cholinesterase Inhibitors (ChEIs)

AD is characterized by presynaptic acetylcholine (ACh) depletion, which contributes to severe memory loss. ChEIs improve cognitive symptoms in patients with mild to moderate AD by inhibiting cholinesterase in the synaptic cleft to establish cholinergic transmission. Consequently, ChEIs are the first-line symptomatic treatment drugs for mild to moderate AD. Clinically approved ChEIs include donepezil, rivastigmine, and galantamine. Donepezil and galantamine are reversible ChEIs, which increase synaptic ACh levels and enhance cognitive function. Rivastigmine, a pseudo-reversible ChEI, also supports cholinergic signaling [3]. ChEIs are commonly well tolerated, but some patients may experience adverse effects, including diarrhea, nausea, vomiting, loss of appetite, and vertigo.

2.2. NMDA Receptor Antagonist

Memantine is an NMDA receptor antagonist and has been approved by the FDA for treating moderate to severe AD [4]. It selectively modulates excessive NMDA receptor activity, reducing glutamate-mediated excitotoxicity while preserving normal synaptic transmission. This mechanism supports cognitive function and memory in AD patients. Common adverse effects include weight gain, dizziness, hallucinations, hypertension, and nervous system disorders. Clinical studies show that memantine combined with ChEIs improves cognitive functions and activities of daily living (ADL) in patients with moderate to severe AD compared to ChEI monotherapy [5].

3. Disease-Modifying Therapies (DMTs)

3.1. Anti-Amyloid Therapies

Since Aβ deposition in the brain is now more recognized as a core pathological feature of AD, anti-Aβ therapy has become a vital direction in DMT drug development. Since 2021, the FDA has approved lecanemab and donanemab as anti-Aβ monoclonal antibodies, and these drugs slow down the disease progression of AD through Aβ. Lecanemab preferentially targets the soluble protofibrils

of Aβ and reduces Aβ in the brain by facilitating Aβ clearance. The main side effect of lecanemab is the amyloid-associated imaging abnormality ARIA, which occurs in about 12-17% of patients [6]. In January 2023, the FDA accelerated approval of lecanemab for patients with early-stage AD, which was converted to formal approval in July 2023. Lecanemab was approved for marketing in January 2024 in China. Donanemab is a humanized monoclonal antibody (mAb) that significantly slows cognitive and functional decline in patients with early AD. The majority of ARIA events, the main side effect of donanemab, are mild to moderate and can be controlled by monitoring and management. In July 2024, the FDA approved the marketing of donanemab injections. On 18 December 2024, the National Drug Administration (NMPA) of China approved the marketing of donanemab injection for the treatment of mild cognitive dysfunction and mild dementia due to Alzheimer's disease. The approval of these anti-Aβ monoclonal antibodies brings new hope for the treatment of AD, but their clinical application still requires attention to long-term efficacy and safety issues.

Inhibition of β-secretase has also been pursued to curb the synthesis of Aβ. As the rate-limiting enzyme in the amyloid degradation process, β-secretase's inhibition reduces the buildup of Aβ and slows down the process of AD. Verubecestat, the pioneering inhibitor of β-secretase entering phase III clinical trials, has a semi-inhibitory concentration of β-secretase of only 2.2 nmolL-1 owing to robust hydrogen bonding between the amidine group and the catalytic dyad. A 78-week randomized controlled trial found that the above dosage failed to improve ADAS-cog and ADAS-induced hyperactivity among patients with mild to moderate AD, as compared with placebo. ADAS-cog and ADCS-ADL scores reported higher rates of adverse events such as rash and sleep disturbances compared with placebo [7]. Considering that it may be too late to start treatment until AD has progressed to moderate levels, the institution conducted an additional trial in patients with prodromal AD, which yielded similar results [8]. β-Secretase inhibitors reduce Aβ levels, but their poor clinical efficacy may be related to the large number of their substrates. Therefore, improving the selectivity of β-secretase inhibitors for amyloid precursor protein (APP) will be a direction for future research.

3.2. Anti-Tau Therapies

Tau is a protein linked to microtubules, whose synthesis is governed by the microtubule-associated protein tau (MAPT) gene, and over-phosphorylation leads to its accumulation in NFT clumps inside the nerve cell. These tangles engage in aberrant interactions with cellular proteins, which consequently compromises their physiological functions. Anti-tau drugs are therefore an important area of research in DMT for AD. Gosuranemab, a humanized IgG4 mAb targeting N-terminal tau, effectively eliminates N-terminal tau from brain intercellular fluid and reduces tau aggregation in cells. Clinical trials in Phase 1 have shown that gosuranemab is safe for human use and exhibits powerful target-locking capability as evidenced by reductions in unbound N-terminal tau levels in the cerebrospinal fluid (CSF) of both healthy individuals and those diagnosed with progressive supranuclear palsy [9]. A Phase II clinical trial on patients with progressive supranuclear palsy compared the efficacy of the gosuranemab treatment group with that of the placebo group. The study results showed that there was no notable disparity in safety between the two cohorts. Nevertheless, this study did not confirm the effectiveness of gosuranemab in mitigating the progression of the disease. Semorinemab, a humanized IgG4 mAb targeting the extracellular tau protein's N-terminal domain, reduces tau protein pathology and neuronal loss. Ongoing clinical trials of semorinemab have not been registered following negative results in both the Lauriet phase II randomized controlled trial and the earlier Tauriel study in prodromal to mild AD [10]. These failures highlight the challenges of targeting extracellular tau, which may be due to poor epitope selection or disease staging. The future outlook for anti-tau therapies remains positive, and further research is needed to optimize tau-targeted interventions.

3.3. Targeting Neuroinflammation

Microglia are resident immune cells in the brain responsible for clearing Aβ plaques. Moderate activation of microglia promotes Aβ clearance, but excessive activation releases pro-inflammatory

factors, leading to neuronal damage. Therefore, regulating the activation state of microglia is an important therapeutic target for AD. In neurodegenerative pathology, Masitinib functions as a tyrosine kinase inhibitor that regulates mast cells and microglia. It shows promise for treating AD, with preclinical studies supporting its neuroprotective effects. For example, long-term masitinib treatment restored spatial learning in an AD mouse model. In ALS models, it reduced neuromuscular junction denervation and motor deficits. Masitinib's safety was evaluated in a recent meta-analysis. According to the report, Masitinib was linked to an increased likelihood of adverse events across several neurodegenerative illnesses compared with placebo. The risk ratio for any adverse event was 1.12, regardless of severity or dose [11]. Current evidence suggests that the use of masitinib in patients with neurodegenerative diseases poses safety concerns. Further dose-range trials are needed to pinpoint the best effective dose of masitinib with the fewest risks in patients with neurodegenerative conditions.

3.4. Synaptic and Neuroprotective Agents

Mitochondrial dysfunction can lead to insufficient energy supply to neurons, thereby impairing their normal function, causing synaptic damage and neuronal death, and accelerating the pathological progression of AD. Additionally, mitochondrial dysfunction is probably linked to neurotoxicity and oxidative stress in AD, leading to neuronal damage and death. Mitoquinone mesylate (MitoQ) is a derivative of ubiquinone. MitoQ is transported across the mitochondrial membrane under the influence of the mitochondrial membrane potential and accumulates within the mitochondrial matrix. It is converted to ubiquinol by the mitochondrial respiratory chain complex, which plays a protective role in mitochondria and achieves a therapeutic effect. In mouse models, MitoQ treatment significantly improved memory decline, reduced brain oxidative stress and synaptic loss, and decreased Aβ accumulation, CASP activation, and tau protein hyperphosphorylation, thereby inhibiting the progression of AD [12]. Insulin influences the metabolism of APP, thereby increasing the risk of AD in patients. Therefore, in the treatment of AD, improving insulin resistance and increasing insulin sensitivity may help mitigate brain pathological damage and cognitive impairments in AD patients. Pioglitazone is an insulin sensitizer that may slow cognitive decline by improving insulin signaling pathways in the brain.

4. Adjunctive and Supportive Drug Therapies

AD's adjunctive and supportive pharmacological strategies are designed to control symptoms that are not directly related to the core pathological process but significantly impact patient health and caregiver burden. For severe agitation or psychosis posing safety risks, antipsychotic medications such as risperidone, quetiapine, and aripiprazole may be used. A retrospective study reported that risperidone was more effective than placebo in reducing the severity of psychotic symptoms in dementia patients. However, the study also found that patients taking risperidone were more likely to experience side effects such as weight gain and movement disorders [13]. More importantly, compared to patients not receiving risperidone, those treated with risperidone had a 3.7% higher risk of death [14]. As a result, all second-generation antipsychotic medications now carry an FDA black box warning regarding increased mortality risk in elderly dementia patients. It is recommended to prescribe the lowest effective dose for the shortest possible duration and to regularly reassess the need for continued treatment. Sleep disorders and anxiety are also common in AD. While some animal studies suggest that melatonin can reduce Aβ production [15], there are still some results not in line with this trend. In the AD (Tg2576) mouse model, there was no noticeable impact on brain APP immune reactivity with the lower melatonin dose (1.5 mg/kg/day) in comparison with untreated animals, and the increased risk of nocturnal falls and respiratory distress with melatonin cannot be ignored.

5. Conclusion

Drug development in AD has produced mixed outcomes. Symptomatic treatments, including ChEIs and memantine, remain the standard of care, with consistent but modest benefits in cognition, function, and behavior. Nevertheless, some patients probably experience adverse effects, including diarrhea, nausea, and neurological disorders. DMTs, especially monoclonal antibodies against Aβ, mark a turning point in AD research. Although lecanemab and donanemab demonstrate the ability to reduce amyloid burden and moderately delay cognitive decline, their development and clinical application still face numerous challenges, including relatively narrow targets, limited symptom improvement, and high rates of adverse reactions. Therapies targeting tau protein and neuroinflammation are still in the early stages, but they highlight a trend toward broader pathological targets in treatment. Adjunctive therapies for psychiatric and behavioral symptoms can improve patient health and reduce caregiver burden, but their efficacy is limited, and safety concerns such as black box warnings restrict their long-term use.

AD is a complex degenerative disease involving multiple factors, with insidious onset and complex diagnosis. Currently available treatments can only temporarily control the disease and cannot achieve a cure. Therefore, future research should further explore the pathogenesis of AD and new therapies through cellular and animal experiments as well as clinical observations. Currently, the primary treatment approach for AD involves pharmacological interventions to alleviate symptoms and slow disease progression. However, existing pharmacological therapies have limited efficacy and associated side effects. Therefore, there is a need to intensify efforts in new drug development, identify novel therapeutic targets and strategies, and shift toward preventive and personalized treatment approaches. Non-pharmacological treatments also merit attention, such as cognitive training, exercise, and dietary modifications, which can also help alleviate symptoms.

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