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Review Article

Alzheimer's Disease: A Comprehensive Review of Pathogenesis, Diagnostic Biomarkers, Clinical Progression, and Evolving Therapeutics

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ABSTRACT

Alzheimer's disease (AD) is the major cause of dementia worldwide and a progressive neurodegenerative disorder, accounting for 60–70% of the estimated 55 million global cases of dementia. The core neuropathological hallmarks, extracellular amyloid-beta (Aβ) plaques and intraneuronal neurofibrillary tangles (NFTs) of hyperphosphorylated tau, activate a complex pathophysiological cascade including chronic neuroinflammation, reactive microgliosis, astrocytic dysfunction, mitochondrial failure, oxidative stress, synaptic breakdown and extensive neuronal loss. The historical reliance on late-stage syndromic definitions has now been replaced by a rigorous biological framework (Revised 2024 Criteria and AT (N) staging), enabling disease identification years prior to overt dementia via cerebrospinal fluid (CSF) assays, molecular positron emission tomography (PET), and increasingly studied blood-based biomarkers such as plasma phosphorylated-tau217 (p-tau217). Conventional pharmacotherapies (acetylcholinesterase inhibitors and memantine) provide modest symptomatic stabilization without altering disease pathology. In contrast, recently approved disease-modifying monoclonal antibodies (lecanemab and donanemab) clear cerebral amyloid plaques and modestly slow cognitive and functional decline in early symptomatic stages. But these therapies have clinical challenges including amyloid-related imaging abnormalities (ARIA), high cost and infrastructure needs. At the same time, multi-domain non-pharmacological approaches, such as structured physical exercise, cognitive stimulation, nutritional optimization and caregiver support, continue to be fundamental pillars of holistic care. This review summarizes the current evidence for the epidemiology of AD, its multifactorial etiology, molecular pathophysiology, clinical course, biological diagnostic criteria, evidence-based pharmacotherapies and emerging

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precision therapeutics.

INTRODUCTION

1 Introduction and Historical Background

Alzheimer's disease (AD) is the leading cause of dementia and a major global health challenge [1]. AD is characterized by progressive decline in episodic memory, executive functioning, visuospatial reasoning, and independence in daily living, imposing substantial emotional, physical, and financial burdens on patients, families, and health care systems [2, 3]. The disease was first described in 1906 by German neuropathologist Alois Alzheimer who noted progressive cognitive decline and hallucinations in Auguste Deter, and associated these with post-mortem argentophilic senile plaques and neurofibrillary tangles [1, 3]. In 1910, Emil Kraepelin named this condition 'Alzheimer's disease' [1].

For decades, AD was thought to be a rare presenile disorder, and dementia in late life was considered to be inevitable senility [1, 3]. Landmark clinicopathological studies in the 1960s and 1970s by Blessed, Tomlinson and Roth revealed that presenile and senile dementias possessed identical plaque and tangle pathology, thus establishing AD as the main cause of cognitive failure in late life [1, 3]. Biochemical breakthroughs in the 1980s identified amyloid-beta as the core constituent of senile plaques and hyperphosphorylated tau as the principal subunit of neurofibrillary tangles [15, 16, 17]. In parallel, the discovery of basal forebrain cholinergic degeneration led to the first approved symptomatic therapies [7, 18].

Contemporary research demonstrates that AD neuropathology develops silently 15 to 25 years prior to symptom onset [5, 6]. Current criteria increasingly distinguish the underlying biological process from the clinical stages of mild cognitive impairment and dementia [5, 7]. This conceptual evolution is supported by validated fluid and imaging biomarkers [5, 6, 19] and the emergence of disease-modifying monoclonal antibodies targeting amyloid-beta [9, 10]. This review examines the epidemiology, etiology, molecular pathogenesis, clinical features, biological diagnosis, pharmacotherapies, non-pharmacological care, and emerging treatment directions in AD.

2. Definition of Alzheimer's Disease: Biological vs. Syndromic Frameworks

Historically, AD was diagnosed syndromically. Diagnosis under the 1984 NINCDS-ADRDA consensus criteria required evidence of progressive dementia that interferes with social occupation, but definitive confirmation could only be made by histopathology at post-mortem [20]. This approach conflated the underlying disease biology with end stage symptoms and neglected the lengthy preclinical and prodromal phases in which pathology accrues silently [5, 6]. Moreover, clinicopathological studies showed that 15%–30% of patients with a clinical diagnosis of AD did not exhibit significant amyloid or tau pathology at autopsy, but instead had alternative pathologies such as dementia with Lewy bodies or vascular disease [20, 21].

Conversely, modern neurobiology describes Alzheimer's disease in biological terms as a detectable neuropathological process in vivo, characterized by extracellular amyloid-beta plaques and intraneuronal hyperphosphorylated tau tangles, irrespective of clinical symptoms [5, 6]. The 2024 criteria describe a biological framework using validated biomarkers; the appropriate test depends on the assay, clinical context, and intended use [5, 6].

This biological framework describes three different stages of disease [5]:

Preclinical AD: Cognitively unimpaired individuals with validated biomarker evidence of brain amyloid-beta and/or pathological tau [5, 6].

AD-related Mild Cognitive Impairment (MCI): Objective cognitive impairment (mainly episodic memory) measurable with independence in basic and complex activities of daily living preserved [5, 7].

AD Dementia: Cognitive decline sufficient to interfere with independence in basic activities of daily living [1, 5].

Importantly, dementia is a non-specific clinical syndrome, which may be caused by vascular lesions, Lewy bodies, frontotemporal degeneration or metabolic disorders [21]. Distinguishing the clinical dementia syndrome from its underlying cause can improve diagnostic precision and help identify appropriate candidates for research or treatment [5, 20].

3. The Epidemiology of Alzheimer's Disease

The global burden of AD is expected to rise [1, 2] with the aging of the world's population. In 2019, the WHO and Alzheimer's Disease International reported that there were approximately 55 million people living with dementia with nearly 10 million new cases every year [1, 2]. AD comprises 60% to 70% of them [1, 22]. In 2019, the global cost of dementia was over 1.3 trillion US dollars and is projected to increase to 2.8 trillion US dollars by 2030 [2, 22]. Global dementia projections vary by source and assumptions; commonly cited estimates indicate substantial growth by 2050, with more than 71% of people with dementia living in low- and middle-income countries (LMICs) [2, 22].

AD incidence increases markedly with age, doubling approximately every 5 years after age 65 [1, 23]. The incidence rises from 2 to 3 per 1000 person-years for ages 65 to 74 to over 35 per 1000 person-years after age 85, when about one third of community-dwelling persons have dementia [1, 23]. Women are more affected, representing two-thirds of diagnoses and informal caregivers [23, 24]. This disparity is amplified by longer life expectancy in women and biological factors including postmenopausal estrogen changes, sex-specific microglial gene expression, increased tau spread in the face of equal amyloid burdens, and increased vulnerability of APOE ε4 [23, 24].

Demographic aging is rapidly increasing the burden of dementia in developing countries like India [25, 26] A meta-analysis of 20 studies with 86,312 participants showed that the pooled prevalence of dementia was 2.0% in adults ≥60 years and 5.8%-8.2% in adults ≥75 years [25]. There are an estimated 5.3 million people living with dementia in India with numbers projected to cross 14 million by 2050 [25, 26]. Underdiagnosis is associated with stigma, limited awareness, uneven access to specialist services, and a shortage of culturally validated assessment tools [25, 26].

Table 1: Global Dementia Burden and Selected Regional Estimates

Region / Entity	Estimated Cases (Millions)	Projected 2050 (Millions)	Dominant Healthcare Challenges
Worldwide (All Dementias)	55.2 M	139.0 – 152.0 M	Global demographic aging, caregiver burnout, soaring healthcare costs.
Low- & Middle-Income Countries	33.5 M (61% global)	105.0 M (71% global)	Severe underdiagnosis (>80%), limited specialist access, high out-of-pocket costs.
India	5.3 M	14.2 M	Societal stigma, low literacy-adapted diagnostics, scarce memory clinics.
East Asia (China, Japan)	15.8 M	38.5 M	Rapid demographic inversion, shrinking working-age caregiving ratios.
North America & Western Europe	12.1 M	22.4 M	DMT infusion capacity constraints, ARIA MRI monitoring backlogs, high drug costs.
Sources: global burden and projections vary by reporting year and method; regional figures should be interpreted as estimates [2, 22, 25, 26].			

4. Etiology and Risk Factors of Alzheimer's Disease

Alzheimer's disease does not usually arise from one cause. Genetic susceptibility, ageing, vascular health, and environmental influences can interact over a person's lifetime. Some factors are involved directly in disease mechanisms, while others increase or reduce the likelihood of developing the condition [1, 22].

4.1. Non-Modifiable Risk Factors

1. **Age**: The strongest risk factor for sporadic AD [1]. Senescence involves telomere shortening, mitochondrial decline, DNA damage, blood–brain barrier breakdown, chronic low-grade inflammation ('inflammaging'), and reduced glymphatic clearance [3, 4].
2. **APOE ε4:** Located on chromosome 19q13.32, APOE is the premier genetic determinant of late-onset AD [27]. The APOE ε4 allele is associated with a dose-dependent increased risk for late-onset AD, although the estimated risk varies by ancestry, age and study design [27,28].ApoE4 impairs Aβ clearance, impairs microglial homeostasis, disrupts

BBB pericytes and facilitates tau phosphorylation [27, 28].

3. **Familial AD:** <1% to 2% of cases, autosomal dominant inheritance with ~100% penetrance, onset between 30 and 55 years [1, 15]. Mutations in APP (chr 21), PSEN1 (chr 14) and PSEN2 (chr 1) affect γ-secretase cleavage, increasing the ratio of Aβ42/Aβ40 and promoting early oligomerization [15].
4. **Down Syndrom**e: Triplication of chromosome 21 results in an extra copy of the APP gene, with lifelong overexpression of APP, a high prevalence of Alzheimer-type neuropathological changes with increasing age, and clinical dementia in >70% of individuals by 60 years of age [15].

4.2. Modifiable risk factors (Lancet Commission 2024)

The 2024 Lancet Commission estimated that 14 potentially modifiable risk factors together account for a substantial proportion of dementia cases at the population level; this estimate is not an individual prediction [22].

Table 2: Potentially Modifiable Dementia Risk Factors Across the Life Course

Life Stage	Modifiable Risk Factor	Relative Risk (RR)	Biological / Pathological Mechanism
Early Life (<18 yrs)	Less Education	1.4	Reduces cognitive reserve; limits synaptic density and neuronal plasticity.
Midlife (45–65 yrs)	Hearing Loss (Untreated)	1.4	Increases cognitive load; promotes auditory deafferentation atrophy.
Midlife	Traumatic Brain Injury (TBI)	1.3	Axonal shearing, microglial activation, blood–brain barrier breakdown.
Midlife	Hypertension (BP ≥130 mmHg)	1.3	Cerebral small vessel disease, white matter lesions, impaired clearance.
Midlife	Excessive Alcohol (>21 units/wk.)	1.2	Direct neurotoxicity, thiamine deficiency, cortical atrophy.
Midlife	Obesity (BMI ≥30 kg/m²)	1.3	Systemic inflammation, insulin resistance, adipokine dysregulation.
Midlife	Elevated LDL Cholesterol	1.3	Atherosclerosis, impaired cerebral perfusion, membrane lipid raft changes.
Late Life (>65 yrs)	Smoking	1.6	Endothelial damage, systemic oxidative stress, accelerated cerebrovascular disease.
Late Life	Depression	1.3	Elevated cortisol, hippocampal atrophy, persistent neuroinflammation.
Late Life	Social Isolation	1.6	Reduced cognitive stimulation and neurogenesis, accelerated decline.
Late Life	Physical Inactivity	1.4	Decreased cerebral blood flow, reduced BDNF expression, insulin resistance.
Late Life	Diabetes Mellitus	1.5	Advanced glycation end-products, cerebral insulin resistance, vascular injury.
Late Life	Air Pollution (PM2.5)	1.1	Ultrafine particulates trigger microglial activation and systemic inflammation.
Late Life	Untreated Vision Loss	1.5	Sensory deprivation, diminished environmental input, reduced cognitive reserve.
Source: risk-factor categories and population-attributable estimates are drawn from the 2024 Lancet Commission and related systematic review. Relative-risk values vary by study and should not be treated as universal estimates [22, 29].			

5. Pathophysiology and Molecular Neuropathology of Alzheimer's Disease

Alzheimer's disease is not a single series of events but rather a more complex set of events because biological changes are interrelated and may amplify each other [3, 4, 16].

5.1. APP Proteolysis and the Amyloid Cascade

The type-I transmembrane glycoprotein amyloid precursor protein (APP) is cleaved via two opposing mechanisms [3, 15]:

1. **Non-amyloidogenic pathway:** Cleavage of the Aβ sequence by α-secretase (ADAM10) generates neuroprotective sAPPα and C83 (CTFα) and decreases the production of intact Aβ [3, 15].
2. **Amyloidogenic:** β-secretase (BACE1) cleaves it to release C99 (CTFβ) and sAPPβ. Further cleavage by the γ-secretase complex (Presenilin 1/2, Nicastrin, APH-1, PEN-2) generates Aβ peptides of different length, mainly Aβ40 and the hydrophobic and aggregation prone Aβ42 [3, 15].

The hydrophobic Aβ42 peptides forming fibrillar senile plaques, soluble oligomers and protofibrils [3, 4]. The most toxic soluble forms of Aβ, oligomers and protofibrils, disrupt NMDA receptor trafficking, block long-term potentiation (LTP), cause synaptic spine collapse and lead to calcium dysregulation [3, 16].

5.2. Tau Hyperphosphorylation and Neurofibrillary Tangles

The MAPT gene encodes tau, a phosphoprotein that is associated with microtubules and stabilises axonal microtubules and promotes axonal transport [16, 17]. In AD, Tau is hyperphosphorylated due to an imbalance between downregulated phosphatases (PP2A) and hyperactive kinases (GSK-3β, CDK5) [16, 17]. Hyperphosphorylated tau misfolds into paired helical filaments, straight filaments, and intraneuronal neurofibrillary tangles (NFTs), detaches from microtubules and destabilises the cytoskeleton [16, 17].

Braak [16, 30] suggested that tau disease follows a predictable hierarchical sequence:

1. **Braak Stages I–II (Transentorhinal):** Usually asymptomatic, confined to the transentorhinal and entorhinal cortexes [30].
2. **Stage III-IV:** Amnestic MCI and mild dementia correspond to Braak Stages III-IV (Limbic), including hippocampus, amygdala and thalamus [30].
3. **Braak Stages V–VI (Isocortical):** Severe dementia and major cognitive loss; includes association and primary neocortices [16, 30].

Trans-synaptic spread of tau pathology, and prion-like seeding. Importantly, neocortical tau distribution is strongly correlated with clinical cognitive decline, synaptic loss and regional brain atrophy [16, 30].

5.3. Amyloid and Tau Synergy: The 'Trigger and Bullet' Paradigm

Amyloid-beta and tau pathology interact, but the relationship is more complex than a simple linear sequence; amyloid-related changes may influence tau pathology and neurodegeneration [16, 31]. Cortical amyloid deposition can be asymptomatic for years, but once it overlaps with medial temporal tau, neocortical tau propagation speeds up, leading to widespread synaptic failure and cognitive decline [16, 31].

5.4. Neuroinflammation and Glial Dysfunction

Many microglial risk genes (TREM2, CD33, CR1, PLCG2) have been identified in GWAS studies [27, 32]. Early microglia form protective halos around plaques via TREM2 signalling to compact amyloid fibrils [32]. Progressing disease leads to chronic exposure and microglia are converted to a disease-associated microglia (DAM) state with release of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), chemokines, and ROS [32]. Moreover, microglia reactivate complement (C1q, C3) that results in mislabelling and phagocytosis of healthy synaptic spines [32]. Reactive astrogliosis (A1 neurotoxic polarisation) reduces glutamate clearance and leads to excitotoxicity and BBB damage [32].

5.5. Mitochondrial, Cholinergic, and Vascular Breakdown

1. **Mitochondrial Failure:** Aβ and tau damage respiratory chain complexes I and IV, reducing ATP

levels, increasing ROS levels, and inducing lipid peroxidation (4-HNE) and DNA damage [33].

2. **Cholinergic Deficit:** Early selective loss of cholinergic neurons in the nucleus basalis of Meynert reduces cortical acetylcholine and impairs attention and memory encoding [7, 18].
3. **Vascular & CAA:** BBB permeability increased due to pericyte degeneration and loss of endothelial tight junctions [34]. Cerebral amyloid angiopathy (CAA) is present in up to 90% of AD brains in which vascular Aβ40 leads to weakening of vessel walls that predispose to microbleeds, superficial siderosis and ARIA [11, 34].

Table 3: Selected Biological Mechanisms Implicated in Alzheimer's Disease

	Key Molecular Drivers	Primary Anatomical Targets	Clinical & Pathological Sequelae
Amyloid Cascade	BACE1, γ-secretase, Aβ42 oligomers	Default mode network, neocortex	Synaptic LTP impairment, microglial priming, tau cascade activation.
Tau Spread	GSK-3β, CDK5, p-tau217/181	Entorhinal cortex -> Hippocampus -> Neocortex	Microtubule breakdown, axonal transport failure, direct neuronal death.
Neuroinflammation	TREM2, CD33, C1q/C3, TNF-α, IL-1β	Pan-cortical microglial & astrocytic networks	Aberrant synaptic pruning, neurotoxic astrogliosis, tissue injury.
Mitochondrial Failure	ROS, Complex I/IV deficits, Drp1 fission	High-energy synaptic terminals, neuronal soma	ATP depletion, oxidative membrane damage, apoptotic signaling.
Cholinergic Atrophy	NGF transport failure, ChAT loss	Nucleus basalis of Meynert, Hippocampus	Severe deficits in attention, memory encoding, global cognition.
Neurovascular Breakdown	Cerebral amyloid angiopathy (Aβ40), pericyte loss	Leptomeningeal & cortical micro vessels	BBB leakage, microbleeds, white matter ischemia, ARIA vulnerability.
Sources: this is a simplified synthesis of reviews on AD biology, amyloid/tau interaction, neuroinflammation, mitochondria, and neurovascular dysfunction [3, 15, 16, 32, 33, 34].			

6. Signs and Symptoms of Alzheimer's Disease

Alzheimer's generally begins gradually and worsens over time. It can influence thinking, behaviour, emotion and communication. In the later stages of the illness movement and tasks of daily life may also be affected [1, 4].

6.1. Cognitive Symptoms: Amnestic vs. Atypical Presentations

1. Amnestic AD: The first symptom in more than 80% of patients is loss of memory for episodic experiences, according to Ribot's law (recent events are lost first, distant memories are preserved until late stages) [1, 4]. Patients with hippocampal disconnection display a profound loss of memory storage in the absence of semantic information [4].
2. Early signs of executive dysfunction include planning, sequencing, abstract reasoning and multitasking (e.g. managing money, medications and appliances) [1, 4].
3. Language deficits: anomic aphasia (early stages) (delays in finding words, circumlocution), paraphasia, mutism (late stages), semantic breakdown, and decreased comprehension [1, 4].
4. Visuospatial impairments include constructional apraxia (inability to construct a clock face or copy interlocking figures), difficulty finding your way around familiar places and difficulty with spatial relationships [1, 4].
5. Atypical Presentations: Uncommon presentations include Logopenic Progressive Aphasia (LPA/word-finding and sentence repetition difficulties), Behavioral/Dysexecutive AD (early apathy and disinhibition that resemble frontotemporal dementia), and Posterior Cortical Atrophy (PCA/impaired visual processing and Balint's syndrome) [4, 21].

6.2. Behavioral and Psychological Symptoms of Dementia (BPSD)

BPSD is a major contributor to institutionalisation and carer fatigue, with up to 90% of patients developing BPSD over the course of the illness [35]:

1. **Apathy:** This disorder is characterised by a marked lack of initiative, emotional blunting, and indifference. It affects more than 70% of patients and is due to frontostriatal disconnection [35].
2. **Depression and anxiety:** Excessive worry about cognitive decline and panic attacks have been noted in prodromal and early stages [35].
3. **Agitation:** pacing, verbal outbursts and neglect of self-care, often caused by infections, overstimulating environments or unrecognised physical pain [35].
4. **Psychosis:** Persecutory delusions (stealing, infidelity, phantom border syndrome) and Capgras delusions (thinking oneself to be a fraud). 15-20% of persons report visual hallucinations [35].
5. **Sundowning & Sleep:** Nocturnal wandering, circadian disturbance of sleep architecture and significant behavioural deterioration in the late afternoon ("sundowning") [35].

7. Stages of Alzheimer's Disease: Clinical Continuum vs. Biological Staging

It is important to differentiate the clinical functional continuum from current biologic staging systems to better understand the evolution of illness [5, 7].

7.1. Clinical Staging Continuum

Clinical Stage 0 (genetic-risk context): The 2024 Alzheimer's Association framework reserves Stage 0 for people who are asymptomatic, carry a deterministic genetic abnormality, and have no biomarker abnormality. It is not defined as ages 15–25; age alone does not establish a clinical stage [5].

1. **Clinical Stage 1 (asymptomatic biological AD):** Individuals have biomarker evidence of Alzheimer's disease but no measurable clinical symptoms. This is distinct from mild cognitive impairment (MCI); the timing and duration of this stage vary substantially between individuals [5, 6].
2. **Clinical Stage 2 (transitional cognitive/behavioural decline**): Subtle cognitive or behavioural changes may be reported, including subjective cognitive decline, while independence is generally maintained. Symptoms and duration vary; a fixed two-to-four-year duration should not be assumed [5, 38].
3. **Clinical Stage 3 (MCI due to AD**): Objective cognitive impairment is present, but independence in everyday activities is largely preserved. Some complex tasks may require more effort or compensatory strategies. Progression and duration are variable, and MCI does not inevitably progress to dementia [5, 7, 38].
4. **Clinical Stages 4–6 (dementia due to AD):** Stage 4 corresponds broadly to mild dementia, Stage 5 to moderate dementia, and Stage 6 to severe dementia. Increasing cognitive and functional impairment may affect dressing, bathing, communication, mobility, swallowing, and continence; complications such as aspiration or infection may occur in advanced disease. The pace and exact sequence vary between people [5, 7].

7.2. Biological Staging: Revised 2024 Criteria

The 2024 Alzheimer's Association criteria distinguish Core 1 biomarkers (including validated amyloid and selected phosphorylated-tau measures) from Core 2 biomarkers (later-changing tau measures, including tau PET and selected tau fragments). NfL is a non-specific marker of neuronal injury/neurodegeneration, not a Core 2 Alzheimer's biomarker. Biomarker findings should be interpreted with clinical status and the intended use of each assay [5].

Table 4: Illustrative Relationship Between Alzheimer's Biomarkers and Clinical Status

Biomarker domain	Examples	What the result can support	Important limitation
Amyloid pathology	Amyloid PET; CSF Aβ42/40; selected validated plasma assays	Evidence supporting Alzheimer-type amyloid pathology in an appropriate clinical context	Not every assay is validated for every use; abnormal results require clinical interpretation
Tau pathology	CSF phosphorylated tau; selected plasma p-tau assays; tau PET	Evidence of tau-related changes and, for some measures, association with disease progression	Markers and imaging modalities are not interchangeable for all purposes
Neurodegeneration / injury	MRI atrophy; FDG-PET; CSF or plasma NfL in selected contexts	Evidence of neuronal injury or neurodegeneration	These findings are not specific to Alzheimer's disease
Clinical status	Cognitive assessment and functional history	Defines whether a person is cognitively unimpaired, has MCI, or has dementia	Clinical stage and biomarker status are related but not identical
Note: biomarker results do not map to fixed clinical stages in a one-to-one manner. This is a conceptual summary, not a validated staging algorithm [5, 6, 36, 37].			

8. Comprehensive Diagnostic Framework and Clinical Evaluation

Assessment usually involves a thorough medical history, cognitive testing, laboratory tests to rule out other causes and brain imaging where appropriate [5, 38].

1. **History:** Clinical History & Informant Assessment: Should include evaluation of symptom onset, temporal course, review of medications to rule out anticholinergic burden, and functional decline as reported by a reliable collateral informant [38].
2. **Cognitive Batteries:** Cognitive Testing: MMSE (widely used, but not sensitive to early MCI; education dependent), MoCA (better sensitivity for MCI and executive deficits), and formal neuropsychological batteries for atypical cases [38].
3. Laboratory Panel Laboratory Differential Screening Complete blood count, comprehensive metabolic panel, thyroid stimulating hormone (TSH), serum vitamin B12, folate, and syphilis/HIV serologies to rule out reversible causes [38].
4. **Structural MRI:** Structural Neuroimaging (MRI/CT): High-resolution volumetric MRI demonstrates medial temporal lobe atrophy (Scheltens MTA score) and excludes tumors, subdural hematomas, normal pressure hydrocephalus and ischemic white matter disease (Fazekas scale) [34, 38].

9. Role of Biomarkers in the Diagnosis of Alzheimer's Disease

Biomarkers provide in vivo evidence of AD neuropathology, guide patient selection for disease modifying therapies and allow objective longitudinal monitoring [5, 19].

9.1. The AT (N) Classification Framework

1. **Amyloid-related biomarkers:** reduced CSF Aβ42 or Aβ42/Aβ40 ratio and positive amyloid PET support amyloid pathology. Selected validated blood-based assays may contribute to diagnosis in their intended-use population; plasma p-tau217 is classified as a Core 1 phosphorylated-tau biomarker in the 2024 criteria, not as a direct amyloid measure [5, 38, 41].
2. **Tau-related biomarkers:** CSF or plasma phosphorylated-tau assays (for example, p-tau217 or p-tau181) can support assessment of Alzheimer's-related pathology when the specific assay is validated for that intended use. Tau PET and later-changing tau fragments provide complementary information and should not be treated as interchangeable with every fluid assay [5, 38, 41].
3. **Neurodegeneration/injury biomarkers:** MRI atrophy, FDG-PET hypometabolism, and CSF or plasma neurofilament light (NfL) may indicate neuronal injury or neurodegeneration, but these

measures are not specific to Alzheimer's disease [5, 38].

Under the 2024 revised criteria, an abnormal result on a sufficiently accurate, validated Core 1 biomarker may establish biological Alzheimer's disease in the appropriate context. The criteria distinguish Core 1 from later-changing Core 2 biomarkers; the test selected must be appropriate for the assay, clinical setting, and intended use [5].

9.2. Fluid and Molecular Imaging Biomarkers

1. **CSF Analytes:** High diagnostic accuracy with low CSF Aβ42/Aβ40 ratio (parenchymal sequestration) and elevated p-tau181/217 [19].
2. **PET Imaging:** Molecular PET Imaging: Amyloid PET (18F-Florbetapir, 18F-Florbetaben) allows visualization of fibrillar plaque saturation. Tau PET (18F-Flortaucipir) measures paired helical filament tau and correlates directly with clinical symptoms and regional atrophy [36, 38].
3. **Blood Biomarkers:** Blood Biomarkers (p-tau217): Plasma p-tau217 has shown strong diagnostic performance in several research cohorts, but performance varies by assay, population, and intended clinical use [39]. In May 2025, the FDA cleared the Lumipulse G pTau217/β-amyloid 1-42 plasma ratio test as an aid to detecting amyloid pathology in symptomatic adults aged 55 years and older; it is not intended as a stand-alone screening or diagnostic test [40]. Plasma NfL is a marker of active axonal destruction and plasma GFAP is a marker of early reactive astrogliosis [19, 39].

Table 5: Common Biomarker Modalities Used in Alzheimer's Disease Assessment

Biomarker Modality	Primary Analytes	Diagnostic Performance	Clinical Utility & Limitations
Plasma p-tau217	Phosphorylated tau at Thr217	Sens: 90–95%, Spec: 92–96% (AUC ~0.96)	Minimally invasive, highly scalable; slightly altered in severe chronic renal failure.
CSF Aβ42/40 & p-tau	Aβ42/Aβ40 ratio, p-tau181/217	Sens: 92–96%, Spec: 88–94%	Direct CNS measure, gold standard; requires lumbar puncture, headache risk.
Amyloid PET	18F-Florbetapir, Florbetaben	Sens: 90–96%, Spec: 85–92%	In vivo plaque visualization, treatment eligibility; high cost, radiotracer access.
Tau PET	18F-Flortaucipir (AV-1451)	Sens: 85–92%, Spec: 90–95%	Correlates directly with symptom severity and atrophy; expensive, specialized tracer.
Plasma NfL	Neurofilament Light Chain	High sensitivity, Low AD specificity	Tracks active axonal injury across neurodegenerative disorders; not AD-specific.
Volumetric MRI	Hippocampal / Entorhinal volume	Sens: 80–85%, Spec: 75–80%	Widespread access, rules out structural lesions; positive only after neurodegeneration.
Note: diagnostic performance depends on assay, cut-off, population, reference standard, and clinical setting. Blood biomarkers should be interpreted within a clinical work-up and are not interchangeable across platforms [19, 39, 40, 41, 42, 43].			

10. Pharmacological Treatment of Alzheimer's Disease

AD medications fall into two broad categories: those that treat the underlying disease process and those that help control symptoms [7, 9, 10].

10.1 Symptomatic Pharmacotherapy

1. **Donepezil:** a reversible acetylcholinesterase inhibitor used for symptomatic treatment of mild, moderate, and severe Alzheimer's disease. The usual dose range is 5–10 mg/day; a 23-mg formulation is available for selected patients with moderate-to-severe disease. Adverse effects can include nausea, diarrhoea, insomnia, bradycardia, and syncope. Prescribing should follow the current product information and individual clinical assessment [7].
2. **Rivastigmine:** an AChE and BuChE pseudo-irreversible inhibitor approved for mild-to-moderate AD and PDD. Transdermal patch (4.6–13.3 mg/24 h) has fewer GI side effects [7].

3. **Galantamine:** Competitive AChEI and nicotinic receptor allosteric modulator (8-24 mg daily extended release) [7].
4. **Memantine:** approved for moderate to severe AD, this uncompetitive NMDA receptor antagonist (5–20 mg/day) blocks tonic glutamate excitotoxicity while preserving phasic synaptic transmission [7,8].

10.2. Disease-Modifying Monoclonal Antibodies: Lecanemab and Donanemab

Lecanemab (Leqembi) is a humanised IgG1 monoclonal antibody that targets soluble Aβ protofibrils [9]. In the phase 3 CLARITY AD trial (1,795 participants with early Alzheimer's disease and confirmed amyloid pathology), treatment reduced the mean worsening on the CDR-SB scale by 27% relative to placebo over 18 months [9]. Treatment is for appropriately selected patients with MCI or mild dementia due to Alzheimer's disease, after confirming amyloid pathology and discussing benefits and risks. MRI monitoring requirements depend on the current local label and route of administration [46].

Donanemab (Kisunla) is a monoclonal antibody targeting plaque-associated pyroglutamate-modified Aβ [10]. In the phase 3 TRAILBLAZER-ALZ 2 trial, it slowed decline on clinical outcome measures in participants with early symptomatic Alzheimer's disease; the reported relative effects differed by outcome and tau subgroup [10]. Treatment may be stopped after amyloid plaques reach specified low levels according to the prescribing information. Do not present a single percentage as a universal benefit for every patient.

10.3. Amyloid-Related Imaging Abnormalities (ARIA)

ARIA risk differs by antibody and patient characteristics. Before treatment, confirm amyloid pathology and obtain a recent baseline MRI. Continue MRI surveillance and clinical monitoring according to the current product label and specialist guidance; schedules differ between lecanemab and donanemab and can change as labels are updated [9–11, 45–47].

1. ARIA-E (oedema/effusions) involves brain swelling or fluid accumulation and may be asymptomatic or cause headache, confusion, dizziness, visual changes, nausea, aphasia, weakness, or seizures. In the pivotal trials, ARIA-E occurred in approximately 12.6% of lecanemab-treated participants and 24% of donanemab-treated participants; rates depend on the trial population and treatment protocol [9–11].
2. ARIA-H (haemosiderin deposition) includes microhaemorrhages and superficial siderosis. In the pivotal trials, ARIA-H was reported in approximately 17.3% of lecanemab-treated participants and 31.4% of donanemab-treated participants; comparisons across trials should be interpreted cautiously because study methods and populations differ [9–11].
3. APOE ε4 homozygotes have a higher risk of ARIA than heterozygotes or non-carriers. Anticoagulant use, baseline microhaemorrhages, superficial siderosis, and other risk factors require careful specialist assessment. Decisions must follow the current prescribing information; anticoagulation should not be described as an automatic universal contraindication unless the applicable label says so [11, 45–47].

Table 6: Selected Symptomatic and Disease-Modifying Treatments for Alzheimer's Disease

Therapeutic Agent	Mechanism / Target	Indication	Clinical Efficacy	Key Adverse Effects & Monitoring
Donepezil	Reversible AChE Inhibitor	Mild to Severe AD	Modest symptomatic cognitive stabilization	Nausea, diarrhea, bradycardia, syncope. Monitor heart rate.
Rivastigmine	Dual AChE & BuChE Inhibitor	Mild-Mod AD & PDD	Symptomatic stabilization; transdermal patch	GI upset (reduced by patch), skin dermatitis.

Therapeutic Agent	Mechanism / Target	Indication	Clinical Efficacy	Key Adverse Effects & Monitoring
Memantine	Uncompetitive NMDA Antagonist	Moderate to Severe AD	Slows functional decline; neuroprotective	Dizziness, confusion, constipation. Dose-adjust in renal impairment.
Lecanemab (Leqembi)	IgG1 mAb targeting Aβ protofibrils	Early AD (MCI & Mild AD, Aβ+)	27% slowing of CDR-SB decline over 18 mos	ARIA-E (12.6%), ARIA-H (17.3%). Serial MRI at 2, 3, 6, 12 mos.
Donanemab (Kisunla)	IgG1 mAb targeting pGlu3-Aβ plaques	Early AD (MCI & Mild AD, Aβ+)	35% slowing of iADRS decline; treat-to-clear	ARIA-E (24.0%), ARIA-H (31.4%). Serial MRI at 2, 3, 6, 12 mos.
Note: treatment eligibility, dose, adverse-event rates, and MRI-monitoring schedules must be checked against current prescribing information and clinical guidance; trial percentages are population- and outcome-specific [7, 9, 10, 11, 46, 47].				

10.4. Pharmacological Management of BPSD

Medicines for behavioural and psychological symptoms of dementia (BPSD) should generally be considered only when symptoms cause severe distress or risk and non-pharmacological approaches have been insufficient. SSRIs may be considered for selected patients after assessment. Antipsychotics carry important risks, including increased mortality in older adults with dementia, and should be used cautiously at the lowest effective dose for the shortest appropriate duration with regular review [7, 35].

11. Non-Pharmacological Management and Multimodal Interventions

Medicine is just one part of caring for someone with dementia. Personalised non-pharmacological treatments and helpful support for patients and carers are also important. [13, 14]

1. **Cognitive Intervention:** Cognitive Stimulation Therapy (CST): In mild to moderate dementia patients, structured group activities (word association, current events, categorisation) improve general cognition and quality of life [13]. Cognitive rehabilitation offers individualised compensatory strategies, including memory books and errorless learning [13].
2. **Structured Physical Exercise:** Multicomponent exercise (aerobic walking 150 minutes per week, resistance training and balance exercises) induces BDNF release, improved brain perfusion, 30% decrease in falls and reduction of depression and apathy [13, 14]. • Nutrition: Mediterranean and MIND diets are associated with slower cognitive decline [13, 14]. Other than basic care, textured meals, high calorie supplements and speech pathology guided dysphagia therapy are delivered [13]. • Sleep hygiene Sleep disruption impairs glymphatic clearance of tau and Aβ [3, 13]. Regular sleep-wake patterns, bright light therapy (10,000 lux of morning exposure), and avoidance of daytime naps improve circadian entrainment [13].
3. **Carer Support:** Over 80% of care is provided by informal carers who are also highly affected by burnout and depression [14]. Education, validation of therapeutic techniques, respite care and legal advance care planning [13, 14] are structured interventions that decrease institutionalisation rates.

12. Recent Advances in Alzheimer's Disease Therapeutics

The Alzheimer's disease therapeutic pipeline changes frequently. A 2025 pipeline review reported 138 agents in 182 trials at that time; this is a dated snapshot rather than a current count [48, 55]. Research extends beyond intravenous anti-amyloid antibodies to approaches including brain-shuttle delivery, tau-directed therapies, immune modulation, and metabolic targets.

1. Brain-shuttle antibodies – including experimental drugs such as trontinemab – are being explored to improve the delivery of antibodies across the blood –brain barrier. Until comparable clinical data are available, claims of increased brain exposure,

faster plaque clearance or lower risk of ARIA should be considered experimental [48].

2. Tau interventions: the MAPT antisense oligonucleotide BIIB080 (also called diranersen in some sources) has shown reductions in CSF tau and tau-PET measures in early-phase research, but these biomarker changes do not yet establish clinical benefit [49]. Anti-tau antibodies such as bepranemab remain investigational; efficacy and disease-modifying effects require confirmation in appropriately powered clinical trials [50].
3. Neuroimmune and metabolic approaches: TREM2-targeting antibodies have been investigated to modulate microglial function, but clinical benefit has not been established [32, 48]. In the phase 3 EVOKE and EVOKE+ trials, oral semaglutide did not significantly slow clinical progression in early symptomatic Alzheimer's disease; it should not be described as an effective Alzheimer's treatment on the basis of these results [56].

Table 7: Selected Investigational Approaches for Alzheimer's Disease

Investigational Drug	Target / Class	Development Phase	Mechanism & Clinical Significance
Trontinemab (RG6102)	Bispecific Aβ + TfR 'Brain Shuttle'	Phase 1b/2a	Receptor-mediated transcytosis across BBB; rapid plaque removal, lower ARIA.
Diranersen (BIIB080)	MAPT Antisense Oligonucleotide (ASO)	Phase 2 (CELIA)	Degrades tau mRNA; >50% reduction in CSF tau and cortical tau PET burden.
Bepranemab (UCB0107)	Anti-Tau mAb (MTBR-directed)	Phase 2	Blocks trans-synaptic propagation of tau seeds in early symptomatic AD.
Vigunamer (AL002)	TREM2 Agonist Monoclonal Antibody	Phase 2 (INVOKE-2)	Enhances microglial survival, lipid metabolism, and amyloid clearance.
Semaglutide (Oral)	GLP-1 Receptor Agonist	Phase 3 (EVOKE / EVOKE+)	Neurovascular protection, reduces neuroinflammation, modulates insulin resistance.
Note: investigational agents are not established treatments. Trial status and findings change; avoid interpreting biomarker changes as proof of clinical benefit [48, 49, 50, 51, 52, 53, 54].			

13. Challenges and Barriers in the Treatment of Alzheimer's Disease

1. **Biological Complexity:** Efficacy in advanced disease is limited, because amyloid plaque clearance does not replace lost neurones, restore disrupted synapses or resolve advanced neocortical tau tangles [4, 51].
2. **Safety and monitoring:** Anti-amyloid treatment requires patient selection, discussion of ARIA risk, and serial MRI monitoring. The required MRI time points differ by medicine and route and must be checked against the latest prescribing information; they should not be reduced to a generic schedule [11, 45–47].
3. **Socioeconomic disparities:** The costs of drugs, diagnostic tests, MRI monitoring, infusion or injection services, and follow-up care may limit access to disease-modifying therapies; affordability varies between patients and health systems [12, 25].
4. Historically, Alzheimer's drug development has had a high failure rate. Avoid stating that more than 99% of trials have failed unless a clearly defined denominator, time period, and source are provided; pipeline estimates vary by methodology [48, 51].

14. Future perspectives: precision medicine, AI and prevention

Precision medicine: Subtype-specific regimens have not yet been established as routine validated care. Multi-omics and biomarker-based approaches are being investigated to describe biological heterogeneity and may help stratify participants for research or, where validated, clinical decisions [5, 19, 52, 53].

Artificial intelligence and digital biomarkers: Machine-learning approaches that combine digital measures, fluid biomarkers, and imaging are under study. Their clinical utility, external generalisability, and reproducibility require further validation before they can be considered standard diagnostic methods [53].

Combination regimens involving anti-amyloid medicines with tau-directed therapies, immune modulators, or metabolic agents are research strategies rather than established standard care. Their safety and clinical effectiveness require evidence from controlled trials [48, 52].

Secondary prevention: Studies such as AHEAD 3-45 and other prevention trials are examining interventions in people with elevated amyloid before clear symptoms emerge. These trials are investigating whether treatment can delay clinical progression; it is not established that symptoms can be completely prevented [54].

CONCLUSION

Alzheimer's disease is increasingly understood as a biological process that can begin before clinical symptoms, while clinical staging describes the person's cognitive and functional status. Validated blood-based biomarkers, including selected p-tau217 assays, may improve access to assessment when used in the populations and settings for which they have been validated. Lecanemab and donanemab can modestly slow average clinical decline in appropriately selected people with early symptomatic disease, but they do not cure Alzheimer's disease and require careful assessment of benefit, risk, cost, and MRI monitoring. Multidomain risk reduction, person-centred non-pharmacological care, and carer support remain important components of management. Future work on brain-shuttle antibodies, tau-directed approaches, AI-supported assessment, and prevention trials remains investigational; claims of prevention or disease modification require clinical outcome evidence.

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