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Commentary

Beyond Amyloid: Rethinking the Foundations of Alzheimer's Disease Pathogenesis and Therapy

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ABSTRACT: For more than three decades, the amyloid cascade hypothesis has framed Alzheimer's disease (AD) as a disorder in which amyloid-β (Aβ) accumulation initiates a pathological cascade leading to neurodegeneration and cognitive decline. Aβ plaque deposition is a robust pathological feature of AD and a useful biomarker target, yet plaques alone do not explain disease onset, clinical heterogeneity, or the pace of symptomatic change. We propose that fibrillar amyloid plaques do not drive AD pathogenesis and instead represent intermediate products of a broader disease process. This amyloid-centered emphasis has shaped research priorities and drug development aimed at lowering amyloid burden. However, amyloid lowering has not produced consistent, clinically meaningful cognitive benefits, exposing a gap between target engagement and patient-centered outcomes. Here, we reevaluate the evidentiary basis and translational performance of the amyloid model using contemporary trial results, biomarker trajectories, and neuropathological observations. We also analyze the scientific, regulatory, and structural forces that sustained amyloid-centered strategies. We advance an integrative view of AD as a staged process involving tau pathology, neuroimmune dysfunction, vascular injury, and aging biology. Progress will depend on earlier and stage-matched intervention, mechanism-informed combination strategies, and regulatory standards anchored to outcomes patients value.

Keywords: Alzheimer's disease, amyloid hypothesis, neurodegeneration, tau pathology, cognitive impairment, therapeutic models

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder and the leading cause of dementia, accounting for 60–70% of all cases and affecting an estimated 57 million people worldwide (World Health Organization, 2021) [1, 2]. In the United States, more than six million individuals currently live with AD, a figure expected to exceed 13 million by 2060 [3]. It remains the sixth leading cause of death nationwide [4]. AD typically begins with memory loss and impaired learning, then progresses to language dysfunction, disorientation, and marked changes in personality and behavior [5].

Although AD is not caused by aging, its prevalence increases sharply with age. The incidence rises from 5.3% among adults aged 65–74 to 34.6% in those over 85 [2, 3]. Symptoms usually appear after the age of 60, though early-onset familial forms, often linked to autosomal dominant mutations, have drawn increasing attention [6]. After diagnosis after age 65, individuals survive on average four to eight years, though survival can extend up to two decades depending on genetic, biological, and clinical factors [2, 6].

The societal and economic costs of AD are immense. In the United States, annual expenditures exceed $345 billion, including an estimated $339 billion in unpaid caregiving [2, 7]. These figures surpass those associated with either cancer or cardiovascular disease [8]. In 2023, the National Institute on Aging (NIA) invested roughly $3.2 billion in AD research, yet no available therapy has succeeded in preventing or halting disease progression. Many researchers attribute this lack of progress to the field's enduring focus on the amyloid hypothesis,

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highlighting the need to reassess long-held assumptions and diversify investigative approaches.

AD was first described in 1906 by Dr. Alois Alzheimer, a German psychiatrist and neuropathologist, who examined the brain of a woman suffering from severe memory loss, aphasia, and behavioral disturbance [9]. He identified two distinctive lesions: extracellular amyloid plaques and intracellular neurofibrillary tangles. Together with synaptic loss, these remain the defining pathological features of AD [3]. Dr. Alzheimer himself did not propose these changes as the cause of dementia. At the time, cognitive decline was largely attributed to vascular pathology, then termed arteriosclerotic dementia [10, 11]. This interpretation persisted until the 1980s, when Glenner and Wong identified amyloid-β (Aβ) peptide as a principal component of plaques and vascular deposits [12-14]. The subsequent discovery of mutations in the amyloid precursor protein (APP) gene in familial early-onset AD further strengthened the link between Aβ and disease pathology [15], establishing amyloid-centric models as the dominant framework for both experimental and translational research [10].

The amyloid hypothesis proposes that the accumulation of Aβ peptides initiates a pathological cascade leading to synaptic failure, neuronal loss, and cognitive decline [16–18]. Mutations in APP, presenilin-1 (PSEN1), and presenilin-2 (PSEN2), which enhance Aβ production or impair its clearance, provide strong genetic support for this model [19–21]. As a result, most therapeutic strategies have focused on Aβ reduction. However, despite promising preclinical results, clinical outcomes have been disappointing. Aβ-targeting agents have failed to produce meaningful cognitive improvement, even in genetically defined high-risk populations, and have often been associated with adverse effects such as cerebral edema and microhemorrhage [22–28].

Decades of investigation have produced amyloid-targeting therapies with modest slowing of clinical decline in selected patients, but overall results remain disappointing. While the amyloid hypothesis has provided a valuable conceptual foundation, it may have constrained the field's perspective. Reassessing core mechanisms and expanding inquiry beyond amyloid biology is now critical.

In this paper, we examine how the dominance of the amyloid hypothesis has shaped the trajectory of AD research, outlining its conceptual and methodological limitations. We argue that meaningful advances will require broader, biologically integrative frameworks capable of addressing the multifactorial nature of AD.

2. Understanding the amyloid hypothesis

2.1 Historical background and definition

The amyloid hypothesis was first proposed by John Hardy and David Allsop in 1991 and refined by Hardy and Gerald Higgins in 1992 [16, 17], It claims that the accumulation of amyloid-β (Aβ) peptide in the brain is a critical initiating event in the development of AD. Misfolded Aβ aggregates into extracellular amyloid plaques, which are believed to trigger a cascade of pathological processes leading to synaptic dysfunction, neuronal loss, and ultimately, memory impairment and cognitive decline [12, 18].

Aβ is a short peptide, typically 38–43 amino acids in length, produced through proteolytic cleavage of amyloid precursor protein (APP) [19]. APP is a transmembrane protein expressed widely in many tissues but is especially abundant at neuronal synapses. Although its precise physiological function remains unclear, evidence suggests roles in neuronal growth, cell signaling, and synaptic plasticity [20, 21].

APP is processed through two competing pathways. In the non-amyloidogenic pathway, α-secretase cleaves APP within the Aβ domain, preventing Aβ formation. This generates a soluble ectodomain (sAPPα) and a membrane-bound fragment (C83). γ-Secretase subsequently cleaves C83 to produce non-toxic products, including the APP intracellular domain (AICD) and p3. sAPPα has been implicated in promoting neuronal survival and synaptic maintenance [33].

In contrast, the amyloidogenic pathway begins with β-secretase (BACE1) cleavage, producing a longer C-terminal fragment (C99). γ-Secretase then processes C99 to generate Aβ peptides of varying lengths, most notably Aβ40 and Aβ42 [22, 23]. Aβ42 is more prone to aggregation, forming soluble oligomers that disrupt synaptic function and promote tau phosphorylation, tangle formation, inflammation, and neuronal death [24-26]. When Aβ production exceeds clearance, these toxic assemblies accumulate and are thought to drive disease progression [27].

This mechanistic framework placed Aβ at the center of AD pathology and, for over three decades, has dominated research priorities and drug development strategies.

2.2 Mechanistic insights into Aβ-induced AD

The amyloid hypothesis holds that abnormal accumulation of Aβ, particularly the Aβ42 isoform, initiates a sequence of events that drive AD. Early in the process, Aβ assembles into soluble oligomers, which show greater synaptotoxicity than insoluble plaque deposits. In electrophysiological assays, these oligomers impair synaptic transmission and disrupt long-term

potentiation (LTP), a widely used measure of synaptic plasticity. These findings support the view that Aβ oligomers interfere with synaptic signaling *in vivo* [24, 25].

As pathology advances, Aβ oligomers appear to promote tau hyperphosphorylation, leading to the formation of neurofibrillary tangles, another hallmark lesion of AD. Increasing evidence supports a direct interaction between Aβ and tau, suggesting that Aβ may initiate or accelerate tau pathology rather than act through an independent pathway [26]

Aβ accumulation also triggers a robust glial response. Activated microglia and astrocytes release pro-inflammatory cytokines and reactive oxygen species (ROS), amplifying oxidative stress and neuronal damage. This inflammatory milieu reinforces Aβ toxicity and sustains a cycle of neurodegeneration [28].

Collectively, synaptic dysfunction, tau aggregation, and chronic inflammation lead to progressive neuronal loss, cortical atrophy, and cognitive impairment. Biomarker and neuroimaging studies show that these pathological changes begin well before clinical symptoms emerge, supporting the view that early Aβ accumulation is a central initiating factor in AD pathogenesis [27].

2.3 Supporting evidence from experimental and clinical studies

Amyloid biology remains important, but limited efficacy and safety risks support a broader search for complementary mechanisms. One of the strongest lines of evidence comes from genetics. Familial early-onset AD is associated with mutations in genes involved in Aβ production and processing, particularly *APP*, *PSEN1*, and *PSEN2*. The presenilins form the catalytic core of the γ-secretase complex, which influences substrate specificity and cleavage efficiency [29, 30].

Early genetic and biochemical studies showed that pathogenic *PSEN1* mutations increase Aβ42 levels in plasma from familial AD (FAD) patients and in experimental models, including transfected cells and transgenic mice. These mutations consistently shift γ-secretase activity toward generating longer Aβ peptides, especially Aβ42, which is more prone to aggregation [31-33]. These findings led to the view that PSEN1 mutations drive FAD by altering APP processing and favoring the overproduction of pathogenic Aβ42 species [31, 34-36].

To date, more than 300 pathogenic *PSEN1* variants have been identified, making it the most common genetic cause of autosomal dominant early-onset AD (www.alzforum.org/mutations/psen-1). PSEN2 mutations are less frequent but appear to act through similar mechanisms [37-39]. In addition to altering amyloid processing, presenilin mutations affect other cellular systems, including calcium regulation, mitochondrial function, and synaptic function. Several *PSEN1* variants impair calcium homeostasis and weaken synaptic plasticity, thereby increasing neuronal vulnerability [40, 41].

Further evidence linking Aβ dysregulation to AD comes from studies of APP mutations. Individuals with Down syndrome, who carry an extra copy of chromosome 21—and thus an extra *APP* gene—almost universally develop early-onset amyloid pathology and dementia [42]. Conversely, a rare *APP* mutation that reduces Aβ production provides substantial protection against both amyloid deposition and cognitive decline, further supporting the role of Aβ dysmetabolism in disease initiation and progression [43].

Animal models have provided some of the strongest experimental support for the amyloid hypothesis (Table 1). Transgenic mice carrying FAD mutations in *APP* or *PSEN* genes develop key features of the disorder, including early amyloid deposition, memory impairment, synaptic loss, and gliosis [44, 45]. These findings established that elevated Aβ alone can trigger downstream neurodegenerative changes. Among Aβ species, soluble oligomers are consistently the most neurotoxic. In experimental systems, they impair synaptic plasticity by reducing LTP and altering long term depression (LTD), and they impair learning and memory, effects that anti-Aβ immunotherapy can partially reverse [24, 25].

Recent studies using human induced pluripotent stem cell (iPSC)-derived neurons from AD patients have replicated several of these phenotypes, including Aβ overproduction and synaptic dysfunction, further supporting Aβ's pathogenic role [46]. Notably, oligomeric Aβ, not plaque-associated Aβ, appears to drive toxicity. These small aggregates interfere with synaptic signaling, promote tau phosphorylation, and induce neuronal damage. Antibody-mediated Aβ clearance reduces these deficits [63]. Spatial mapping of oligomer distribution reveals a strong correlation between Aβ accumulation and local synaptic impairment, reinforcing a causal link in disease progression [27].

Clinical biomarker and imaging studies align closely with these experimental findings. Cerebrospinal fluid (CSF) analyses and amyloid PET imaging show that amyloid deposition typically precedes tau pathology, cortical atrophy, and measurable cognitive decline by many years [47]. These findings suggest that amyloid accumulation is an early initiating event in AD [48, 49]. Longitudinal studies suggest that amyloid accumulation begins silently up to two decades before symptom onset, especially in carriers of the APOE ε4 allele, individuals with autosomal dominant AD mutations, and those with Down syndrome [64]. The *APOE ε4* is associated with an

increased cerebral amyloid burden and faster clinical progression [49-51].

Table 1. Animal evidence supporting the amyloid hypothesis

Model	Genetic Background	Key Findings (Edited)	Link to Amyloid Hypothesis	Ref.
Tg2576 (APPswe)	Human APP with Swedish mutation	Progressive Aβ plaque deposition from ~9 months; associated memory deficits	Supports the association between Aβ accumulation and cognitive decline	[45]
APP/PSEN1 (e.g., APPswe/PS1dE9)	Human APP (Swedish mutation) and PSEN1 exon-9 deletion	Accelerated Aβ42 accumulation and plaque formation; early-onset cognitive impairment	Demonstrates synergistic effects of APP and PSEN1 mutations on Aβ pathology	[52]
3xTg-AD (APPswe, PSEN1M146V, tauP301L)	APP, PSEN1, and tau mutations	Sequential development of Aβ plaques, followed by tau tangles and memory loss	Recapitulates the temporal progression of human AD; Aβ pathology precedes tau pathology	[53]
App^{NL-G-F} (Knock-in)	Swedish, Iberian, and Arctic APP mutations	Physiological APP expression; Aβ42 accumulation and plaque formation without overexpression	Validates the role of APP mutations and Aβ42 in amyloid pathology under native regulatory control	[54]
PDAPP	Human APP with Indiana mutation	Age-dependent Aβ plaque deposition and synaptic dysfunction	Provides early evidence of Aβ42-driven neurotoxicity and cognitive decline	[44]
AppG-F (Knock-in)	Human APP with Arctic and Iberian mutations (excluding Swedish)	Early Aβ oligomer formation and memory deficits without APP overexpression	Demonstrates that specific APP mutations alone can induce AD-relevant phenotypes via Aβ42 accumulation	[54]
APP/PSEN1/APOE4	Human APP (Swedish mutation), PSEN1, and APOE4 knock-in	Increased Aβ plaque burden, earlier cognitive decline, and enhanced neuroinflammation	Demonstrates interaction between Aβ pathology and the APOE4 risk allele, aligning with human genetic data	[55]
5xFAD	Human APP (Swedish, Florida, London mutations) and PSEN1 (M146L, L286V), driven by Thy1 promoter	Very early and aggressive Aβ42 deposition (~2 months), neuronal loss, gliosis, and cognitive decline	Shows that Aβ42 overproduction alone is sufficient to drive early neurodegeneration	[56]

Additional insight comes from systemic amyloidosis, where amyloid-reducing therapies have produced clinical benefits. Although the tissues and proteins involved differ, these results provide indirect support for amyloid-lowering strategies in AD [57].

Taken together, converging evidence from genetic models, patient-derived neurons, biomarker studies, and clinical observations continue to support the amyloid hypothesis as a central framework for understanding AD pathogenesis, even as its therapeutic implications remain under active investigation (Table 2).

3. Critical appraisal of the amyloid hypothesis

For over thirty years, the amyloid hypothesis has shaped the direction of AD research. Its appeal lay in the prospect of a single molecular trigger capable of explaining complex neurodegenerative processes. However, persistent gaps between theory and clinical outcomes have revealed their limitations. Amyloid burden does not correlate reliably with clinical decline, and many individuals with extensive plaque accumulation remain cognitively intact [58-61]. These findings suggest that while Aβ deposition marks disease presence, it is unlikely to drive progression on its own.

Clinical trials have underscored these concerns. Monoclonal antibodies such as aducanumab, lecanemab, and donanemab have shown, at best, modest effects when administered early in the disease course [59-61]. [71, 72, 75]. Benefits are limited, adverse events are common, and the rationale for continued reliance on Aβ-targeted therapies has become increasingly uncertain. What began as a unifying framework now appears to be one part of a broader pathological process, still relevant but insufficient to explain the full course of AD.

3.1 Discrepancies between amyloid pathology and cognitive impairment

The amyloid cascade hypothesis proposes that Aβ accumulation initiates the neurodegenerative process of AD. Initially, the amyloid model offered a compelling and straightforward explanation. However, as clinical and pathological data have grown, inconsistencies have emerged. The correlation between amyloid burden and cognitive decline is weak: some individuals with extensive plaque accumulation remain cognitively intact, while others with comparatively low levels of Aβ display severe dementia.

Table 2. Summary of evidence supporting the amyloid hypothesis in AD

Category	Evidence	Description (Edited for Clarity and Academic Tone)	Evidence Type	Ref.
Neuropathology	Progressive Aβ Deposition in All AD Patients	AD brains consistently exhibit progressive Aβ accumulation, followed by neuritic and glial cytopathology in regions associated with memory and cognition.	Clinical	[27]
Genetics	APP Mutations Cause Familial AD	Mutations in APP increase Aβ42 production, leading to early-onset familial AD.	Clinical	[32]
Genetics	Trisomy 21 and APP Gene Dosage Effects	Individuals with Down syndrome (trisomy 21), who carry an extra APP gene copy, develop early Aβ plaque pathology.	Clinical	[62]
Genetics	Protective APP Mutation Reduces AD Risk	A rare APP mutation that reduces Aβ production confers protection against AD and cognitive decline.	Clinical	[43]
Genetics	Presenilin Mutations Promote Aβ42 Production	PSEN1 and PSEN2 mutations increase the Aβ42/Aβ40 ratio, driving early-onset AD.	Clinical	[33]
Genetics	ApoE4 Increases Aβ Aggregation and Risk	The ApoE4 allele impairs Aβ clearance and promotes aggregation, significantly increasing AD risk.	Clinical	[50]
Neurobiology	Neurotoxic Effects of Aβ42 Oligomers	Aβ42 oligomers disrupt synaptic transmission and impair memory in animal models.	Experimental	[63]
Neurobiology	Aβ Induces Tau Pathology and Dystrophy	Aβ42 oligomers trigger tau phosphorylation and neuritic damage, effects that can be mitigated by anti-Aβ antibodies.	Experimental	[27]
Neurobiology	Spatial Correlation Between Aβ and Synapse Loss	Aβ oligomers localize near plaques, where adjacent synapses exhibit marked dysfunction.	Experimental	[27]
Biomarkers	Biomarker Evidence for Temporal Ordering	Reductions in CSF Aβ42 and amyloid-PET positivity precede tau pathology and symptom onset by several years.	Clinical	[47]
Biomarkers	Aβ Accumulates Decades Before Symptoms Begin	CSF and PET imaging studies reveal Aβ deposition occurs 10–20 years prior to clinical onset.	Clinical	[51]
Biomarkers	Brain Amyloid Burden Correlates with ApoE Genotype and Disease Risk	Individuals with ApoE4 show greater brain Aβ accumulation and faster clinical progression in CSF and imaging studies.	Clinical	[50]
Therapeutics	Post Hoc Trial Data Suggest Early Benefit	Post hoc analyses of antibody trials (e.g., aducanumab, lecanemab, donanemab) suggest modest cognitive benefit when initiated early.	Clinical	[60, 61]
Comparative	Lessons from Other Amyloidoses	Therapeutic success in reducing amyloid burden in systemic amyloidoses supports similar strategies in AD.	Clinical	[57]
Experimental Models	Cross-Species Plaque Formation in Transgenic Models	Mice engineered with human APP mutations develop Aβ plaques and exhibit cognitive impairments.	Experimental	[44, 45]
Experimental Models	Human iPSC-Derived Neurons Recapitulate Aβ Pathology	iPSC-derived neurons from AD patients overproduce Aβ and develop downstream pathological features.	Experimental	[46]

Experimental Models	Prion-Like Seeding Behavior of Aβ Aggregates	Misfolded Aβ aggregates propagate in a prion-like manner in vivo, spreading pathology between brain regions.	Experimental	[64]

These findings have prompted a re-evaluation of the amyloid model. Amyloid pathology may indicate disease presence, but it does not fully account for disease severity or progression. Alzheimer's now appears to involve a network of overlapping pathological processes, with Aβ contributing significantly, but not exclusively, to the disease course.

3.1.1 Weak relationship between plaque burden and clinical symptoms

Autopsy findings have long complicated the straightforward logic of the amyloid model. Approximately one-third of cognitively intact older adults show extensive Aβ plaque deposition at death, indicating that amyloid accumulation alone does not inevitably lead to dementia [65, 66]. Clinical imaging studies revealed the same pattern: some individuals live for years with heavy amyloid loads and stable cognition, while others with relatively modest deposits experience rapid decline [67, 68]. The correlation between plaque burden and clinical severity is, at best, weak. Fibrillar amyloid plaques do not drive Alzheimer's pathogenesis. They reflect intermediate products of earlier Aβ dysmetabolism and downstream tau, vascular, and neuroimmune cascades. Aβ contributes to risk, but other processes drive clinical progression. Tau aggregation, vascular injury, inflammation, and metabolic stress likely contribute to neurodegeneration [69].

Large cohort studies have reached similar conclusion. In more than 500 autopsy cases from the MRC Cognitive Function and Ageing Study, Wharton and colleagues (2009) [70] found only a weak association between neuritic plaques and dementia, whereas neurofibrillary tangle burden, measured by Braak stage, correlated closely with cognitive impairment. Nelson et al. (2012) [68] likewise reported that many individuals with dense plaques remained cognitively intact, while others with advanced dementia showed minimal amyloid pathology.
Neuroimaging studies reinforce these observations. In the Mayo Clinic Study of Aging, Jack et al. (2018) [71] reported that amyloid deposition plateaus early and shows little connection to ongoing cognitive decline. Giannakopoulos et al. (2003) [72] reported similar findings from postmortem analyses, concluding that synaptic loss and tau pathology, rather than plaque burden, best predicted clinical status.

Taken together, these findings support a prolonged preclinical phase during which fibrillar amyloid accumulates with few symptoms. Many older adults show high plaque burden on autopsy or amyloid PET yet remain cognitively intact, which argues that amyloid alone does not determine clinical disease and supports a broader search for complementary mechanisms.

3.1.2 Cognitive resilience in individuals with elevated amyloid levels

Numerous postmortem and imaging studies have revealed a striking paradox: many older adults with substantial Aβ deposition remain cognitively normal. Price and Morris [65] once referred to these cases as "preclinical AD," though the term now appears overly presumptive. Some of these individuals live well into old age without ever showing signs of dementia, despite carrying amyloid burdens indistinguishable from those of symptomatic patients. Using PiB-PET imaging, Aizenstein and colleagues [73] found that approximately 25% of cognitively normal adults in their seventies and eighties exhibited amyloid levels comparable to those reports for AD. A larger meta-analysis by Jansen et al. [74], which included over 7,500 participants across 55 studies, reached similar conclusions: roughly 25% of individuals aged 70–79 and up to 40% over 80 were amyloid-positive.

Autopsy studies have occasionally taken this paradox to the extreme. Some individuals die with brains that, by conventional neuropathological standards, dense plaques and advanced tau pathology, should have produced severe dementia. Yet, they remained cognitively intact throughout life. This phenomenon, often described as cognitive resilience [75], has become a focus of growing interest. Evidence suggests that enhanced synaptic plasticity, restricted tau propagation, and greater neural reserve may buffer against amyloid toxicity. Resilient brains also tend to exhibit lower levels of microglial activation and fewer dystrophic neurites compared to symptomatic individuals with similar plaque and tangle burdens [75, 76]. The related concept of cognitive reserve, associated with higher education, intellectual engagement, and lifestyle factors, may further delay the clinical onset of disease despite substantial neuropathology [77].

Critics of the amyloid hypothesis often cite these asymptomatic yet plaque-rich individuals as evidence against a direct causal link between Aβ and cognitive decline [65]. Proponents counter that such individuals may represent prodromal cases whose symptoms have not yet emerged [78]. Still, the field has shifted toward a more refined understanding of Aβ toxicity. Soluble oligomers, rather than insoluble plaques, are increasingly recognized as the primary neurotoxic species [79, 80].

Koffie et al. (2009) reported a halo of oligomeric Aβ surrounding plaques and found that oligomer enrichment near plaques correlates with local excitatory synapse loss [81], Esparza et al. (2013) found that the relationship between oligomer levels and plaque burden differs between dementia cases and high pathology controls, supporting a role for plaque associated oligomerization in clinical expression beyond plaque burden alone [82].

3.1.3 Dementia cases with minimal or absent amyloid pathology

The inverse pattern is equally informative: Individuals who meet clinical criteria for dementia but show little or no Aβ accumulation. These cases, classified as suspected non-Alzheimer's pathophysiology (SNAP), comprise roughly one-quarter of patients with mild cognitive impairment or dementia, according to Jack et al. [83]. Autopsy studies support this observation. In the Arizona Study of Aging and Neurodegenerative Disorders, Beach and colleagues (2015) [84] reported that some individuals diagnosed antemortem with probable AD exhibited minimal amyloid pathology at autopsy. Instead, their brains showed alternative lesions, including tau aggregates, TDP-43 pathology, hippocampal sclerosis, or cerebrovascular injury, each linked to cognitive decline.

These findings show that pathology rarely appears alone. Schneider et al. [13] reported that mixed pathology is common in late life. Many patients show combinations of amyloid, tau, Lewy bodies, infarcts, or microvascular injury. These patterns vary across individuals and do not follow a single sequence. This complexity reduces support for amyloid centered explanations and points toward broader models that account for vascular, immune, and metabolic factors.

3.1.4 Comparative significance of Tau pathology

The uneven relationship between amyloid plaque burden and cognitive decline has led many researchers to question whether amyloid-β truly lies at the center of Alzheimer's pathology [67, 68]. Tau, by contrast, shows a much stronger and more consistent association with clinical symptoms. The density and distribution of neurofibrillary tangles closely track with the cognitive impairment, a relationship confirmed across large neuropathological cohorts [68]. Indeed, tau pathology can appear in the absence of amyloid, particularly in sporadic cases, suggesting that these two pathologies may originate through distinct biological pathways rather than a unified cascade [68].

Experimental models have reinforced the central role of tau in neuronal injury. In animals and cell culture systems, increased amyloid-β production accelerates tau aggregation, whereas elevated tau does not appear to promote Aβ accumulation [69]. This asymmetry has shaped a more nuanced view of disease progression: amyloid-β may initiate the pathological process, but tau is the primary driver of neurodegeneration. Once tau aggregation begins, it spreads through anatomically connected neural circuits, promoting synaptic dysfunction, neuronal loss, and progressive cognitive decline [67, 68].

3.2 Clinical challenges in targeting amyloid

3.2.1 Overview of clinical trial outcomes

For decades, AD research has centered on a singular objective: to neutralize amyloid-β. The rationale was clear. Aβ plaques define the disease pathologically, and early studies suggested that reducing amyloid could reverse cognitive deficits. Drug development followed this logic [78, 85]. From immunotherapies to β- and γ-secretase inhibitors, nearly every major pharmaceutical effort has, at some point, aimed to reduce amyloid accumulation [86].

The clinical record, however, has been sobering. One of the earliest large-scale attempts, the AN1792 vaccine trial, was halted in 2002 after several participants developed meningoencephalitis [87]. Efforts to inhibit γ-secretase followed a similar trajectory—promising in preclinical studies, ineffective or harmful in humans. Tarenflurbil (R-flurbiprofen) failed to improve cognition in phase III trials and caused adverse effects [88]. Semagacestat, another γ-secretase inhibitor, not only lacked benefit but appeared to worsen cognition and increase cancer risk, leading to early termination [89, 90]. These outcomes align with evidence that γ-secretase supports neuronal and synaptic function and that broad γ-secretase inhibition can produce mechanism-based toxicities, including Notch-related adverse effects.

Passive immunotherapies provided limited clinical benefit. Solanezumab, targeting soluble Aβ, lowered peripheral amyloid levels but had no effect on cognition in multiple large trials [91, 92]. Bapineuzumab, aimed at fibrillar Aβ, also failed to deliver clinical benefit and was associated with amyloid-related imaging abnormalities (ARIA), particularly in APOE ε4 carriers [93-95].

Efforts to block β-secretase (BACE1) ended similarly. Verubecestat, atabecestat, and LY2886721 were all discontinued due to lack of efficacy or safety concerns, including cognitive worsening and liver toxicity [96, 97]. Even avagacestat, a supposedly more selective γ-secretase inhibitor, proved both poorly tolerated and clinically ineffective [98, 99].

More recently, monoclonal antibodies targeting aggregated Aβ have demonstrated clear biomarker effects

but only marginal clinical improvements. Aducanumab, controversially approved by the FDA in 2021, reduced plaque burden but produced inconsistent cognitive outcomes—the EMERGE trial showed a modest benefit, while ENGAGE did not [100, 101]. Crenezumab failed to meet its endpoints [102]. Donanemab, though statistically positive in early symptomatic patients with low tau burden, yielded only modest slowing of decline and raised safety concerns [60]. Gantenerumab, despite robust amyloid clearance, provided no measurable cognitive advantage [103, 104].

After decades of investment and a long succession of null or inconclusive trials, a hard conclusion has emerged: clearing amyloid does not reliably restore cognitive function. These repeated failures have weakened confidence in the amyloid cascade as a comprehensive model of AD and have compelled the field to look beyond a single molecular target. Table 3 summarizes the key trials that have reshaped this understanding.

Table 3. Summary of failed and controversial amyloid-targeting trials in AD.

Drug	Target	Mechanism of Action	Trial Phase/ Year	Outcome	Remarks	Ref.
Solanezumab	Soluble Aβ monomers	Anti-Aβ monoclonal antibody	Phase III/2016	Failed	Did not slow cognitive decline in preclinical AD.	[91, 105]
Bapineuzumab	Fibrillar Aβ	Anti-Aβ monoclonal antibody	Phase III/2012	Failed	No cognitive benefit; increased ARIA in APOE ε4 carriers.	[94]
Crenezumab	Aβ oligomers	Anti-Aβ monoclonal antibody	Phase III/2019	Failed	No reduction in clinical decline in early AD.	[106, 107]
Semagacestat	γ-secretase	γ-Secretase inhibitor	Phase III/2010	Failed	Worsened cognition and associated with adverse effects.	[89]
Verubecestat	β-secretase (BACE1)	BACE1 inhibitor	Phase III/2018	Failed	No cognitive or functional benefit; safety concerns raised.	[96]
Atabecestat	β-secretase (BACE1)	BACE1 inhibitor	Phase II/2021	Failed	Associated with cognitive worsening; trials were terminated early.	[97]
Gantenerumab	Fibrillar Aβ	Anti-Aβ monoclonal antibody	Phase III/2023	Failed	Reduced amyloid plaque load but did not slow clinical decline.	[104]
Aducanumab	Aggregated Aβ	Anti-Aβ monoclonal antibody	Phase III/2021	Controversial approval	Approved despite inconsistent efficacy; sparked regulatory debate.	[108]
Donanemab	Aβ plaques	Anti-Aβ monoclonal antibody	Phase III/2023	Modest improvement	Slowed cognitive and functional decline in early symptomatic AD.	[60]

Why have clinical outcomes remained so underwhelming? One of the simplest and most persuasive explanations is timing [109]. Most anti-amyloid interventions begin far too late, long after the cascade of neurodegeneration is underway. By the time plaques are abundant enough to detect clinically, substantial neuronal loss, synaptic disruption, and network reorganization have already occurred. In animal studies, early treatment can mitigate downstream tau pathology, but once degeneration begins, amyloid removal has little impact [110]. Many clincal trials have recruited participants at these later stages, making therapeutic failure likely even when amyloid is effectively cleared.

Other factors further complicate outcomes. Genetic variation, vascular status, and coexisting pathologies create a heterogeneity that most trial designs fail to address (Box 1**)**. Acknowledging this, recent trials have shifted focus to earlier stages, targeting cognitively normal individuals with biomarker evidence of amyloid accumulation [85] and stratifying cohorts by tau burden or APOE4 status [78, 111].

Even so, prevention has remained elusive. Trials in asymptomatic but high-risk participants, such as APOE ε4 carriers or those with elevated amyloid on PET, have not succeeded in halting disease onset [23]. Nor have anti-amyloid antibodies shown benefit in autosomal dominant AD linked to APP, PSEN1, or PSEN2 mutations [111]. Instead, many of these treatments have introduced new risks, including cerebral edema, microhemorrhages, and, in some cases, accelerated cognitive decline [94, 112]. After decades of effort and refinement, the message is increasingly clear: removing amyloid may alter imaging findings, but it does not change the clinical trajectory.

Current amyloid-directed therapies, despite their sophistication, address only part of the problem. They can reduce plaque burden but do not reverse the complex biological processes that underlie cognitive decline. AD is not the result of a single disrupted pathway but a

convergence of metabolic, vascular, immune, and neurodegenerative mechanisms that unfold over decades. Meaningful progress will require strategies that address this complexity directly, combining pharmacologic and behavioral interventions to slow decline and preserve cognitive resilience across diverse patient populations.

3.2.2 Limited clinical efficacy despite amyloid reduction

Numerous trials have revealed a consistent and sobering pattern: anti-amyloid therapies can clear plaques, yet the mind remains largely unchanged. Monoclonal antibodies such as solanezumab, bapineuzumab, and crenezumab reduce soluble, fibrillar, and oligomeric Aβ species, as confirmed by CSF biomarkers and imaging [91, 92, 94]. The newer generation, aducanumab, gantenerumab, lecanemab, and donanemab, has achieved more substantial reductions in plaque burden, verified by PET imaging [100, 101, 113, 114]. Still, cognitive outcomes have been underwhelming. In the EMERGE and ENGAGE trials, aducanumab produced a modest slowing of decline in one study and no benefit in the other [100]. Lecanemab reached statistical significance on the CDR-SB in the CLARITY-AD trial, but the mean difference, less than 0.5 points on an 18-point scale, was clinically negligible [113]. Donanemab showed a somewhat stronger signal, though benefits were limited to individuals with low baseline tau, again highlighting the importance of timing and disease stage [116]

Box 1. Timing and Heterogeneity as Key Barriers to Aβ-Targeting Therapy Success

Timing of Intervention

- Aβ accumulation begins decades before the onset of clinical symptoms [49, 115].
- Most clinical trial participants are enrolled after symptom onset and already exhibit significant neurodegeneration.
- Therapeutic intervention at this stage is likely too late to meaningfully alter disease progression.
- These observations support the view that Aβ acts as an early initiator of pathology, rather than the primary driver of late-stage neurodegeneration.

Patient Heterogeneity

- Variability in patient characteristics significantly influences treatment response and trial outcomes.
- Key sources of heterogeneity include:
  - APOE genotype
  - Disease stage at enrollment
  - Baseline tau pathology
  - Comorbid vascular or inflammatory conditions
- These differences contribute to variable therapeutic efficacy and may obscure treatment effects in clinical trials [116, 117].

Recent oral small-molecule approaches aimed at synaptic resilience also report signals of clinical benefit distinct from anti-amyloid antibodies. Blarcamesine (ANAVEX2-73), a sigma-1 receptor agonist, reported slowing of cognitive decline at 48 weeks on ADAS-Cog13 in an early Alzheimer's Phase IIb/III trial, with mixed effects across functional endpoints and supportive biomarker analyses reported by investigators and secondary sources [118]. Zervimesine (CT1812), a sigma-2 receptor modulator developed to displace synaptotoxic Aβ oligomers, did not meet a key efficacy endpoint in the full Phase 2 SHINE population, but a prespecified subgroup with lower baseline plasma p-tau217 showed large relative slowing on ADAS-Cog11 and MMSE in company analyses, alongside biomarker shifts (Clinical trial ID: NCT03507790)[119, 120]. These findings align with your timing and heterogeneity framework and highlight growing use of blood-based tau markers for enrichment. Ongoing Phase 3 planning underscores the need for confirmatory trials before firm conclusions.

These findings expose the central paradox of amyloid-focused therapy: plaques can be removed, but the disease persists. The disconnect between amyloid clearance and cognitive benefit suggests that Aβ removal alone is insufficient, particularly after neurodegeneration has begun. Effective intervention will likely require earlier treatment or targeting downstream mechanisms beyond amyloid (see Box 2) [115, 121].

Box 2. Why Aβ Reduction Fails to Halt AD Progression

Amyloid-targeting treatments may falter because they address the spark, not the fire. By the time therapy begins, downstream mechanisms—tau aggregation, neuroinflammation, synaptic loss, and widespread neuronal injury—are already well advanced. Among these, tau pathology shows the closest link to cognitive decline [93]. Even trials that have pushed intervention earlier into the preclinical phase have yet to stop these secondary cascades [84].

Lessons from past failures are now reshaping the direction of Alzheimer's research. Current trials prioritize earlier intervention, enrolling cognitively normal individuals who show amyloid accumulation on PET or CSF biomarkers [85], and stratifying participants by tau burden and genetic risk, including APOE ε4 status [78,

92]. AD reflects interacting amyloid, tau, neuro-inflammatory, and synaptic pathologies that evolve over decades, so effective therapy should use prespecified, stage-defined combinations aligned to target engagement and a limited biomarker panel.

3.2.3 Safety concerns and adverse effects

Despite their biological rationale, amyloid-targeting therapies bring significant clinical risks. The most frequent complication is amyloid-related imaging abnormality (ARIA), detected by MRI as either vasogenic edema (ARIA-E) or microhemorrhages and hemosiderin deposits (ARIA-H). Higher doses raise rates of ARIA across agents. Bapineuzumab, aducanumab, donanemab, and gantenerumab show clear dose response patterns with high incidence levels [122]. In patients treated with aducanumab, ARIA edema occurs in about 35 percent and ARIA hemorrhage at 19 percent. Rates are lower with lecanemab at 12 percent and 17 percent [100, 122].

These risks limit broad use in older adults with cerebrovascular vulnerability. Recent trials have been designed with eligibility, frequent MRI monitoring, and more attention to genotype-based risk, especially APOE status. The side effect profile narrows who receives treatment and forces difficult decisions about risk compared with modest and uncertain benefits.

3.2.4 Controversies in regulatory approvals

The FDA's 2021 approval of aducanumab marked a turning point, less for scientific progress and more for the dispute it created. The agency used the Accelerated Approval pathway and relied on evidence of plaque reduction rather than consistent cognitive benefit. In the pivotal trials, EMERGE reported a modest slowing of decline while ENGAGE showed no benefit [100, 112]. The advisory committee voted strongly against approval, and several members resigned soon after.

Approvals of lecanemab and donanemab have brought similar concerns. Amyloid reduction is measurable, but it has not shown clear validity as a surrogate for meaningful clinical outcomes. These issues have increased pressure for stronger evidentiary requirements, greater transparency in regulatory decisions, and clearer evaluation of cost and risk [123, 124]. The debate reflects a deeper uncertainty about how to treat AD and what level of evidence should count as proof of effectiveness.

3.3 Limitations from Animal Models and Genetic Studies

For decades, the amyloid hypothesis shaped work on AD. Evidence from animal studies, genetics, and population data shows important conflicts that weaken the idea of Aβ as the sole driver of degeneration. New findings show limited alignment between plaque burden and symptoms. Genetic risk often points to inflammatory and vascular pathways instead of Aβ production. These points reduce confidence in a single mechanism model.

3.3.1 Limitations and conflicting data from transgenic and knock-in models

Transgenic mouse models carrying human *APP* or *PSEN1* mutations have long been the workhorses of Alzheimer's research. These models develop abundant amyloid plaques and have served as platforms for testing numerous anti-amyloid therapies. Yet their resemblance to human disease ends there [125]. Despite significant plaque accumulation, these animals rarely exhibit widespread neuronal loss, tangle pathology, or progressive cognitive decline that define clinical AD [126, 127]. Their brains remain largely intact, and even when amyloid is cleared, cognitive function seldom improves [125, 128]. The implication is clear and unsettling: neurodegeneration can progress independently of amyloid burden.

A deeper limitation lies in the construction of the models themselves. Most rely on overexpression systems that drive supraphysiological levels of mutant *APP* or *PSEN1*. This often leads to experimental artifacts, aberrant protein aggregation, gliosis, seizures, that do not resemble typical late-onset AD [129]. Such distortions risk overemphasizing amyloid's role and obscuring alternative pathogenic mechanisms. In response, newer knock-in models have introduced humanized mutations at physiological expression levels. These mice accumulate amyloid more gradually and display subtler phenotypes, arguably more reflective of human disease [54]. Still, neurodegeneration in these models remains modest, offering little evidence that Aβ alone is sufficient to cause widespread neuronal failure.

Genetic studies of presenilin function further complicate the picture. Xi et al. [130] found that PS1 deletion enhanced β-catenin signaling and promoted tumor formation, while Saura et al. [131] showed that conditional knockout of PS1 and PS2 in the postnatal forebrain led to synaptic dysfunction and neuronal loss in the absence of amyloid pathology. Subsequent work attributed these deficits to dysregulated neuro-inflammatory signaling, not Aβ toxicity [132]. These findings challenge the therapeutic rationale for γ-secretase inhibition and highlight how genetic manipulations can produce disease phenotypes that diverge sharply from those seen in human AD.

After years of reliance on these reductionist models, the field is beginning to acknowledge their limitations. While valuable for mechanistic exploration, they have proven poor predictors of clinical outcomes, reinforcing a narrow interpretation of the amyloid cascade and sidelining other hypotheses. Moving forward, progress will likely depend on models that better reflect the biology of sporadic, late-onset AD, models that incorporate aging, metabolism, inflammation, and human-derived systems to generate insights relevant to the human condition rather than constrained laboratory constructs.

3.3.2 Genetic and epidemiological evidence questioning amyloid centrality

Another major challenge to the amyloid hypothesis comes from genetics and epidemiology. Mutations in APP, PSEN1, and PSEN2 provide clear evidence that amyloid plays a causal role in rare, early-onset FAD. However, these cases represent less than one percent of all diagnoses. The vast majority of cases, sporadic late-onset AD, appears to follow a different trajectory shaped by aging, vascular injury, metabolic dysfunction, and inflammation. In these patients, the link to amyloid often appears weak, indirect, or absent.

The *APOE ε4* allele remains the strongest genetic risk factor for sporadic AD. While it does influence amyloid aggregation and clearance, its biological effects extend well beyond amyloid metabolism. APOE4 disrupts lipid transport, promotes glial activation, and compromises cerebrovascular integrity. Increasing evidence suggests that its pathogenicity is driven as much by immune and metabolic dysfunction as by amyloid-related pathways [133, 134].

Epidemiological findings reinforce this view. Large-scale amyloid PET studies have shown that substantial plaque deposition is common among cognitively normal older adults and poorly predicts future cognitive decline [71, 73]. These data undermine the reliability of amyloid as a biomarker and cast doubt on its value as an exclusive therapeutic target, particularly in preclinical stages of the disease.

Autopsy studies further complicate the picture. Some individuals clinically diagnosed with AD show minimal amyloid pathology at death, while others die with extensive plaques yet retain intact cognition, a phenomenon known as cognitive resilience [67, 68]. These discrepancies highlight the limitations of an amyloid-centric model. The emerging evidence points to a broader array of disease mechanisms, including tau accumulation, vascular injury, and neuroinflammation, that more closely track with symptom progression. In particular, the consistently stronger association between tau pathology and clinical decline has helped shift focus away from amyloid as the sole initiator of disease [135].

4. Methodological concerns and scientific integrity

4.1 Methodological limitations in amyloid-focused research

The limits of the amyloid hypothesis reflect biology and the research ecosystem shaped around it. Its simplicity helped unify the field around shared tools, cohorts, biomarkers, and trial infrastructure, and those advances clarified where amyloid fits and where it does not. At the same time, long-running emphasis on a single cascade influenced funding and study design, which constrained work on interacting mechanisms and stage-dependent drivers. The field now sits in a stronger position to move beyond a one-pathway model because the amyloid era produced the methods and evidence needed to define its boundaries [58].

At the experimental level, the problem begins with the models. The field's reliance on transgenic mice overexpressing human APP and PSEN1 mutations has generated a large body of work focused on amyloid plaque formation—often at the expense of other pathological features. These models efficiently produce Aβ, but they seldom exhibit the widespread neuronal loss, cognitive decline, or mixed pathologies characteristic of human AD. Their artificial design—including non-native promoters and supraphysiological expression levels—introduces artifacts that can obscure rather than illuminate disease mechanisms. Even newer knock-in models, which express human mutations at physiological levels, tend to show only mild phenotypes and slow amyloid accumulation [54, 127]. As a result, much of the preclinical literature reflects engineered amyloidosis more than authentic AD.

The deeper issue, however, is structural. For years, amyloid-centered research has dominated the allocation of funding, the publication landscape, and the framing of key scientific questions. Alternative lines of inquiry—focusing on tau, vascular dysfunction, immune signaling, or metabolic disturbance—have often been underfunded and underexplored [86, 131]. In this way, the field's commitment to amyloid became self-reinforcing: scientific success was often measured by how well results aligned with the prevailing model, not by how comprehensively they explained the disease. Overcoming this bias will require more than improved therapies or refined models, which will require a shift in how the field defines priorities and frames the fundamental questions worth asking.

4.2 Lessons from the Aβ*56 study retraction

A major case of methodological controversy came from the collapse of a widely cited 2006 Nature paper by Sylvain Lesné and colleagues that claimed the Aβ56 oligomer caused memory loss [136]. In 2022, investigative reporting identified image manipulation in multiple papers from the same group. More than twenty studies came under review, and the Aβ56 paper was formally retracted in 2024 [125, 137].

Senior author Karen Ashe defended the broader research direction, but the credibility of the findings fell sharply. Independent groups had struggled for years to reproduce the results. Many questioned whether Aβ56 was a meaningful biological entity. A mechanism once promoted as a major advance became an example of how an attractive idea can harden into accepted truth when it aligns with dominant models.

The episode showed the risks of allowing high impact but unverified findings to guide research priorities and funding. It also exposed how fragile consensus becomes when key data fail to reproduce. These events highlight the need for strong transparency, reproducible methods, and openness to varied approaches instead of continued loyalty to a single, insufficiently tested model.

5. Factors sustaining the amyloid hypothesis

Despite growing doubts about its validity and decades of disappointing trial outcomes, the amyloid hypothesis still sits at the center of Alzheimer's research [100, 138]. Its persistence reflects more than scientific conviction. It stems from historical momentum, large financial commitments, and institutional structures that shape how the field defines success.

5.1 Influence of historical and commercial interests

Amyloid's enduring influence on the field is, in part, historical. As one of the earliest and most fully developed models of AD [16], it provided a coherent narrative—simple, testable, and intuitively appealing. Over time, that narrative solidified into orthodoxy. Generations of researchers were trained to interpret findings through the lens of amyloid, and confirmation bias helped reinforce the model [58, 59]. Few fields have been as resistant to abandoning a paradigm that once seemed so complete.

Financial investment has further entrenched belief. Pharmaceutical companies have invested billions in anti-amyloid programs, creating commercial and institutional infrastructure reluctant to concede failure [139, 140]. Regulatory acceptance of surrogate endpoints—such as reductions in amyloid PET signal or cerebrospinal Aβ levels—has sustained this trajectory. Even in the absence of meaningful clinical improvement, biomarker success provided a rationale to continue[141].

5.2 Structural factors in research funding and regulation

The dominance of amyloid research has also been reinforced through the institutional structures of funding and publication. For years, grant agencies prioritized proposals framed within the Aβ paradigm, creating a feedback loop in which funding, visibility, and career advancement favored researchers who supported the prevailing model [142]. Positive results were more likely to be published in high-impact journals, shaping citation patterns and further entrenching amyloid as the central framework of Alzheimer's research.

Regulatory policy added another layer of reinforcement. The U.S. FDA's acceptance of biomarker shifts—such as reductions in amyloid PET signal or CSF Aβ levels—as sufficient for drug approval [141] effectively established amyloid as a default therapeutic endpoint. This convergence of academic, commercial, and regulatory incentives allowed the model to persist even in the face of ambiguous or disappointing clinical outcomes.

5.3 Societal and political dynamics in Alzheimer's research

Beyond the lab, amyloid shaped a public story. The idea that one misfolded protein explained AD and offered a path to treatment gained strong support from media, advocacy groups, and the public [143]. It provided a clear target and a hopeful message. That clarity made it politically attractive.

Advocacy organizations and philanthropic groups reinforced this focus by directing attention and funding toward amyloid research. Governments followed. The U.S. National Plan to Address AD, along with similar efforts elsewhere, invested heavily in amyloid centered strategies. The momentum was psychological and financial. Moving beyond amyloid required revising expectations and facing the disappointment of a promise that did not materialize.

6. Impact of amyloid hypothesis dominance

What began as a unifying model has, over time, become a limiting framework. The amyloid-β hypothesis once brought coherence to a complex disease, but its prolonged dominance has shaped not only scientific thinking, but also policy, public perception, and research funding. The consequences extend well beyond the laboratory.

6.1 Effects on research funding distribution

For decades, the gravitational pull of the amyloid model has shaped how dollars are distributed in both academia and industry [142]. Grant panels, drug pipelines, and review boards consistently favored proposals that reinforced the familiar narrative of plaque clearance and Aβ reduction [145]. The result was a research monoculture, productive in volume, but narrow in scope, that marginalized promising alternative approaches, from tau biology and vascular dysfunction to immune, metabolic, and mitochondrial pathways [144, 145].

A recent policy shift signals possible course correction. In October 2024, the White House extended the *National Alzheimer's Project Act* (NAPA) through 2035, expanding its advisory membership and elevating risk reduction to a national priority. The Department of Health and Human Services plans to revise the National Plan by 2025, incorporating lessons from the past decade. These are important steps, but real change will depend on sustained efforts to realign priorities and ensure that new research is translated into practice, not simply absorbed into old frameworks.

6.2 Stagnation in therapeutic advances

Despite decades of trials, amyloid-lowering therapies have yielded little meaningful improvement in cognition or daily function [83]. The gap between biomarker success and clinical outcomes has become increasingly difficult to ignore [91, 94]. Drugs like aducanumab and lecanemab, though approved, have shown only modest benefits and introduced new safety risks [23, 152]. This persistent mismatch points to a structural flaw: the field has prioritized target engagement over patient-centered outcomes.

6.3 Delay in investigating alternative mechanisms

The field's sustained focus on amyloid came at a cost. While attention and resources flowed toward plaque clearance, other critical mechanisms, early tau pathology, neuroinflammation, cerebrovascular compromise, mitochondrial dysfunction, and glymphatic failure, remained underexplored [58, 139, 146, 147]. Many of these processes may precede amyloid accumulation or drive disease progression independently. Neglecting them may have cost the field opportunities to intervene earlier and more effectively [121, 139].

6.4 Erosion of public trust and scientific credibility

Repeated clinical disappointments have taken a toll not only on research momentum but also on public confidence. Many patients and caregivers enrolled in demanding, expensive trials with little to show for it. The field's reluctance to critically reassess its central hypothesis has drawn criticism for fostering intellectual complacency. The retraction of the Aβ*56 study following confirmed data manipulation [137] further exposed weaknesses in reproducibility and oversight. These episodes have raised uncomfortable but necessary questions about scientific integrity and transparency—questions the field must now confront to regain public trust.

6.5 Implications for industry investment and innovation

Pharmaceutical and biotech companies have invested billions in Aβ-targeting drugs, many of which failed in late-stage trials [139]. These high-profile failures have shaken investor confidence and may deter future investment in neurodegeneration research [148]. If the amyloid framework collapses without producing meaningful clinical gains, the fallout could discourage innovation precisely when more diversified, risk-tolerant strategies are most urgently needed.

6.6 Lost Opportunities in early disease intervention

Perhaps the most damaging consequence lies in what was overlooked. By concentrating on plaque removal, researchers missed key upstream processes that began decades before symptoms emerge [146]. Recent multimodal and systems-level studies suggest that Alzheimer's arises from an interplay of aging, vascular dysfunction, and immune disturbance—an ecosystem of gradual breakdown, not a linear cascade. The longer amyloid dominated attention, the further the field drifted from identifying and targeting these early, potentially reversible stages.

6.7 Broader reflections on scientific culture and policy

The trajectory of the amyloid hypothesis reveals deep-rooted cultural issues in science itself [58]. The marginalization of dissenting perspectives reflects structural flaws in funding mechanisms, peer review, and publication practices—systems that too often reward consensus over exploration [149]. Restoring balance will require embracing replication, tolerating failure, and welcoming course correction as essential features of progress [150].

Regulatory bodies must also evolve. The routine approval of drugs based on surrogate biomarkers rather than clinical benefit has blurred the line between mechanistic progress and meaningful outcomes. Amyloid reduction alone is no longer enough. A higher evidentiary standard is needed—one that reflects the complexity of

Alzheimer's and measures success by how well we preserve cognitive function, not simply how much we reduce signal on a scan.

7. Ethical and regulatory implications

In 2014, Jack de la Torre posed a pointed question in the *New England Journal of Medicine*: why does the amyloid hypothesis persist despite mounting evidence against it and a lack of convincing therapeutic benefit [151]? A decade later, that question resonates even more sharply. The FDA's accelerated approvals of aducanumab (2021) and lecanemab (2023) [18, 19]. extended the reach of the hypothesis but intensified the controversy. Many scientists and bioethicists questioned whether the available evidence justified approval, warning that these decisions placed patient safety and public trust at risk [152].

Central to these concerns is the FDA's increasing reliance on surrogate endpoints, such as reductions in amyloid PET signal or cerebrospinal Aβ levels, as proxies for clinical benefit [153, 154]. The approval of aducanumab, granted after early trial termination and over the near-unanimous objection of the FDA's advisory committee [141, 155], brought this tension into sharp relief. It raised not only scientific and safety questions but ethical ones: is it justifiable to approve an expensive therapy with uncertain clinical benefit? Critics argue that doing so may expose vulnerable patients to harm while diverting resources from more promising avenues [152]. This episode has triggered a broader ethical reckoning [156, 157]. Regulators are entrusted with protecting patients—especially those who are vulnerable or desperate for hope—from interventions that offer minimal or uncertain benefit. Upholding rigorous standards, transparency, and independence in regulatory decision-making is not bureaucratic detail; it is the foundation of ethical clinical practice. These events have underscored the need to examine how scientific, commercial, and political pressures can reshape the definition of "evidence" [124, 153, 154].

7.1 Enhancing patient autonomy and informed decision-making

When a field organizes drug development around a single dominant target, approvals and clinical adoption can move forward even when clinical benefit is modest, heterogeneous, or uncertain, shifting the burden of interpretation to patients and clinicians. When therapies offer only modest or uncertain benefits, the ethics of consent and access become complex [157]. Patients and families, often navigating fear and urgency, may overestimate what these treatments deliver, especially when described as "slowing decline." With annual costs in the tens of thousands of dollars, the financial burden is substantial, and disparities in access are likely to widen, particularly among underrepresented or lower-income populations.

Clinicians then carry the practical consequences of that pathway focus. They must translate population-level trial effects into individualized decisions, while also weighing monitoring demands, risks, and out-of-pocket cost. When efficacy remains limited or short-lived, the clinical default can drift toward treatment without clear net benefit for a given patient, increasing workload and moral distress and straining equitable access [100].

7.2 Improving regulatory oversight and standards

Regulatory agencies are tasked with balancing innovation and protection. The approvals of aducanumab and lecanemab have reignited debate over how that balance should be managed in slowly progressive, complex diseases like Alzheimer's [158]. Many argue that these cases lowered the evidentiary bar without sufficient justification, setting a troubling precedent where biomarker change is mistaken for clinical improvement. Rebuilding confidence will require more than procedural tweaks. Regulatory frameworks must be transparent, evidence-based, and subject to independent oversight. Conditional approvals should include mandated post-marketing trials, clear communication of uncertainty, and predefined clinical endpoints. Only with such rigor can regulatory bodies maintain credibility with both the scientific community and the public.

7.3 Rebuilding scientific trust and integrity

The controversy surrounding amyloid-targeting therapies has shaken public trust—not only in specific drugs, but in the institutions that govern biomedical science [159]. Rebuilding that trust will require sustained commitment to methodological rigor, reproducibility, and stakeholder engagement. Patients, clinicians, ethicists, and independent researchers must be involved not just in post hoc evaluation, but in shaping the development and review process itself.

Intellectual honesty about the disease is essential. Alzheimer's is a biologically complex syndrome, not a single protein disorder. Regulatory frameworks should support combination therapies, individualized treatment, and diverse biomarker endpoints that reflect this heterogeneity. High evidentiary standards, open data sharing, and transparent scientific debate support progress and strengthen the field.

8. Future Directions for Alzheimer's Research

Over the past three decades, accumulating has steadily reshaped our understanding of AD. Tau pathology, synaptic loss, and neuroinflammation correlate far more closely with cognitive decline than amyloid burden ever has [48, 69, 135]. While amyloid-β remains a hallmark of the disease, its status as the central driver has become increasingly difficult to defend. The limitations of traditional transgenic models—and the recent retraction of influential Aβ-focused studies—have further eroded confidence in the hypothesis [137, 160].

To move forward, the field must adopt models that more accurately reflect the biological and clinical complexity of human Alzheimer's. New systems should capture early disease processes, incorporate aging, and account for the comorbidities that shape real-world progression [161]. Translational progress will also depend on targeting the processes amyloid left in its shadow—tau propagation, glial and vascular dysfunction, immune dysregulation, mitochondrial failure [28, 162, 163]. Equally critical are the broader determinants of vulnerability—genetic risk, educational background, socioeconomic factors, and medical conditions such as hypertension, diabetes, stroke, alcohol use, and head traum[164, 165].

Longitudinal human studies that integrate imaging, molecular biomarkers, and detailed clinical assessments will be central to this next phase. Recent progress in tau PET, blood-based markers of neuroinflammation and synaptic injury, and imaging of vascular health now enables more precise mapping of disease trajectories [166-168]. Digital biomarkers, capturing subtle behavioral and cognitive changes in daily life, may soon offer a continuous, ecologically valid view of progression and response to therapy n [169].

But shifting conceptual models is not enough. Structural changes are also required. Funding must support the full pipeline—from basic mechanistic work and model development to validation in clinical settings. Regulatory agencies must prioritize outcomes that reflect real functional benefit, not just biomarker shifts, and maintain high standards for safety and transparency [170]. Scientific journals and peer reviewers must remain open to rigorous, paradigm-challenging work that reframes core assumptions and tests new questions [144].

The long dominance of the amyloid hypothesis has brought both progress and caution. It provided coherence in a fragmented field, but also narrowed its scope, leading to decades of therapeutic disappointment. The path forward demands a broader perspective—one that reflects the biological diversity of Alzheimer's, embraces methodological pluralism, and redefines success not by how well we clear a molecular target, but by how much we preserve the mind and the life it anchors.

Conflict of interest

The authors have declared that no conflict of interest exists.

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