

REVIEW ARTICLE

Neurodegeneration in Alzheimer's disease: A narrative review of mechanistic insights and emerging therapeutic approaches

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder responsible for 50–75% of dementia cases worldwide, primarily affecting individuals over 65 years of age. It is characterized by cognitive decline, memory loss, and behavioral abnormalities. Key pathological features include extracellular β -amyloid (A β) plaques, intracellular neurofibrillary tangles of hyperphosphorylated tau protein, mitochondrial dysfunction, and cholinergic system impairment. Despite extensive research, the precise etiology remains unclear, and current treatments only alleviate symptoms without halting disease progression. A comprehensive literature review was conducted using peer-reviewed articles from PubMed, Scopus, and Google Scholar, emphasizing recent studies on molecular mechanisms, risk factors, diagnostics, and therapies. Major pathogenic mechanisms identified include oxidative stress, tau hyperphosphorylation, A β aggregation, and synaptic degeneration. Non-modifiable risk factors such as aging, genetic mutations in amyloid precursor protein, phosphatidylinositol-binding clathrinid assembly protein, presenilin 1/2, and the apolipoprotein E ϵ 4 allele play significant roles, whereas modifiable risks involve lifestyle factors and comorbidities such as diabetes. Diagnostic advancements highlight the promise of blood-based biomarkers, although current practices rely heavily on cerebrospinal fluid markers and neuroimaging. Approved pharmacological interventions, including cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, provide limited symptomatic relief. Ongoing research into A β - and tau-targeted therapies has yielded mixed results. In addition, novel approaches such as tripartite motif-containing protein 2-mediated tau clearance and deep cervical lymphatic-venous anastomosis are being explored for their potential in targeting intracellular aggregates and enhancing brain waste clearance. AD emerges as a multifactorial condition driven by a complex interplay of biological, genetic, and environmental factors. Although substantial progress has been made in understanding its pathophysiology, effective disease-modifying therapies remain elusive. Continued advances in biomarker discovery and personalized therapeutic strategies offer hope for improved early detection and targeted treatment approaches.

Keywords: Alzheimer's disease; Neurodegeneration; Amyloid-beta; Mitochondrial dysfunction; Biomarkers

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1. Introduction

Alzheimer's disease (AD) is a multifactorial, progressive, irreversible neurodegenerative brain disorder characterized by a specific onset and progression of age-related cognitive and functional decline that leads to death.¹ It gradually causes patients to experience moderate cognitive impairment—a form of brain failure—that worsens over time. Approximately 95% of AD cases are late-onset, occurring after the age of 60–65, whereas the remaining 5% are early-onset, typically developing before this age.² Dementia is regarded as a prominent characteristic of AD, occurring in 50–75% of cases, and it interferes with day-to-day functioning. It impairs problem-solving and planning abilities, hampers the completion of daily tasks at work, home, or during leisure activities, causes confusion about time or place, makes it difficult to understand visual cues and spatial relationships, and leads to new difficulties in speaking and writing.¹ Globally, about 55 million people are currently living with dementia; this figure is expected to increase to 150 million by 2050.³ Symptoms of AD include behavioral abnormalities, memory loss, and cognitive difficulties.^{4,5} Although numerous theories attempt to explain its etiology, AD is ultimately caused by damage to brain cells, including amyloid precursor protein (APP)-induced β -amyloid ($A\beta$) plaques (senile plaques) and tau protein-induced neurofibrillary tangles (NFTs). These pathological features together induce the accumulation and degeneration of neurons, which activate microglia cells and encourage neuroinflammation in the brain.⁶ In addition, recent research suggests that mitochondria play a critical role in the pathogenesis of AD. Abnormal energy metabolism, elevated oxidative stress levels, imbalanced mitochondrial dynamics, aberrant mitophagy, and aging are hallmarks of mitochondrial dysfunction in AD patients.⁷ These aberrant mechanisms contribute to $A\beta$ synthesis, may promote aberrant tau protein phosphorylation via complex signaling networks, and can initiate a series of inflammatory reactions that worsen neuronal damage.^{8–10} The factors contributing to AD include both inherited and modifiable risk factors. Modifiable risk variables include smoking, food, age, obesity, and family history. The genetic risk factors include the apolipoprotein E (APOE) $\epsilon 4$ allele, phosphatidylinositol-binding clathrinid assembly protein, presenilin-1 (PSEN1), presenilin-2 (PSEN2), tau, and $A\beta$ protein precursor.¹¹ It has been reported that social interaction, cognitive function, and a balanced diet may help to reduce the risk.^{12,13} Diagnosing AD remains challenging, as there are currently no reliable tests for early-stage detection.¹⁴ Clinical examinations, psychological evaluation, cognitive testing, and brain imaging are the mainstays of diagnosis, which is strengthened by biomarkers such as tau and amyloid

levels in blood or cerebrospinal fluid (CSF) levels, as well as positron emission tomography (PET) scans.^{15,16} Unfortunately, there is no known permanent treatment for AD, and present treatments mostly aim to control symptoms and slow disease progression. Glutamate regulators and cholinesterase inhibitors are frequently administered to help reduce cognitive problems; however, more recent medications such as donepezil, rivastigmine, galantamine, memantine, and a combination of donepezil and memantine have been shown to help control symptoms of AD.¹⁷ Recent studies on neuroinflammation and tau pathology shed light on the complex processes driving disease progression. In addition to anti-amyloid and anti-tau monoclonal antibodies such as aducanumab, lecanemab, and donanemab, innovative strategies are being developed. These include tripartite motif-containing protein 21 (TRIM21)-mediated tau degradation through the proteasomal system and deep cervical lymphatic venous anastomosis (DC-LVA), a surgical method aimed at enhancing brain waste clearance. Such innovations highlight the shift toward targeted, disease-modifying therapies, expanding future treatment possibilities. The goal of this review is to present a comprehensive analysis of AD, including its pathology, diagnostic challenges, and both established and emerging therapeutic strategies.

2. Methods

This narrative review aimed to gather the most recent data on the origin, risk factors, diagnosis, and emerging treatments of AD. Literature was sourced from Google Scholar, Web of Science, PubMed, and Scopus. The keywords used included “Alzheimer's disease,” “neurodegeneration,” “amyloid-beta,” “tau,” “cholinergic system,” “mitochondrial dysfunction,” and “therapies.” Only peer-reviewed, English-language articles relevant to AD pathogenesis or treatments were included. Studies were excluded if they lacked methodological rigor and full-text access. To highlight the primary pathogenic mechanisms and developments in AD treatment, the selected materials were organized thematically.

3. Pathophysiology

AD is a progressive, unremitting, neurodegenerative disorder that affects wide areas of the cerebral cortex and hippocampus.¹⁷ Typically, abnormalities begin in the frontal and temporal lobes of the brain and gradually spread to other parts of the neocortex, with progression rates varying noticeably among individuals. The $A\beta$ and tau proteins have substantial evidence supporting their roles as contributors to AD.¹⁸ In addition, various factors such as cholinergic dysfunction, oxidative stress, and mitochondrial impairment also play an important role in

AD.¹⁹ Collectively, these degenerative processes cause the brain to gradually shrink, especially in the hippocampus and cerebral cortex, resulting in hallmark symptoms such as behavioral changes, disorientation, and memory loss (Figure 1).

3.1. A β plaques

APP is a single-pass transmembrane protein with a large extracellular domain expressed in neuronal cells.²⁰ The aberrant cleavage of APP is considered the primary cause of AD. Two successive phases are involved in this cleavage: β -secretase (BACE1) acts at the ectodomain, followed by γ -secretase at an intramembranous location.²¹ These proteolytic events generate A β , a 4 kDa peptide fragment derived from APP.²² The process predominantly produces A β 40 and A β 42,²³ of which A β 42 is highly hydrophobic and prone to aggregation.²⁴ Initially, A β 42 aggregates into soluble oligomers, which assemble into protofibrils and eventually form insoluble fibrils.²⁵ These fibrils accumulate extracellularly as plaques in the brain, which is a characteristic of AD pathogenesis.²⁶ Excessive A β fibril accumulation in the synaptic cleft disrupts neuronal signaling by interfering with regular synaptic connections.^{26,25} APP is abundantly expressed in

brain neurons, vascular cells, and blood cells (including platelets), with lower expression in astrocytes. The progressive oligomerization and deposition of A β plaques are central to the neurodegenerative processes observed in AD.²⁷ Genetic studies have linked mutations in *PSEN1*,²⁸ *PSEN2*,²⁹ and *APOE*²⁹ to A β pathology.

3.2. Tau protein

Tau protein is a microtubule-associated protein that is commonly found in both the cytosol and axons of neurons.³⁰ Microtubules form the structural backbone of neurons, stabilized in specific orientations to create axons and dendrites.³¹ They are essential for axonal transport, mediated by motor proteins such as kinesin and dynein, which facilitate efficient neuronal signal transmission. The primary role of tau is to stabilize microtubules and support axonal transport.

Protein kinases (PKs) responsible for normal tau phosphorylation are classified into proline-directed PKs (PDPKs), non-PDPKs, and tyrosine PKs.³² Increased extracellular A β levels activate kinases, leading to hyperphosphorylation of tau. This modification alters tau's conformation and charge, exposes the microtubule-binding domain, and promotes tau self-aggregation.³³⁻³⁵ Eventually,

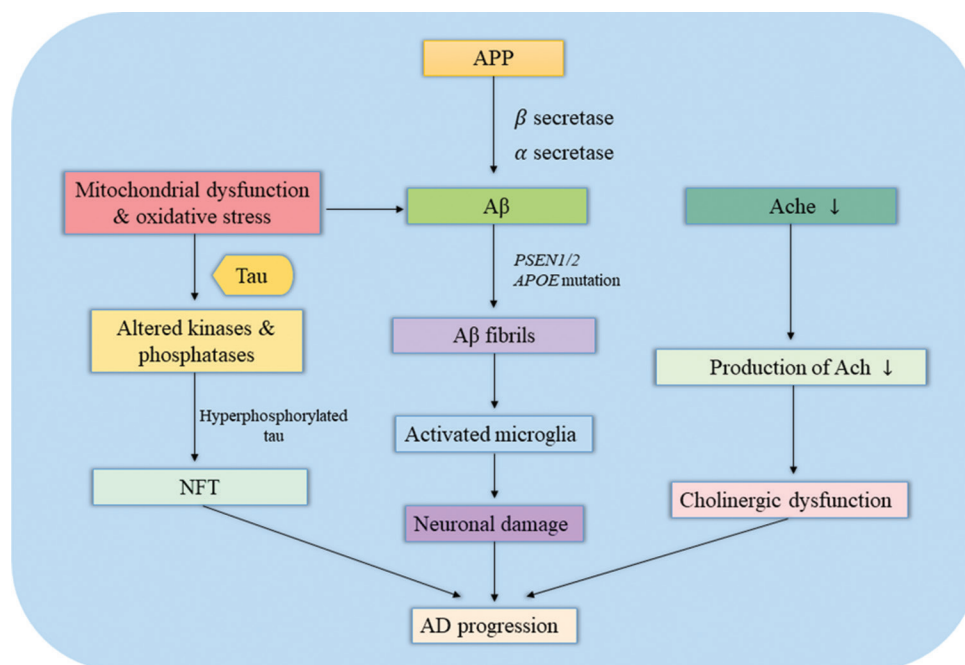


Figure 1. Mechanism of Alzheimer's disease (AD) progression. This schematic illustrates the main biochemical pathways involved in the development of AD. Aberrant processing of amyloid precursor protein by β -secretase and γ -secretase, influenced by genetic modifications such as phosphatidylinositol-binding clathrinid assembly protein, presenilin 1/2 or apolipoprotein E, results in β -amyloid (A β) accumulation and fibril formation. These aggregates activate microglia, leading to neuronal loss and subsequent AD pathology. Mitochondrial failure and oxidative stress can affect tau protein regulation, either independently or in combination with A β . This causes hyperphosphorylation and neurofibrillary tangle production, which ultimately leads to neuronal death. In parallel, A β reduces acetylcholinesterase activity, resulting in decreased acetylcholine synthesis and cholinergic dysfunction, which leads to cognitive decline. These interconnected networks collectively drive the neurodegeneration associated with AD. Image created by the authors.

these tau oligomers transform into NFTs^{36,37}—highly insoluble fibrillary structures within neurons that disrupt microtubule stability and impair connectivity between neurons during signal processing and cell signaling.^{30,35} It also results in cognitive insufficiencies due to a lack of proper axonal transport. Aberrant phosphorylation of tau ultimately leads to neuronal death.³⁸ The onset and progression of AD are more closely linked to tau pathology rather than to A β accumulation.³⁹

3.3. The cholinergic system

One of the most noticeable pathologies of AD is cholinergic depletion. According to the cholinergic hypothesis, reduction of cholinergic function in the central nervous system (CNS) is a major contributor to cognitive impairment in AD.⁴⁰ Accumulation and deposition of A β plaques, tau protein hyperphosphorylation, and the acetylcholinesterase (AChE) activity are all implicated in this dysfunction. The human brain contains a large number of cholinergic neurons, which are essential for cognition, and their dysfunction plays a major role in the memory and learning impairments in AD.⁴¹ Acetylcholine (ACh), produced by choline acetyltransferase from choline, acetyl-CoA, and ATP, is necessary for cholinergic neurotransmission and neurovascular coupling.⁴² In AD, reduced choline acetyltransferase activity decreases ACh production, exacerbating cognitive decline. Excessive ACh breakdown by AChE further disrupts synaptic transmission. As the cholinergic system regulates neurogenesis, neuronal differentiation, synaptic plasticity, and neuroprotection, its dysfunction accelerates both cognitive deterioration and disease progression.⁴³

In addition, basal forebrain cholinergic neurons (BFCNs), which depend on nerve growth factor for survival and differentiation, are essential for learning, memory, and cognition.^{44,45} Nicotinic ACh receptors, especially the $\alpha 7$ subtype, are abundant in the hippocampus and predominate in cortical and hippocampal areas.⁴⁶ MicroRNA regulation, elevated brain-derived neurotrophic factor, and increased phosphorylated cAMP response element-binding protein (p-CREB/CREB) expression in certain brain areas are all associated with memory formation.⁴⁷ In AD, cholinergic atrophy, cognitive decline, and hippocampus dysfunction are the outcomes of BFCN malfunction or degeneration, which also contributes to neuroinflammation.⁴⁸ Furthermore, degeneration of the nucleus basalis of Meynert, which is a major cholinergic hub, speeds up the onset of AD by compromising cortical activity coordination during learning.⁴⁹

3.4. Mitochondrial dysfunction and oxidative stress

Mitochondria, the cell's "powerhouses," produce ATP through oxidative phosphorylation and regulate signal

transduction, calcium homeostasis, lipid production, and cellular metabolism. They are also the primary source of reactive oxygen species (ROS), which typically act as signaling molecules to regulate cellular processes and are produced at low levels during oxidative phosphorylation. However, excessive ROS generation resulting from impaired mitochondrial function can cause oxidative stress, harming cellular structures and processes. Mitochondrial dysfunction is most prominent in the brains of AD patients and leads to impaired energy metabolism. Energy-producing enzymes, such as mitochondrial glutamate dehydrogenase, cytochrome c oxidase, and α -ketoglutarate dehydrogenase, exhibit dramatically reduced activity,⁵⁰ whereas succinate dehydrogenase and malate dehydrogenase have significantly increased activity.⁵¹ Pathological conditions affecting mitochondrial metabolism, such as excessive calcium ion (Ca^{2+}) transfer from the endoplasmic reticulum or elevated cytosolic Ca^{2+} levels, can induce oxidative stress, disrupt ion exchange, and decrease ATP generation, ultimately leading to cell damage and death.⁵² Reduced ATP levels, increased ROS formation, mitochondrial dysfunction, and calcium imbalance are all observed in AD brains, often preceding the onset of clinical symptoms.⁵³

Several factors contribute to oxidative stress in AD. Iron present in NFTs and A β deposits promotes the formation of advanced glycation end products, which in turn stimulate the generation of hydroxyl radicals from hydrogen peroxide.^{54,55} Accumulation of aluminum in NFT-containing neurons further stimulates iron-induced lipid peroxidation.^{55,56} The immune cell, such as activated microglia, emits nitric oxide and superoxide (O_2^-),⁵⁷ which can combine to create peroxynitrite, leaving nitrotyrosine as a diagnostic biomarker.^{58,59} In addition, A β peptides directly produce ROS, and mitochondria remain a major source of oxidative stress in AD due to genetic defects and impairments in metabolic enzymes that hinder ATP production and enhance ROS production.^{60,61}

4. Biomarkers to diagnose AD

The pathological hallmarks of AD include tau-containing NFTs and A β plaques, which result in neuronal and synaptic loss, neurotransmitter shortages, neuroinflammation, and reactive astrocytes, all of which contribute to cognitive impairment.⁶² Although cognitive tests and episodic memory assessments have demonstrated value in predicting progression to AD, it is now widely recognized that biomarkers can significantly improve diagnostic accuracy. Biomarkers provide an objective means of detecting AD by identifying pathological changes before the onset of noticeable clinical symptoms. Most AD biomarkers fall into two categories: Pathophysiologic biomarkers and

topographic biomarkers. Pathophysiologic biomarkers reflect specific disease lesions and include amyloid PET imaging, CSF amyloid and tau protein concentrations, and plasma levels of amyloid, tau, and other protein markers. Topographic biomarkers indicate the regional effects of AD pathology and include fluorodeoxyglucose (FDG)-PET evidence of regional hypometabolism, tau PET imaging, and regional or local atrophy detected by structural magnetic resonance imaging (MRI).⁶³

4.1. CSF biomarkers

As the CSF is known to have direct contact with the extracellular fluid of the cerebral ventricles, the concentration of particular markers in the CSF may serve as a predictor of the biochemical alterations occurring in the brain and CNS. In addition, CSF samples can be obtained during a lumbar puncture without the need for extremely specialized equipment, and the risk of complications is minimized if the procedure is carried out by a skilled and certified professional. Nevertheless, it is still considered an intrusive examination that might cause radial limb pains, spinal headaches, and even fatal complications—if sterility is compromised.^{64–66} CSF biomarkers can identify tau and A β peptides, with alterations frequently appearing before changes are visible on neuroimaging.⁶⁷ While phosphorylated tau (pTau) is more specific to AD pathology, total tau (tTau) indicates neuronal injury.^{68,69} Key biomarkers for early AD detection include A β 42, A β 40, pTau181, pTau217, and tTau.⁷⁰ tTau and pTau are associated with neurodegeneration and NFTs,⁷¹ whereas A β 42 concentrations and the A β 42/40 ratio decrease with A β plaque accumulation.⁷² The pTau181/A β 42 ratio can distinguish frontal variants of AD from frontotemporal dementia (FTD),⁷³ and pTau231 may support the detection of incipient AD.⁷⁴ Neurofilament light (NfL) chain, due to its high sensitivity, is sometimes preferred over tTau in clinical settings.⁶⁷ Other emerging CSF biomarkers—such as glial fibrillary acidic protein, neurogranin, and YKL-40—may assist in disease staging and prognosis rather than differential diagnosis.^{75–77}

4.2. Blood-based biomarkers

Early research on plasma A β , as documented in the AlzBiomarker database (<https://www.alzforum.org/alzbiomarker>), showed inconsistent results due to assay variability, with no reliable change in plasma A β 42 or A β 40 levels in AD.⁷⁸ The establishment of an ultrasensitive single-molecule array (Simoa) test enhanced detection and showed that amyloid PET-positive people have a lower plasma A β 42/A β 40 ratio, which was comparable to CSF results but with less pronounced separation.^{79–81} More recently, immunoprecipitation mass spectrometry-based

tests confirmed the diagnostic value of a reduced plasma A β 42/A β 40 ratio, achieving approximately 90% accuracy.^{82,83} While promising, these methods still face specificity challenges due to non-cerebral expression of A β (such as from blood platelets).⁸⁴

Ultrasensitive assays show that plasma tau concentrations are higher in AD dementia, though less distinctly than in CSF.^{78,85} There are conflicting reports about plasma tau in MCI.⁸⁶ Higher plasma tTau has been linked to faster cognitive decline⁸⁷ and incident AD dementia.⁸⁸ Plasma pTau181 correlates more strongly with A β /tau PET and clinical features than tTau,⁸⁹ consistent with other studies using immunomagnetic reduction⁹⁰ and Simoa.⁹¹

Plasma NfL, an intra-axonal structural protein released during axonal injury, is a robust biomarker of neurodegeneration across neurodegenerative disorders.⁹² It is elevated in both familial and sporadic AD, correlates strongly with CSF NfL, and can be measured in either serum or plasma.⁹² In familial AD, NfL rises about 10 years before expected symptom onset;⁹³ in sporadic AD, increases may occur later and be influenced by aging (~3% annual CSF increase) or comorbidities.^{94,95}

4.3. PET markers

PET imaging with different ligands can help differentiate AD from other neurodegenerative diseases and identify typical versus atypical patterns. FDG-PET detects regional hypometabolism, typically in the bilateral parietal and medial temporal areas, including the precuneus, in AD.^{96,97} In addition, it aids in the diagnosis of non-AD dementias such as FTD and dementia with Lewy bodies.⁹⁸ Although it offers better diagnostic information than MRI, FDG-PET is less frequently used in routine care.

Amyloid PET, primarily utilized in research, offers a high sensitivity (92%) and specificity (100%) for detecting fibrillar A β plaques.^{78,99} In contrast to FDG-PET, amyloid deposition patterns are similar in both typical and atypical AD.¹⁰⁰ Tau PET—also primarily research-focused—detects NFTs with 92–100% sensitivity and 52–92% specificity,¹⁰¹ correlates with short-term disease progression (3–5 years), and predicts cognitive deterioration in asymptomatic individuals.^{102,103} In contrast to amyloid PET, Tau PET patterns differ by phenotype, exhibiting clear deposition patterns in amnesic AD, logopenic aphasia, and posterior cortical atrophy, reflecting clinical characteristics.¹⁰⁴ Although they are infrequently employed in clinical practice, emerging PET biomarkers, including translocator protein PET (neuroinflammation) and synaptic vesicle glycoprotein 2A PET (synaptic density), are being studied for disease staging and prognostication.^{98,105}

4.4. MRI markers

As a topographic biomarker for AD, MRI reveals volume loss and grey matter atrophy, which are signs of neurodegeneration.⁶⁷ Due to its low variability and ability to assess therapeutic efficacy with smaller clinical trial sample sizes, serial structural MRI is recommended for monitoring disease development.¹⁰⁶ Other MRI tests include: (1) T2-weighted or susceptibility-weighted MRI, which measures vascular activity and detects cerebral amyloid angiopathy;¹⁰⁷ (2) resting state functional MRI, which evaluates changes in functional brain connectivity that may precede structural brain changes;¹⁰⁸ and (3) diffusion tensor imaging MRI, which evaluates damage to white matter.¹⁰⁹ Although these approaches are not yet widely used in clinical trials or routine practice, they may become more crucial in the management of amyloid-related imaging abnormalities (ARIA) during anti-amyloid therapy. Atypical AD exhibits symptom-specific atrophy, frequently avoiding the hippocampus in its early stages, whereas typical AD exhibits atrophy that begins in the medial temporal lobe and spreads to the lateral temporal and parietal cortices.⁹⁷ Even though they manifest later in the course of the disease, MRI alterations are consistent with FDG-PET results. In amnesic syndrome, hippocampal volume on MRI correlates strongly with memory impairment.¹¹⁰

5. Treatment of AD

AD treatment includes both symptomatic and emerging disease-modifying approaches. Traditional pharmacological therapies for mild to moderate AD include cholinesterase inhibitors (donepezil, rivastigmine, and galantamine), which aim to enhance cholinergic neurotransmission and provide certain cognitive and functional benefits.¹¹¹ In moderate to severe phases, memantine—an N-methyl-D-aspartate receptor antagonist—is used to reduce excitotoxicity and regulate glutamate activity.¹¹² In recent years, there has been increased interest in disease-modifying therapies that target the underlying pathophysiology of AD. The use of monoclonal antibodies such as aducanumab and lecanemab is a novel treatment targeting A β accumulation in the brain. Lecanemab may lessen cognitive decline in early-stage AD.¹¹³ Furthermore, new therapies are being explored to address tau pathology and neuroinflammation. Non-pharmacological interventions include social engagement, physical exercise, and cognitive stimulation that improve quality of life and help maintain functional independence.¹¹⁴

6. Modern approaches to AD management

6.1. Immunotherapy targeting the amyloid protein

The deposition of A β in the brain—a defining feature of AD—is the main target of monoclonal antibody-based immunotherapy, which has emerged as a promising therapeutic approach. These laboratory-engineered antibodies are designed to specifically identify A β peptides and trigger processes that decrease amyloid load and mitigate associated neurotoxicity. One critical mechanism involves the neutralization of soluble A β . By targeting these soluble fragments before they aggregate into insoluble plaques, monoclonal antibodies help prevent plaque formation and subsequent neuronal damage. Another mechanism is the facilitation of plaque clearance: Antibodies bind to amyloid plaques, marking them for recognition by microglial cells, the brain's innate immune defenders, which then phagocytose and degrade the antibody-bound deposits. A third mechanism targets A β conformation, with certain antibodies disrupting structural folding to prevent the formation of toxic fibrillar aggregates that contribute to neuronal dysfunction.^{115,116}

6.2. Aducanumab: From controversy to conditional acceptance

Monoclonal antibodies have demonstrated promise in different phases of AD-related clinical studies. A notable example that targets A β plaques is Aducanumab, which was developed by Biogen. On June 07, 2021, the U.S. Food and Drug Administration (FDA) granted the rapid clearance for Aducanumab to treat mild AD, marking the first approval of a potentially disease-modifying therapy in nearly two decades.¹¹⁷ However, its approval was controversial due to erratic trial outcomes and the reliance on amyloid reduction as the main endpoint in the absence of convincing proof of associated therapeutic benefit.

Aducanumab selectively targets both aggregated insoluble and soluble forms of A β .¹¹⁵ It binds to plaques containing amyloid and A β oligomers in the brain, even at low concentrations, and activates microglia to facilitate amyloid clearance. A β plaques have been consistently reduced by aducanumab in a dose- and duration-dependent manner in the phase 1b trial (PRIME).^{116,118} However, results from the Phase III ENGAGE and EMERGE trials were not inconsistent. At the maximum dosage, EMERGE demonstrated a 23% decrease in clinical decline, whereas ENGAGE did not reach its primary endpoint.^{119,120} *Post hoc* analyses suggested that a subset of patients might derive modest benefit, prompting cautious optimism. Nonetheless, concerns about safety remain, particularly regarding

amyloid-ARIA, which includes microhemorrhages and brain edema.^{119,121} In 2024, Biogen announced it would discontinue commercial sales of aducanumab and redirect resources toward other Alzheimer's programs, including agents with potentially greater clinical impact.¹²² Currently, aducanumab is not recommended for routine clinical use. However, the ongoing Phase 3b/4 ENVISION trial aims to evaluate its efficacy in patients with early-stage AD, potentially providing more definitive evidence regarding its disease-modifying potential and informing future clinical decisions.^{120,123}

6.3. Lecanemab: A potentially effective AD treatment

Lecanemab is a humanized monoclonal antibody with a strong affinity for soluble A β protofibrils, which have been reported to be more neurotoxic than monomers or insoluble fibrils.^{113,124} It was approved by the U.S. FDA on January 06, 2023, for early-stage AD patients.¹²⁵ Its mechanism of action involves attaching to and neutralizing A β protofibrils—tiny, soluble precursors to the big, insoluble amyloid plaques characteristic of AD. Lecanemab seeks to disrupt the amyloid cascade at an earlier point by targeting these early-stage, more toxic forms of A β ,¹²⁶ potentially preventing or minimizing neuronal damage before the formation of big plaques. This mechanism contrasts with that of aducanumab, which mainly targets the densely packed, aggregated, insoluble A β plaques.¹¹⁶ Since lecanemab neutralizes small protofibrils rather than breaking up large plaques, it is expected to carry a lower risk of ARIA.¹¹³ In a phase 2b randomized, double-blind, placebo-controlled trial involving 854 participants with early AD, lecanemab produced mixed results.¹²⁶ Over the first 12 months, composite cognitive scores did not differ significantly between treatment and placebo groups. However, by 18 months, a clear dose- and time-dependent effect on amyloid clearance was evident. The optimal regimen—10 mg/kg intravenously every 2 weeks—significantly reduced amyloid plaque burden as measured by PET imaging and slowed clinical deterioration on selected cognitive and functional measures. Notably, fewer than 3% of participants experienced symptomatic ARIA with edema (ARIA-E), although the overall incidence of ARIA-E was 9.9%.^{126,127}

These findings supported the phase 3 CLARITY AD trial, which enrolled 1,795 patients with early AD for an 18-month therapy evaluation.^{113,127,128} The mean amyloid levels in the therapy group dropped to 22.99 centiloids—below the amyloid positive threshold of about 30 centiloids—indicating a considerable amyloid clearance. More importantly, the clinical dementia rating—sum of boxes and other standardized tests showed a slight

but statistically significant reduction of cognitive and functional decline compared to placebo. In addition to amyloid removal, lecanemab was linked to reductions in neuroinflammation and tau pathology, consistent with its proposed disease-modifying mechanism.¹²⁹

6.4. Donanemab: A precision strategy for AD therapy

Donanemab is an immunoglobulin G1 monoclonal antibody that targets the insoluble, mutated, and N-terminal-shortened form of A β found solely in brain amyloid plaques. Upon binding to this truncated A β , donanemab promotes plaque clearance via microglial-mediated phagocytosis.¹³⁰ In July 2024, the FDA authorized donanemab to treat adults with early symptomatic AD and verified amyloid pathology.¹³¹ This targeted approach allows selective elimination of neurotoxic aggregates while disrupting the amyloid cascade that underpins AD pathogenesis. Phase 1 trials using ¹⁸F florbetapir PET imaging demonstrated that donanemab significantly reduced amyloid plaque load.¹³² The Trailblazer-ALZ trial—a double-blind, phase 2, placebo-controlled research—also evaluated donanemab's safety and efficacy in patients with early symptomatic AD, intermediate tau levels, and increased amyloid verified by PET scans. Using the integrated AD rating scale, the donanemab study found a 32% reduction in AD development compared to the placebo group after 76 weeks. The therapy also demonstrated an 85% reduction in amyloid plaques, with 68% of patients reaching amyloid-negative status.¹³³

6.5. TRIM21-mediated intracellular tau clearance

TRIM21, a cytosolic Fc receptor and E3 ubiquitin ligase, is a key mediator of intracellular immune defense and has emerged as a potential therapeutic target in neurodegenerative disease. Initially identified as a modulator of antiviral immunity, TRIM21 binds to intracellular substrates tagged with antibodies, resulting in its proteasomal degradation through the ubiquitin–proteasome system (UPS).^{134–136} It is a strong therapeutic contender for neuroinflammation-related disorders due to its high expression in multiple organs, including the CNS, and its control by type I (Interferon [IFN]-alpha) and type II (IFN- β).^{137,138}

Later studies have broadened the function of TRIM21 to tauopathies, including AD, in which intracellular tau accumulation drives pathology. In a process akin to viral clearance, McEwan *et al.*¹³⁹ showed that TRIM21 could identify and eliminate antibody-tagged tau aggregates via UPS, aided by the molecular unfoldase valosin-containing protein (VCP/p97). For therapeutic purposes, researchers have engineered this mechanism using RING-Bait

technology—comprising the TRIM21 RING domain fused to anti-tau nanobodies or tau protein. Upon introduction into cells, the construct mimics natural TRIM21 activation: Dimerization of the RING domain triggers E3 ligase activity, selectively degrading tau fibrils.^{140,141} In cell models (e.g., HEK293 cells expressing P301S tau), RING-tau constructs eliminated existing tau aggregates and blocked heparin-induced seeded aggregation, while sparing physiological soluble tau. Comparable results were observed in primary neurons from Tau P301S mice.¹⁴¹ Inhibitors of the proteasome (MG-132), VCP (NMS-873), and E1 ubiquitin-activating enzyme (TAK-243) abolished this effect, confirming UPS dependence. *In vivo*, systemic delivery of RING-tau via AAV9P31 significantly reduced tau aggregates and improved motor performance in Tg2541 (Tau P301S) mice.¹⁴¹ Benn *et al.*¹⁴² later developed a similar TRIM21 RING–anti-tau nanobody fusion, achieving aggregate clearance in both cellular and animal models without affecting monomeric tau.¹⁴³ While these approaches enable highly selective tau aggregate removal, a major translational hurdle remains—efficient delivery of RING-Bait degrader into the human brain.

Taken together, these findings underscore TRIM21's unique potential in selectively targeting and eliminating intracellular tau aggregates. Whether by leveraging its natural Fc-receptor function¹³⁹ or through engineered constructs such as RING-Bait,^{141–143} TRIM21-based strategies represent a novel and promising therapeutic approach for tauopathies such as AD.

6.6. DC-LVA

DC-LVA is a microsurgical technique proposed for AD. This technique reconstructs a drainage channel between the venous system and meningeal lymphatics to improve the interstitial fluid and CSF clearance.¹⁴⁴ One of the main concerns in AD pathophysiology is the removal of cerebral metabolic waste.¹⁴⁵ In the past, the CNS was considered devoid of a typical lymphatic system, with metabolic waste thought to drain into venous circulation via arachnoid granulations.¹⁴⁶ Nonetheless, recent research has identified meningeal lymphatic vessels linking to deep cervical lymph nodes, providing a direct anatomical route for CSF and ISF drainage.^{147,148}

In a prospective clinical trial, Chen *et al.*¹⁴⁹ treated 26 biomarker-positive AD patients with a modified lymphatic venous anastomosis, with 60% of caregivers reporting cognitive improvement alongside moderate mini-mental state examination score improvements. Although CSF biomarkers (A β 42, p-tau) were not significantly reduced, trends indicated possible long-term gains. Similarly, Ma *et al.* reported cognitive improvement following the procedure but noted variability of surgical techniques and small sample sizes

as limiting factors. Notwithstanding its potential, DC-LVA has drawbacks, such as extreme microsurgical complexity, the inability to confirm shunt patency during surgery, and sporadic side effects such as temporary accessory nerve damage.¹⁴⁹ Large, randomized controlled trials are needed to validate efficacy, improve methods, and evaluate safety. Future applications may combine DC-LVA with non-invasive neuromodulatory techniques or anti-A β agents.¹⁵⁰

7. Conclusion

AD is caused by a complex interplay of pathological processes, including A β plaque formation and NFTs from hyperphosphorylated tau protein. These mechanisms lead to neuronal malfunction, neuroinflammation, and cognitive impairment. Although the amyloid hypothesis is crucial for understanding AD, inconsistent therapeutic outcomes underscore the disease's complexity. Complementary hypotheses, including the cholinergic and tau hypotheses, highlight the necessity for comprehensive treatment strategies. Monoclonal antibodies such as aducanumab, lecanemab, and donanemab have shown promise in targeting AB plaques but carry risks such as amyloid-ARIA, emphasizing the need for cautious patient selection. Meanwhile, new strategies such as TRIM21-mediated tau degradation and DC-LVA offer novel routes for targeting intracellular aggregates and improving waste clearance, respectively. Future research should focus on discovering accurate biomarkers for early diagnosis, establishing strategies to limit side effects, and investigating combination therapies to improve treatment success. A multidimensional strategy, incorporating non-pharmacological therapies such as cognitive training and lifestyle changes, alongside pharmacological treatments, is crucial. Addressing these challenges is essential to improving outcomes and quality of life for AD patients and their families.

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Conflict of interest

The authors declare that they have no competing interests.

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