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# ALZHEIMER'S TODAY: THE BREAKTHROUGHS AND HURDLES IN MANAGING THE DISEASE

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**ABSTRACT:** Alzheimer's disease (AD) is a progressive neurodegenerative disorder and leading cause of dementia, imposing a rapidly growing clinical and socioeconomic burden worldwide. This narrative review summarizes current understanding of AD pathophysiology, advances in diagnostics, and emerging therapeutic approaches. Hallmark mechanisms include amyloid-β plaque deposition, tau hyperphosphorylation, mitochondrial dysfunction, oxidative stress, glutamatergic excitotoxicity, metal dyshomeostasis and defective autophagy, all converging on synaptic failure and neuronal loss. The 2018 NIA–AA ATN (amyloid, tau, neurodegeneration) framework has shifted diagnosis toward a biomarker-based, biological definition of AD, incorporating CSF, PET, MRI and novel blood, saliva and tear biomarkers, as well as microRNA signatures for earlier detection across the preclinical–MCI–dementia continuum. Symptomatic therapies with acetylcholinesterase inhibitors and the NMDA antagonist memantine remain standard of care, while monoclonal antibodies such as aducanumab and lecanemab represent first-generation disease-modifying agents but raise concerns regarding amyloid-related imaging abnormalities and cost. Ongoing trials of biologics and small molecules targeting amyloid, tau, inflammation, oxidative stress and neuroprotection highlight a transition toward precision, multi-targeted strategies. Continued research into accessible biomarkers, safer long-acting formulations and adherence-enhancing approaches is essential to reduce the future global burden of AD.

**INTRODUCTION:** Alzheimer's disease (AD), first described by Alois Alzheimer as "senile dementia," is a progressive neurodegenerative disorder leading to cognitive decline, functional dependence, and ultimately death [1]. It is the leading cause of dementia, affecting over 35 million people worldwide, with the number expected to quadruple by 2050 [2].

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The World Health Organization (WHO) has recognized AD as a global health priority because it progresses silently in its early neuropathological stages, making timely diagnosis extremely challenging [3].

The global burden of AD is immense. In the United States, 6.7 million individuals were living with AD in 2019, with projections suggesting 14 million cases by 2050. The economic cost of treatment was estimated at 340 billion US dollars in 2019 and could rise to 1.1 trillion US dollars by 2050 [4]. In Australia, approximately 472,000 people were affected in 2019, a number predicted to rise to 589,000 by 2028. Dementia due to AD is the second leading cause of death in the country, with

care costs amounting to 3.0 billion dollars in 2018–19 and expected to double by 2058. Around 70% of all dementia cases in Australia are attributed to AD, with the total annual cost of dementia estimated at 15 billion dollars, including healthcare, aged care services, and informal caregiving [5]. These figures highlight the enormous demographic and economic implications of AD worldwide.

The pathological hallmarks of AD are amyloid plaques and neurofibrillary tangles (NFTs) [6]. Amyloid-β plaques begin to accumulate nearly two decades before the onset of symptoms due to defective clearance or overproduction of the peptide [7]. NFTs, composed of hyperphosphorylated tau protein, emerge around 10–15 years before clinical manifestations [8]. Beyond the pivotal role of Aβ and tau, a spectrum of other factors may contribute to the pathology of AD, such as acetylcholine deficiency, neuroinflammation, oxidative stress, biometal dyshomeostasis, glutamate imbalance, insulin resistance, gut microbiome abnormalities, cholesterol homeostasis disruption, mitochondrial dysfunction, and autophagy abnormalities [9, 10]. In 2018, the National Institute on Aging and Alzheimer's Association (NIA-AA) revised diagnostic criteria, shifting the definition of AD from a purely clinical to a biological perspective [11].

The disease progresses along a continuum. In the earliest phase, preclinical AD, patients show pathological changes without symptoms, and this stage may last 6–10 years depending on age at onset [12]. Some individuals also experience mild behavioural impairment (MBI), characterized by neuropsychiatric symptoms before cognitive decline [13]. Progression to mild cognitive impairment (MCI) is influenced by factors such as age, sex, and apolipoprotein E (ApoE) status [14]. Not all individuals with AD pathology develop symptoms, but longitudinal studies show that 20–29% of those with preclinical AD transition to MCI within 3–4 years. MCI due to AD is marked by memory deficits, language difficulty, impaired executive function, and visuospatial problems, though patients often retain independence [16]. Over time, 32–70% of MCI cases progress to AD dementia within 3–4 years, with significant cognitive decline, behavioral disturbances, and dependency on caregivers [17].

Early diagnosis has become a major focus of research, shifting from confirming symptomatic AD to detecting the disease during its silent phases [18]. The NIA-AA has introduced a biomarker-based "ATN" framework: A (amyloid-β deposition), T (tau pathology), and N (neurodegeneration) [9]. These biomarkers can be measured in cerebrospinal fluid (CSF) or through imaging methods such as PET scans [19]. Current research emphasizes not only the validation of amyloid and tau biomarkers but also the discovery of novel markers and understanding their longitudinal evolution across the AD continuum. This approach is crucial for developing disease-modifying and preventive strategies as the prevalence of AD is increasing globally, posing significant challenges to healthcare systems and societies.

**Pathophysiology:** The exact mechanisms of Alzheimer's disease (AD) pathogenesis remain unclear, but abnormal accumulation of beta-amyloid plaques and tau tangles is central. Beta-amyloid plaques arise from insoluble peptide aggregates produced through the amyloidogenic cleavage of amyloid precursor protein (APP). These plaques disrupt synaptic communication, trigger inflammation and oxidative stress, and promote neuronal degeneration. Tau tangles form when tau proteins undergo abnormal phosphorylation, leading to microtubule destabilization, impaired axonal transport, and eventual neuronal dysfunction.

Genetics plays a critical role in AD. While most cases are sporadic, a small proportion are familial or early-onset AD (EOAD), associated with mutations in presenilin 2 (PSEN2, chromosome 1), APP (chromosome 21), and presenilin 1 (PSEN1, chromosome 14). These mutations promote amyloid and tau pathology [20]. In sporadic AD, the apolipoprotein E (ApoE) gene variants—ApoE2, ApoE3, and ApoE4—are key risk factors. Among them, ApoE4 is strongly associated with increased amyloid accumulation and earlier cognitive decline [21].

Progression of AD is marked by gradual neuronal loss and brain atrophy, particularly in the hippocampus and cerebral cortex, regions essential for memory and cognition. The loss of neurons and synaptic connections explains the decline across

cognitive domains. Current therapeutic research aims to target amyloid and tau accumulation, enhance their clearance, and reduce neuroinflammation. Approaches such as immuno-therapy and precision medicine hold promise in tackling the multifactorial nature of AD.

Overall, AD pathogenesis reflects a complex interplay between genetic and environmental factors. Understanding how beta-amyloid plaques, tau tangles, and neuroinflammatory processes interact remains vital for developing innovative strategies to slow or prevent neurodegeneration.

**TAU Protein:** As a major component of NFTs, tau protein exhibits a spatial and temporal distribution that strongly correlates with clinical symptoms, making it a highly specific pathological biomarker in AD patients [22]. Tau is a microtubule-associated protein predominantly expressed in the axons of neurons, with lower expression levels in dendrites, soma, and glial cells [23]. It hosts numerous phosphorylation sites across its N-terminal region, C-terminal region, and repeat region, which are regulated by a balance of various kinases and phosphatases to maintain normal neuronal physiological functions [24]. Under pathological conditions, an imbalanced activity of phosphatases and kinases leads to hyperphosphorylation of tau [25]. This process leads to the detachment of tau protein from microtubules, followed by conformational changes and mislocalization, accumulation of tau oligomers, paired helical filaments (PHFs), and NFTs within the cell body and dendrites. These changes ultimately impair neuronal function and cause cell death [26]. In recent years, there has been a heightened focus on tau deposition, including the correlation between tau deposition, brain atrophy, and glucose metabolism in both typical and atypical AD,[27] as well as the effects of tau deposition at the molecular and cellular levels [28].

Additional factors such as oxidative stress, impaired protein folding in the endoplasmic reticulum, and dysfunction of proteasome- or autophagy-mediated clearance further accelerate tau and amyloid aggregation with aging. These processes ultimately lead to neuronal dysfunction and death. Interestingly, mutations in the tau gene on chromosome 17 have been linked to frontotemporal dementia with Parkinsonism but not to AD, indicating distinct genetic pathways for different neurodegenerative disorders [29].

Understanding tau pathology remains critical for therapeutic development, with current research focusing on strategies to prevent tau hyperphosphorylation, aggregation, and NFT formation as potential means to slow AD progression.

**β-Amyloid (aβ):** Aβ peptides, composed of 39–43 amino acids, are naturally present in the brain and are derived from the amyloid precursor protein (APP) through enzymatic cleavage. In the amyloidogenic pathway, APP is cleaved by β-secretase and γ-secretase, producing β-amyloid fragments that can accumulate abnormally. APP is normally inserted into the endoplasmic reticulum during translation, [30] and while its expression supports cell growth, cleavage by β- and γ-secretases—particularly under conditions like growth factor deprivation generates Aβ peptides with potentially harmful properties [31]. Normally, β-amyloid is cleared by lysosomes and vesicles.

Amyloid accumulation also activates microglia. Initially protective through phagocytosis, microglia eventually become overloaded, impairing Aβ degradation and releasing pro-inflammatory mediators, nitric oxide, and cytokines. This shift promotes chronic neuroinflammation, which contributes to neuronal damage and neurodegeneration in AD. Thus, abnormal production, aggregation, and impaired clearance of Aβ peptides lie at the core of AD pathology.

**Oxidative Stress:** Oxidative stress is a major factor in Alzheimer's disease (AD) pathology and aging. In AD, factors such as metal accumulation, overexpression of related enzymes (e.g., NADPH oxidase), and mitochondrial dysfunction are involved in producing excessive ROS, surpassing the ability of the endogenous antioxidant system and resulting in an oxidative imbalance. It will damage neuronal membrane lipids, proteins, and nucleic acids, ultimately causing neuronal cell death [32]. Oxidative stress has garnered wide spread attention as a significant factor in the pathogenesis of AD. Nevertheless, the interplay between Aβ and oxidative stress, [33] as well as their sequence within AD, [34, 35] require further research and exploration.

**Metal Ion Hypothesis:** Under normal physiological conditions, trace metals help preserve the delicate balance of the neuronal metal ion milieu. When this equilibrium is disturbed due to inappropriate accumulation or mislocalization of metal ions metal dyshomeostasis can occur, and imbalances in $Fe^{2+}$, $Cu^{2+}$, and $Zn^{2+}$ have been strongly linked to AD [36]. The build-up of these biometals within Aβ plaques and neurofibrillary tangles (NFTs) is thought to be crucial in driving abnormal protein aggregation. They can influence key enzymatic activities, modify protein conformation, and interfere with protein clearance pathways. In particular, iron-mediated oxidative stress increases the release of iron from iron-containing proteins, promoting the intracellular reduction of $Fe^{3+}$ to $Fe^{2+}$. Excess $Fe^{2+}$ can then trigger ferroptosis and lipid peroxidation by generating reactive oxygen species (ROS) via the Fenton reaction, ultimately culminating in neuronal injury and death. In a similar manner, $Cu^{+}$ can directly bind to lipoylated dihydrolipoyl transacetylase (DLAT), promoting aggregation of lipoylated DLAT and resulting in cuproptosis [36]. Moreover, sequestration of these metals within protein deposits can lead to a functional deficiency of bioavailable metal ions, which may further contribute to cognitive decline in AD.

**Glutamatergic Excitotoxicity:** Glutamate primarily acts on NMDA receptors to regulate the entry of sodium and calcium ions into neurons. Under normal conditions, magnesium ions block the NMDA receptor channel, thereby limiting cation influx. In Alzheimer's disease, however, NMDA receptors become excessively activated, leading to the removal of magnesium from the channel and allowing an abnormal increase in sodium and calcium ion entry into neurons [37]. The influx of sodium ions into neurons leads to transient cellular swelling, whereas elevated calcium levels trigger multiple $Ca^{2+}$-dependent pathways. These include increased production of reactive oxygen species (ROS), impairment of mitochondrial function, and activation of necrotic and apoptotic mechanisms, collectively culminating in irreversible excitotoxic injury to neurons [38]. The observed changes in the inhibitory neurotransmitter system, exemplified by γ-aminobutyric acid, [39] and the potential for excitotoxicity to alter cognitive levels earlier than Aβ and tau pathologies, [37] suggest that excitotoxicity might hold greater potential in AD treatment.

**Abnormal Autophagy:** Autophagy is a highly conserved metabolic degradation pathway that preserves cellular homeostasis by transporting intracellular protein aggregates and damaged organelles to lysosomes, where they are broken down and recycled [40]. However, the marked buildup of autophagic vacuoles within swollen (nutrient-deprived) neurons has been associated with Aβ/APP-βCTF, indicating that autophagic clearance is profoundly impaired under pathological conditions and is closely connected to amyloid pathology [41]. These observations have brought autophagy into sharp focus in contemporary research on the pathogenesis of AD. Emerging data suggest that genetic alterations, downregulation of autophagy-related proteins, and abnormalities in vesicular trafficking are key contributors to autophagic dysfunction. Such impairments disrupt crucial clearance steps, including substrate engulfment, autophagosome biogenesis, fusion of autophagosomes with lysosomes, and the integrity and function of lysosomes themselves [42]. Autophagy-stimulating drugs including small molecule therapies and gene therapies, have shown significant neuroprotective potential in various AD animal models, suggesting a potential intervention option [40]. However, the challenges posed by the broad targets of autophagy modulators, and lack of appropriate in vivo autophagic flux detection methods, hinder further clinical applications of these drugs [43].

**Diagnostic Criteria:** The process of diagnosing AD can be categorized into the subsequent stages: identification, evaluation/differentiation, diagnosis, and treatment. Clinicians must employ suitable diagnostic techniques when examining a patient who is suspected of having AD in its initial phases.

**Identification:** The diagnosis of dementia begins not with formal tests but with suspicion during the "trigger phase," when early signs suggest a possible syndrome. A challenge in Alzheimer's disease (AD) is the reluctance of patients, families, and even physicians to acknowledge or diagnose the condition due to its severity, irreversibility, and

associated stigma. Families often compensate for impairments by gradually taking over responsibilities, unintentionally masking disease progression and delaying recognition. To confirm AD-related symptoms, healthcare providers should evaluate patients showing even minor cognitive or behavioral changes using validated tools designed to detect early-stage disease.

**Evaluation of a Memory Complaint – Clinical Assessment Tools:** Clinical assessment of memory complaints relies on interviews, questionnaires, and cognitive tests to detect early Alzheimer's disease (AD). Commonly used tools include the Mini-Cog, Mini-Mental State Examination (MMSE), and Montreal Cognitive Assessment (MoCA), which vary in sensitivity. MMSE assesses overall cognition but has low sensitivity, while MoCA is more sensitive and covers multiple domains, including memory [18]. Neuropsychological tests such as the Rey Auditory Verbal Learning Test (RAVLT) are widely used, with performance strongly reflecting AD pathology, making it an effective early marker [44]. The Clinical Dementia Rating (CDR) scale, and particularly the CDR–Sum of Boxes (CDR-SB), has been shown to reliably detect dementia onset and track progression, with higher scores predicting conversion from pre-dementia states, though it is less useful for consistently detecting treatment effects [45]. Another key tool is the AD Assessment Scale–Cognitive Subscale (ADAS-Cog), long used to measure deficits in memory, language, and praxis. Modifications such as ADAS-11 and ADAS-13 improve sensitivity to early decline, with higher scores reflecting greater impairment (range 0–70 for ADAS-11, 0–85 for ADAS-13) [46]. Recent evaluations suggest that tools like ADAS-13, MoCA, RAVLT, the Everyday Cognition Questionnaire (ECog), and the Functional Abilities Questionnaire (FAQ) are strong predictors of AD progression, while some tests like TMT-B and RAVLT are less specific. Notably, ECog showed particularly strong predictive power, and its use alongside MoCA, ADAS-13, and RAVLT is recommended for comprehensive screening of AD across stages [44].

**Structural Imaging:** Structural imaging, particularly MRI, provides important insights into cognitive decline but is mainly used to exclude other causes rather than to confirm Alzheimer's disease (AD). MRI generates detailed images of brain tissue, allowing measurement of brain volume and detection of atrophy in key regions such as the hippocampus and entorhinal cortex, which are essential for memory and learning [50]. In AD, reduced volume in these areas, along with enlarged ventricles, white matter hyperintensities, microbleeds, and structural signs linked to amyloid plaques and neurofibrillary tangles, can be observed. PET imaging, using radioactive tracers, measures amyloid and tau accumulation, key biomarkers of AD [51]. Another technique, FDG-PET, evaluates glucose metabolism in the brain, reflecting neuronal activity. While not useful for diagnosing preclinical AD due to a lack of specificity, FDG-PET can help detect hypometabolism and neurodegeneration in symptomatic patients, supporting AD diagnosis in clinical practice.

**Confirming AD Pathology:** Advances in healthcare have improved methods for confirming Alzheimer's disease (AD) pathology, which remains difficult to diagnose due to its complex and progressive nature. Modern approaches combine genetic and protein marker analysis, advanced imaging techniques, and cerebrospinal fluid (CSF) biomarker testing to detect amyloid and tau pathology and neurodegeneration. Since pathological changes begin long before symptoms appear, the presence of biomarkers in preclinical phases does not always predict the development of clinical AD, and single biomarkers provide limited prognostic value. To address this, recent efforts emphasize combining multiple biomarkers for better precision. Jack and colleagues proposed the ATN classification, which categorizes biomarkers into amyloid (A), tau (T), and neurodegeneration (N), each scored as normal (–) or abnormal (+). This framework shifts focus from traditional clinical assessments to underlying pathology. The ATN model creates eight possible biomarker profiles, from A-T-N- (no pathology) to A+T+N+ (pathology in all categories). Importantly, any profile with an A+ is considered indicative of AD-related changes. Recent studies confirm that the ATN system can predict cognitive decline and disease progression, highlighting its value in early and accurate diagnosis.

**Biomarkers A and Pathologic Tau (At Classification):** Biomarkers for Alzheimer's disease (AD) focus on amyloid (A) and tau (T) pathology. In the A+ group, aggregated Aβ peptides primarily Aβ1-40 and Aβ1-42 are central, with Aβ1-42 being the main component of senile plaques, a key feature for neuropathological diagnosis. These plaques can be detected by cortical amyloid PET imaging or by measuring Aβ1-42 and Aβ1-40 in cerebrospinal fluid (CSF) using ELISA. In early AD, CSF Aβ1-42 decreases due to plaque deposition, and the Aβ1-42/Aβ1-40 ratio provides a more reliable marker of amyloid aggregation.

Tau pathology (T+) involves hyperphosphorylation of tau, which detaches from microtubules, becomes unstable, and aggregates into paired helical filaments (PHFs) and neurofibrillary tangles (NFTs). Aggregated tau can be detected by PET imaging, while elevated phosphorylated tau (p-tau) in CSF particularly pTau181 is a robust indicator of AD, correlating with disease severity and distinguishing AD from other tauopathies [53]. Other isoforms, such as pTau199, pTau231, and, more recently, plasma p-tau181 and p-tau217, also show strong diagnostic accuracy [55]. For example, the BioFINDER study demonstrated that plasma p-tau217 predicts progression to AD dementia and cognitive decline [58]. Combining CSF p-tau with Aβ42 and total tau (t-tau) has become a standard in AD diagnostics, with evidence showing that Aβ42 levels decline decades before symptoms appear [54]. Integrating Aβ42/Aβ40 or Aβ42/Aβ38 ratios with tau markers enhances diagnostic sensitivity and specificity to about 85–95%. Recently, blood-based biomarkers have gained attention. Rissman *et al*. (2024) used plasma p-tau217, p-tau181, and Aβ42/Aβ40 ratios measured by LC-MS/MS to predict amyloid PET status in cognitively unimpaired individuals, with the best performance achieved when plasma p-tau217 was combined with the Aβ42/Aβ40 ratio [59]. These advances highlight the growing role of both CSF and blood-based biomarkers in early and precise AD detection.

**Biomarkers of Neurodegeneration or Neuronal Injury (N classification):** The biomarkers observed in the N+ group indicate the presence of neurodegeneration. Axonal degeneration is a prominent characteristic of AD and is more strongly associated with the beginning of cognitive impairment compared to other clinical aspects. Neurodegeneration in brains affected by AD can be identified by the use of FDG PET hypometabolism and MRI. Nevertheless, studies have demonstrated that persons with AD exhibit elevated levels of t-tau in the CSF, and these levels are strongly associated with the extent of neurodegeneration. However, neurodegeneration is not exclusive to AD and can be observed in various other illnesses affecting the neurological system. Nevertheless, when employed alongside other indicators, t-tau can offer crucial insights into an individual's placement on the AD spectrum and the extent of their cognitive decline [60].

**Other Promising Biomarkers:** Blood-based biomarkers have emerged as less invasive alternatives to cerebrospinal fluid (CSF) testing, offering easier accessibility for diagnosing and monitoring Alzheimer's disease (AD). Recommended for use in memory clinics, promising candidates include plasma Aβ42, Aβ42/40 ratio, p-tau, t-tau, neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), and soluble TREM2 (sTREM2) [61]. However, limited availability, high cost, and variability mean plasma biomarkers still require optimization before widespread use.

Saliva has gained attention as a non-invasive biomarker source due to its connection with CSF proteins. Studies have identified salivary Aβ40, Aβ42, p-tau, t-tau, and lactoferrin as potential markers, with Aβ42 particularly effective in distinguishing AD from other neurological disorders [62].

Despite advantages, saliva biomarkers can be influenced by circadian rhythms, flow rate, and enzymatic degradation, necessitating standardization. Similarly, tears have shown promise since amyloid and tau deposits are detectable in ocular tissues. Elevated tear Aβ42 has been reported in preclinical and AD patients, with studies demonstrating strong specificity and sensitivity for distinguishing AD and MCI from healthy individuals [63]. Tear biomarkers are attractive due to their non-invasive, inexpensive, and practical collection methods.

MicroRNAs (miRNAs), small non-coding RNAs regulating gene expression, represent another promising biomarker class. They can be detected in blood, CSF, exosomes, and brain tissue and have been shown to accurately differentiate AD from healthy individuals. A meta-analysis demonstrated high diagnostic performance with a sensitivity of 0.80 and specificity of 0.83 [64]. Recent studies further support their potential as reliable markers for early AD detection and disease characterization [6]. Collectively, blood, saliva, tears, and miRNAs expand the diagnostic toolbox, holding promise for more accessible and accurate detection of AD.

**Therapeutic Interventions for AD:** Given the diverse pathological pathways of Alzheimer's disease (AD), combination therapy is considered more beneficial than monotherapy [65]. The goal of treatment is to improve cognition and memory by targeting neuronal dysfunction. Currently, the FDA has approved two drug classes: acetylcholinesterase (AChE) inhibitors (donepezil, galantamine, rivastigmine) and NMDA receptor antagonists (memantine). Their efficacy is often assessed with scales such as the Alzheimer's Disease Assessment–Cognitive Subscale (ADAS-Cog) and the Disability Assessment in Dementia (DAD).

**NMDA Receptor Antagonist:** Glutamate, an excitatory neurotransmitter, regulates memory, learning, and neuronal plasticity *via* NMDA receptors. In AD, overstimulation causes excess calcium influx, excitotoxicity, and neuronal death. NMDA receptor antagonists reduce calcium entry, protecting neurons and improving cognition.

**Memantine:** Memantine is an uncompetitive NMDA receptor blocker, structurally related to amantadine. It has neuroprotective effects in AD and other neurological conditions [65]. Orally administered memantine is well absorbed, partially metabolized in the liver, and blocks excessive calcium entry through NMDA receptors. It also regulates glutamate transporters in glial cells. By reducing excitotoxicity and tau hyperphosphorylation, memantine improves cognition and is generally well tolerated. Side effects include dizziness, headache, confusion, constipation, urinary infections, and agitation.

**Acetylcholinesterase (AChE) Inhibitors:** These drugs prevent acetylcholine breakdown in the synaptic cleft, enhancing cholinergic signalling in the hippocampus, cortex, and forebrain. This improves memory and cognitive function in AD patients [66]. The FDA has approved three agents: donepezil, galantamine, and rivastigmine.

**Donepezil:** Approved in 1996 for all stages of AD, donepezil is a reversible, selective AChE inhibitor. Besides AD, it has shown benefits in cerebrovascular cognitive impairment, traumatic brain injury, Parkinson's disease dementia, and Down syndrome [67]. Donepezil is slowly absorbed, highly protein-bound, and primarily metabolized in the liver, with reduced clearance in cirrhosis. It inhibits AChE activity by 63–77% at standard doses, improving episodic and semantic memory.

**Galantamine:** Galantamine, a plant-derived alkaloid, was FDA-approved in 2001 for mild-to-moderate AD [68]. In addition to AChE inhibition, it acts as a positive allosteric modulator of nicotinic receptors, thereby enhancing synaptic plasticity and cognitive function by increasing the receptors' sensitivity to acetylcholine. It is metabolized by CYP3A4 and CYP2D6 enzymes and follows linear kinetics. Side effects include gastrointestinal disturbances, bradycardia, and hypotension, but meta-analyses confirm its safety and efficacy in mild-to-moderate dementia.

**Rivastigmine:** Rivastigmine, a synthetic physostigmine derivative, was FDA-approved in 1997. It is a carbamate ester providing long-acting reversible inhibition of AChE. Orally administered rivastigmine is rapidly absorbed and metabolized by cholinesterase-mediated hydrolysis and N-demethylation in the liver. Clinical doses of 6–12 mg improve cognition and MMSE scores by preventing acetylcholine degradation at cholinergic synapses [69].

**Combination Therapy and Associated Problems:** Combination therapy with memantine and donepezil has been approved for moderate to severe Alzheimer's disease (AD) and has shown greater efficacy than monotherapy in improving cognition, behavior, and daily functioning. A meta-analysis of 54 trials by Guo et al. confirmed that combination therapy significantly improved social and cognitive outcomes, though at a higher economic cost [53].

Similarly, Glinz *et al.* reviewed nine controlled trials (n=2604) and concluded that the combination of memantine and AChE inhibitors was more effective than AChE inhibitors alone, though adverse event reporting was insufficient [54]. Chen *et al.* also reported significant improvements with combination therapy but highlighted common gastrointestinal side effects such as nausea, vomiting, and diarrhoea [55]. Matsunaga *et al.*, analysing seven studies with 2182 participants, found overall benefits across cognition, behavior, and daily activity, with good tolerability [56].

Despite its proven benefits, combination therapy faces challenges, including digestive side effects, high costs, and reduced compliance due to frequent dosing, especially in elderly patients. Progressive memory decline also contributes to non-adherence, leading to relapse. To address this, long-acting injectable (LAI) formulations are being explored as a way to improve adherence, reduce relapse, and potentially lower treatment costs. Incorporating LAIs into AD therapy could optimize effectiveness, minimize side effects, and improve quality of life while reducing the overall disease burden.

**Antibodies for Amyloid Clearance:** Currently available NMDA receptor antagonists and AChE inhibitors only provide symptomatic relief in Alzheimer's disease (AD) without slowing progression. Since beta amyloid plaques and tau aggregates drive pathology, monoclonal antibodies (MABs) targeting amyloid have been developed as disease-modifying therapies. The FDA has approved two such antibodies aducanumab and lecanemab.[57] These antibodies bind to amyloid aggregates in the brain, triggering clearance by microglia through FC receptor–mediated phagocytosis, promoting dissolution and efflux of aggregates, or altering equilibrium via the peripheral sink effect to reduce brain amyloid levels [58].

Aducanumab, a human IgG1 antibody approved in 2021, shows strong selectivity for aggregated amyloid and reduces both soluble and insoluble forms in a dose-dependent manner [70]. Lecanemab, approved in 2023, preferentially targets soluble protofibrils and has demonstrated disease-modifying potential in both human and animal studies [71]. Both are administered intravenously, with aducanumab given every four weeks and lecanemab every two weeks. Despite their promise, concerns remain regarding efficacy and safety. The most notable adverse effect is amyloid-related imaging abnormalities (ARIA), including cerebral edema and microhaemorrhages, which can cause neurological symptoms and even death.[59] Corticosteroid co-therapy has been suggested to reduce ARIA risk.

For antibody-based therapy to be effective, key requirements include the ability to cross the blood–brain barrier, improve cognition, demonstrate amyloid clearance, and minimize side effects.[53] While these MABs represent a significant step toward disease-modifying treatment, their clinical value continues to be debated.

**Investigational New Drugs Under Trial:** The pathological complexity and continuous progression of AD impede the therapeutic efficacy, leading to an increase in the global burden of the disease. Currently, clinical data from the companies developing different biologic drugs and small molecules (with molecular weight <1000 Da) targeting various pathways are compiled in this section to increase the understanding of advancement in this area.[72] However, these therapeutic molecules are still under different phases of investigation or trials. The data obtained from the ClinicalTrials.gov database indicated that a total of 121 studies of investigational typearein different phases (Phase 1–4) as of 1 January 2024. A total of 5, 46, and 39 trials were registered within Phases 1, 2, and 3, respectively, studying biological and small molecules targeting inflammatory, plasticity/neuroprotection, oxidative stress, amyloid, and tau clearance pathways to reverse the disease progression.

Biological product shows high efficacy in clearing tau and amyloid aggregates via different pathways associated with disease progression. Two monoclonal antibodies, aducanumab and lecanemab, received accelerated approval as anti-amyloid agents. Donanemab, a third candidate in this line, has not received approval yet, probably due to the insufficient data showing efficacy. Besides the therapeutic efficacy, the side effects of these agents, such as ARIA, can lead to brain atrophy in some cases, questioning their safety.

There is an increased trend towards the developmental process of biological products these days, probably because they have higher profit margins as compared to small molecules. Around 2% of total approved drugs are biological molecules, whereas they account for 37% of total spending [61]. The small molecules are easy to develop and formulate, but their role in clearing tau and amyloid is still under evaluation.

**CONCLUSION:** Alzheimer's disease (AD) presents a growing global challenge, with its prevalence and economic burden projected to rise sharply by 2050. Characterized by amyloid-β plaques, tau tangles, mitochondrial dysfunction, and oxidative stress, Alzheimer's disease demands early diagnosis and innovative treatments. The ATN biomarker framework, utilizing CSF, blood, saliva, and tear-based markers alongside PET and MRI, facilitates early detection in preclinical stages. Current therapies, including acetylcholinesterase inhibitors and NMDA receptor antagonists, provide symptomatic relief, while monoclonal antibodies like aducanumab and lecanemab target amyloid clearance, though concerns like amyloid-related imaging abnormalities (ARIA) remain. Investigational drugs, with 121 trials as of January 2024, focus on biologics like donanemab and small molecules targeting amyloid, tau, inflammation, and neuroprotection. These therapies show promise for disease modification but face safety and efficacy challenges. Continued research into safer drugs, accessible diagnostics, and socioeconomic strategies is vital to reduce AD's impact and improve patient outcomes.

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