Neuropharmacological perspectives on Alzheimer's disease

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Abstract
Alzheimer's disease (AD) is one of the most prevalent neurodegenerative disorders, characterized by the progressive loss of nerve cells across various regions of the brain. Pathologically, it is associated with intracellular neurofibrillary tangles and extracellular amyloid protein deposits, which disrupt neural transmission and lead to cognitive decline. Nutrition and lifestyle factors play a crucial role in both the development and prevention of AD. Early diagnosis relies on sensitive biomarkers capable of distinguishing between different causes of dementia. Emerging therapeutic strategies, including the use of induced pluripotent stem cells, show promise in addressing the underlying pathology. The primary hypotheses explaining AD pathogenesis include the cholinergic, tau, and amyloid hypotheses, with additional risk factors such as age, genetics, head trauma, vascular diseases, infections, and environmental influences. Currently approved pharmacotherapies—cholinesterase inhibitors and NMDA receptor antagonists—alleviate symptoms but do not cure or prevent disease progression. Contemporary research focuses on multiple pathological processes, including tau protein dysregulation, β-amyloid accumulation, oxidative stress, neuroinflammation, and cholinergic dysfunction, aiming to develop disease-modifying treatments. This review provides a comprehensive neuropharmacological perspective on AD, emphasizing the underlying mechanisms, risk factors, and current and emerging pharmacotherapeutic strategies for its management.

Keywords: Alzheimer's disease, Acetyl cholinesterase inhibitors, Neuropharmacological, Pharmacotherapeutic

Introduction

Alzheimer's disease (AD) is the leading cause of dementia, accounting for approximately 60%–80% of cases worldwide, as reported by the World Health Organization [1,10,13]. Dementia is a major contributor to cognitive impairment and functional dependence globally. AD is a progressive neurodegenerative disorder primarily affecting memory, thinking skills, and cognitive abilities, ultimately compromising the ability to perform daily tasks. The disease predominantly impacts the temporal lobe, entorhinal cortex, and hippocampus, and as it progresses, the cerebral cortex becomes involved, affecting language, reasoning, and social behavior, which may ultimately lead to death [1].

Pathologically, AD is characterized by the accumulation of amyloid plaques, neurofibrillary tangles, and Lewy bodies in the brain [4]. The involvement of the medial temporal lobe, including the entorhinal cortex and hippocampus, disrupts anterograde episodic memory, manifesting as the forgetting of everyday details [3,4]. Although early symptoms may seem mild, they are often noticeable to both patients and caregivers. The current diagnostic criteria for AD focus on cognitive deficits severe enough to impair daily functioning, commonly referred to as mild cognitive impairment (MCI). Approximately 10% of MCI patients progress to AD annually [11,12].

As the disease advances, cognitive and functional abilities—including visuospatial and executive functions—deteriorate. Later stages are associated with increased dependency and severe neurological impairments, such as akinetic mutism. Reduced mobility often leads to death within 6–12 years due to complications like pulmonary or venous embolism. AD diagnosis is primarily based on clinical evaluation, supported by neuroimaging to rule out other conditions presenting with similar symptoms. In the near future, diagnostic criteria may also include laboratory tests, such as biomarker analysis, genetic testing, and molecular or functional neuroimaging, to improve early and late-stage detection.

The etiology of AD remains incompletely understood, and no treatment currently exists to eradicate the disease. Available pharmacological therapies, including acetylcholinesterase inhibitors, NMDA receptor antagonists, and antioxidants, aim primarily to slow disease progression and manage symptoms [6,9,14]. Understanding how these medications interact with neural pathways is critical, and various neuropharmacological mechanisms have been explored in the literature.

History

The first case of AD was reported in 1906 by German psychiatrist and pathologist Dr. Alois Alzheimer, who observed pathological changes in the brain of a female patient with severe cognitive impairment. Over the next five years, eleven additional cases were documented, giving rise to the term Alzheimer's disease [11]. Initially, the term Senile Dementia of Alzheimer's Type (SDAT) described patients aged 65 and above, whereas classical AD referred to younger patients. Over time, Alzheimer's disease has come to

encompass individuals of all ages exhibiting the characteristic neuropathology and clinical symptoms.

Globally, nearly 47 million individuals were affected by dementia in 2015, with projections of 75 million by 2030 and 131 million by 2050 [13]. The annual incidence is estimated at 4.6 million new cases, equivalent to one new patient every seven seconds. Aging is a major risk factor; for example, the Canadian Study on Health and Aging reported that approximately 10% of individuals aged 65 and older are affected by dementia, increasing to 35% in those aged 85 and above [15].

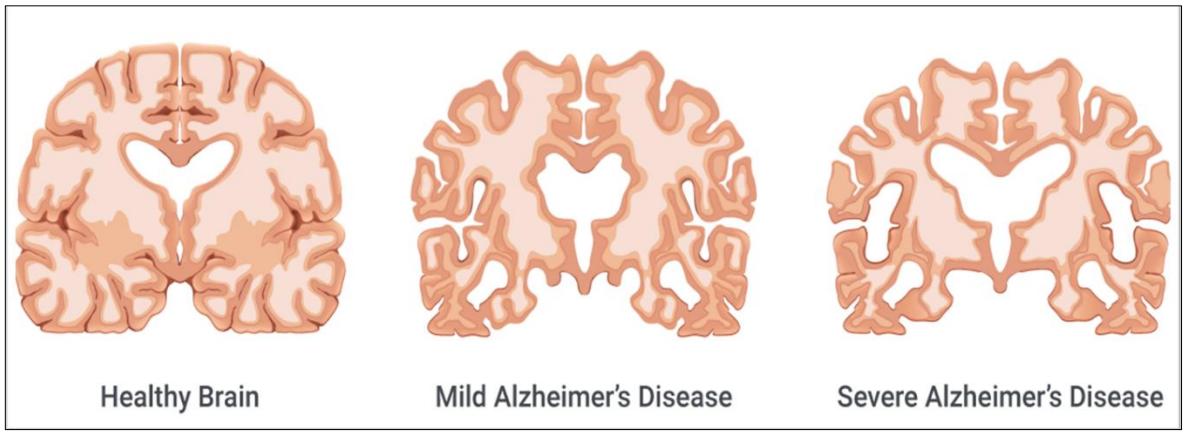

Fig 1: Illustrates the progression of Alzheimer's disease

Genetics of Alzheimer's Disease

Alzheimer's disease (AD) is inherited in approximately 2% of cases through autosomal dominant transmission, known as early-onset familial AD (EOFAD) [18]. Early-onset AD, also referred to as younger-onset AD, occurs before the age of 65 and accounts for only 5–10% of all AD cases [19]. Roughly 60% of these patients have a positive family history, with 13% exhibiting autosomal dominant inheritance [20]. Most early-onset AD cases, however, resemble late-onset AD and are not linked to specific genetic mutations.

EOFAD is directly associated with mutations in three key genes: amyloid-beta precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2) [44]. Most APP and presenilin mutations increase the production of amyloid beta (Aβ)42, the primary component of amyloid plaques. Some mutations alter the Aβ42/Aβ40 ratio without increasing total Aβ42 levels. Additional genes, including ABCA7 and SORL1, have also been implicated in autosomal dominant AD [2,4,15,21].

The majority of AD cases are sporadic, arising from the complex interaction of genetic and environmental factors. Sporadic AD typically manifests after age 65, with less than 5% showing early onset [18]. The APOEε4 allele is the most significant genetic risk factor for sporadic AD [22]. APOE, coding for the lipid carrier protein apolipoprotein E (ApoE), has four alleles, with ε4 increasing AD risk threefold. Although ε4 carriers constitute roughly 25% of the population, they represent nearly 50% of AD cases [10,16,22,44]. Multiple allelic variants in the genome further elevate the risk of AD.

Hypotheses related to Alzheimer's disease

Amyloid hypothesis

The amyloid hypothesis, also known as the amyloid cascade hypothesis, has been the dominant framework for understanding AD pathophysiology for over 25 years [16]. It posits that Aβ deposition is the primary causative agent in AD, triggering neurofibrillary tangles, neuronal death, vascular damage, and dementia [23]. Anti-Aβ therapeutic strategies aim to reduce Aβ production by targeting β- and γ-secretase [17]. While Aβ remains a key initiator in early disease, increasing evidence suggests it may be necessary but not sufficient for late-stage pathology [25].

Tau Hypothesis

Neurofibrillary tangles, composed of hyperphosphorylated tau protein, represent another hallmark of AD. Pathological tau aggregation disrupts axon integrity, contributing to neurodegeneration [40]. Tau undergoes various post-translational modifications, including phosphorylation, acetylation, monomethylation, dimethylation, ubiquitylation, and arginine methylation [26]. The development of tau-targeting therapies is challenging due to limited understanding of AD mechanisms, insufficient biomarkers for diagnosis and treatment monitoring, and the restrictive blood-brain barrier [27].

Cholinergic Hypothesis

The cholinergic hypothesis emphasizes acetylcholine (ACh) deficiency as a central contributor to AD symptoms [28]. Neuronal loss in the basal forebrain, particularly the nucleus basalis of Meynert, leads to reduced cholinergic innervation of the cerebral cortex. Central cholinergic antagonists, such as atropine, can mimic AD-like cognitive deficits, supporting the hypothesis that cholinergic insufficiency drives AD-related cognitive decline [31]. Other neurotransmitter systems, including glutamate, serotonin (5-HT), and neuropeptides, are also affected. Cholinesterase inhibitors, such as Tacrine, were developed based on this hypothesis and represent the first clinically approved pharmacological treatment for AD [30].

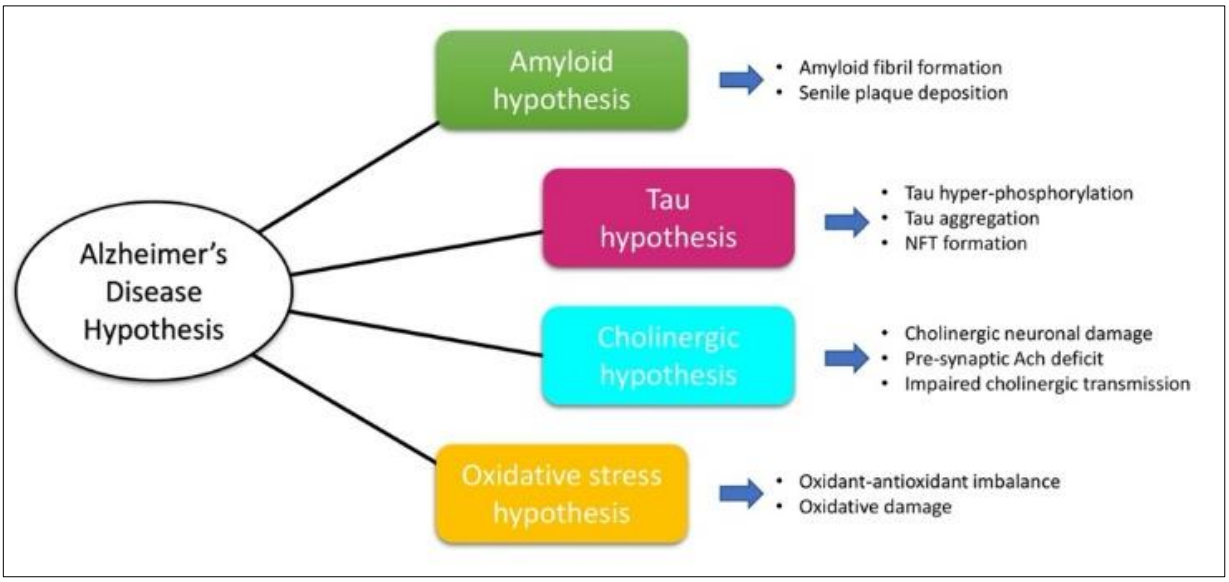

Fig 2: Hypothesis of AD and deficits actually happening and leading to disease progression and damage

Signs and symptoms of Alzheimer's disease

Alzheimer's disease (AD) develops gradually, with symptoms often initially attributed to normal aging. The rate of progression varies among individuals, and in some cases, worsening may be influenced by other medical conditions. Prompt medical evaluation is recommended for individuals whose symptoms rapidly worsen, as treatable factors may contribute to cognitive decline. AD symptoms are commonly categorized into three stages: early, middle, and late.

Early Stage

The hallmark of early-stage AD is memory impairment, particularly short-term memory loss. Patients may forget recent conversations, misplace items, struggle to recall names of objects or places, and repeat questions. Other early signs include poor judgment, difficulty making decisions, reduced flexibility, and hesitation in trying new activities [54]. Cognitive decline may extend beyond memory, affecting language, executive functions, perception (agnosia), and motor planning (apraxia) in some patients [56]. Not all types of memory are equally affected; episodic, semantic, and implicit memories often remain relatively intact compared to recent memories [55].

Middle Stage

As AD progresses, memory deficits worsen and additional cognitive and behavioral symptoms emerge. Patients may experience confusion, disorientation, and spatial navigation difficulties, including getting lost. Behavioral changes such as obsessive-compulsive tendencies, impulsivity, paranoia, delusions, and suspiciousness towards caregivers are common. Language impairments (aphasia), disturbed sleep, mood alterations, and hallucinations may also occur [54]. Functional independence declines, with patients requiring assistance for many daily activities. Speech difficulties manifest as word-finding problems and paraphasias, while reading and writing abilities deteriorate [55]. Motor coordination becomes impaired, increasing the risk of falls, and long-term memory gradually declines [56].

Late Stage

The late stage of AD is the most severe, characterized by profound cognitive and functional impairments. Patients may experience hallucinations, delusions, aggression, and heightened dependency on caregivers [55]. Full-time assistance is often required for basic activities such as eating, mobility, and personal hygiene [54]. Language ability diminishes to simple phrases or single words, eventually progressing to total aphasia. While aggression may persist, apathy and fatigue become predominant. Patients ultimately lose the ability to perform even fundamental tasks independently, with significant muscle wasting and immobility. Mortality is typically due to secondary complications such as pneumonia or infections from pressure ulcers, rather than AD itself [55,56].

Table 1: Signs and symptoms observed in AD during different phases of disease

Signs and symptoms of Alzheimer's Disease		
Early phase	**Middle phase**	**Late phase**
▪ Coming up with correct names ▪ Agnosia and apraxia ▪ Alteration in episodic, implicit and semantic memory ▪ Losing or misplacing items ▪ Increased trouble with planning and organizing ▪ Memory impairments	▪ Feeling moody or withdrawn, especially in socially or mentally challenging situations ▪ Having trouble in controlling bowel and bladder movements ▪ Getting lost and unable recall time ▪ Delusions and paranoia about family and caregivers ▪ Initial aphasia and paraphasia ▪ Disturbed sleep cycle	▪ Aggressive and demanding behavior in patients ▪ Complete aphasia ▪ Complete dependence on other person/caregiver ▪ Having difficulty in communication ▪ Vulnerable to diseases like pneumonia, ulcers ▪ Changes in physical abilities like walking, eating, swallowing, etc. ▪ Loss of awareness of surroundings

Treatment of Alzheimer's disease: Neuropharmacological perspectives

Alzheimer's disease (AD) remains incurable, and current therapeutic strategies primarily focus on symptomatic management rather than disease modification. Pharmacological interventions aim to slow cognitive decline, improve quality of life, and mitigate behavioral and psychological symptoms.

Cholinergic-based therapy

Cognitive symptoms of AD are largely treated by optimizing cholinergic neurotransmission. Cholinesterase inhibitors (AChEIs) such as Donepezil, Rivastigmine, and Galantamine are first-line agents, especially in mild-to-moderate AD [32]. These agents inhibit acetylcholinesterase, enhancing acetylcholine availability in the synaptic cleft, thereby improving memory, attention, and learning.

- Galantamine functions as both a reversible AChE inhibitor and a positive allosteric modulator of nicotinic receptors, enhancing cholinergic signaling in the central nervous system. Clinical studies demonstrate improvements in cognition, daily functioning, and behavioral symptoms [53].
- Tacrine, the first approved AChEI, is less commonly used due to hepatotoxicity and adverse effects [32].

Glutamatergic Therapy

Memantine, an NMDA receptor antagonist, is used in moderate-to-severe AD, either as monotherapy or in combination with cholinesterase inhibitors [5,33]. It binds the NMDA receptor ion channel at the magnesium site, reducing glutamate-induced excitotoxicity without impairing normal synaptic transmission. Memantine slows cognitive decline and helps manage neuropsychiatric symptoms, though its disease-modifying potential remains uncertain. Common adverse effects include dizziness and headaches [5].

Behavioral and psychiatric symptom management

Behavioral and psychological symptoms of dementia (BPSD), particularly in late-stage AD, require combined pharmacological and non-pharmacological approaches [34].

- Antipsychotics (e.g., Olanzapine) may help with agitation or aggression, acting on multiple neurotransmitter receptors (dopamine, serotonin, histamine, muscarinic, and alpha-1 adrenergic receptors) [50].
- Mood stabilizers such as Carbamazepine have been explored for early BPSD management, while SSRIs or atypical antidepressants are preferred when anxiety or depression coexists [35].

Muscarinic Receptor Agonists

Muscarinic agonists, particularly M1/M4-selective agents like Xanomeline, are under investigation for cognitive enhancement in AD. These drugs modulate cholinergic signaling in cortical and subcortical circuits, potentially improving memory and executive function with fewer peripheral side effects [42,43].

Antioxidant and Neuroprotective Strategies

Oxidative stress contributes significantly to AD pathophysiology. Melatonin has demonstrated antioxidant properties, reducing amyloid-beta (Aβ) toxicity, tau hyperphosphorylation, and apoptosis in preclinical models [56–58]. Selegiline (L-deprenyl), a selective MAO-B inhibitor, exhibits neuroprotective effects by reducing oxidative damage and supporting neuronal survival [51,52].

Hormone Replacement Therapy

Estrogen has been proposed to exert neuroprotective effects via modulation of cerebral blood flow, neurotrophic support, antioxidant activity, and suppression of ApoE-mediated pathology. Clinical trials are ongoing to balance efficacy with safety in hormone replacement therapy for AD prevention and management [15,26,58].

Emerging and adjunctive therapies

Research continues on disease-modifying strategies, including secretase inhibitors, immunotherapy, stem cell therapy, and biomarker-guided interventions. These approaches aim to target amyloid-beta aggregation, tau pathology, and synaptic dysfunction at early stages, potentially altering disease progression.

Conclusion

AD pathogenesis involves extracellular amyloid plaques, intracellular neurofibrillary tangles, synaptic loss, and neuronal death. While genetics, notably ApoE4, and metabolic dysfunctions contribute to risk, current treatments, including AChEIs and NMDA antagonists, only alleviate symptoms

without addressing the underlying pathology. Future neuropharmacological strategies focusing on disease-modifying agents, stem cell therapies, and biomarker-driven early interventions hold promise for more effective management and prevention of AD.

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