

Alzheimer's Disease: Current Insights into Risk Factors, Molecular Pathophysiology, Diagnosis, Biomarkers, and Therapeutic Strategies

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ABSTRACT

Alzheimer's disease is the most common cause of dementia and a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and functional disability. In view to increasing their global prevalence, substantial socioeconomic burden, and lack of curative treatment, Alzheimer's disease remains a major public health challenge. This review provides a comprehensive overview of the epidemiology, risk factors, pathophysiology, diagnosis, biomarkers, and current therapeutic strategies for Alzheimer's disease. The disease is influenced by complex

interactions among genetic, environmental, vascular, metabolic, and lifestyle-related factors. Major genetic determinants include mutations in APP, PSEN1, and PSEN2, as well as the APOE ϵ 4 allele, while aging remains the strongest non-modifiable risk factor. The pathogenesis of Alzheimer's disease involves amyloid- β accumulation, tau hyperphosphorylation, neurofibrillary tangle formation, synaptic dysfunction, neuroinflammation, oxidative stress, mitochondrial impairment, defective autophagy, blood-brain barrier disruption, and progressive neuronal loss. Advances in diagnosis now integrate clinical and cognitive assessments with neuroimaging and fluid biomarkers, including cerebrospinal fluid, blood, urine, and genetic markers, enabling earlier and more accurate detection. Current management combines symptomatic therapies, including acetylcholinesterase inhibitors and NMDA receptor antagonists, with non-pharmacological interventions such as lifestyle modification, physical activity, dietary optimization, and cognitive training. Recent disease-modifying therapies, particularly anti-amyloid monoclonal antibodies such as lecanemab and donanemab, have demonstrated promising clinical benefits in slowing disease progression. Emerging therapeutic approaches targeting mitochondrial dysfunction, insulin signaling, oxidative stress, autophagy, neuroinflammation, and metabolic pathways may further improve treatment outcomes. Continued research into disease mechanisms, biomarker discovery, and precision medicine is essential for developing more effective diagnostic tools and personalized therapeutic strategies for Alzheimer's disease.

Keywords: Cognitive Decline, Synaptic Dysfunction, Defective Autophagy, Insulin Signaling, Amyloid- β , APOE ϵ 4 Allele

Introduction

Alzheimer's disease (AD) is the most common cause of dementia and accounts for approximately 60–80% of all dementia cases worldwide [1–3]. First described by Alois Alzheimer and later named by Kraepelin in 1910, Alzheimer's disease is now recognized as a heterogeneous clinical syndrome with multiple pathological subtypes rather than a single disease entity [4–6]. The disease progresses gradually, causing progressive neuronal loss that leads to cognitive impairment, memory decline, and functional disability [7]. The pathological hallmarks of Alzheimer's disease include extracellular deposition of β -amyloid ($A\beta$) plaques, intracellular accumulation of hyperphosphorylated tau protein forming neurofibrillary tangles (NFTs), and cerebral amyloid angiopathy (CAA), in which amyloid accumulates within cerebral blood vessels [8, 9]. According to the revised National Institute on Aging–Alzheimer's Association (NIA-AA) ABC criteria, these pathological changes are associated with neuronal loss, cerebral atrophy, gliosis, dystrophic neurites, and synaptic degeneration [8–13]. The coexistence of senile plaques containing $A\beta$ 40 and $A\beta$ 42 peptides and tau-positive NFTs remains the defining neuropathological feature of Alzheimer's disease [10–13].

Epidemiology of Alzheimer's disease

The global number of people living with dementia is projected to increase from 57.4 million in 2019 to 152.8 million by 2050 [14]. Dementia has become one of the

leading causes of death worldwide and is expected to rank among the top two causes by 2040 [15]. The economic burden is projected to reach USD 2.54 trillion by 2030 and USD 9.12 trillion by 2050 [16]. Despite advances in diagnosis and management, Alzheimer's disease remains incurable, and its mortality burden is expected to more than double over the next two decades [17, 18].

Etiology and Risk Factors of Alzheimer's disease

Alzheimer's disease is a multifactorial disorder influenced by genetic, environmental, and vascular factors. Its characteristic pathological features include β -amyloid ($A\beta$) senile plaques and tau-containing neurofibrillary tangles [19, 20]. Advancing age is the strongest risk factor, while sex, ethnicity, socioeconomic status, and cardiovascular health also influence disease risk [21, 22]. Recent evidence has identified more than 60 environmental risk factors, including air pollution, heavy metals, occupational exposures, and trace elements, that may contribute to Alzheimer's disease development [23]. In addition, vascular aging and blood–brain barrier dysfunction play important roles in disease pathogenesis by promoting neurodegeneration and impaired brain homeostasis [24, 25] (Figure 1).

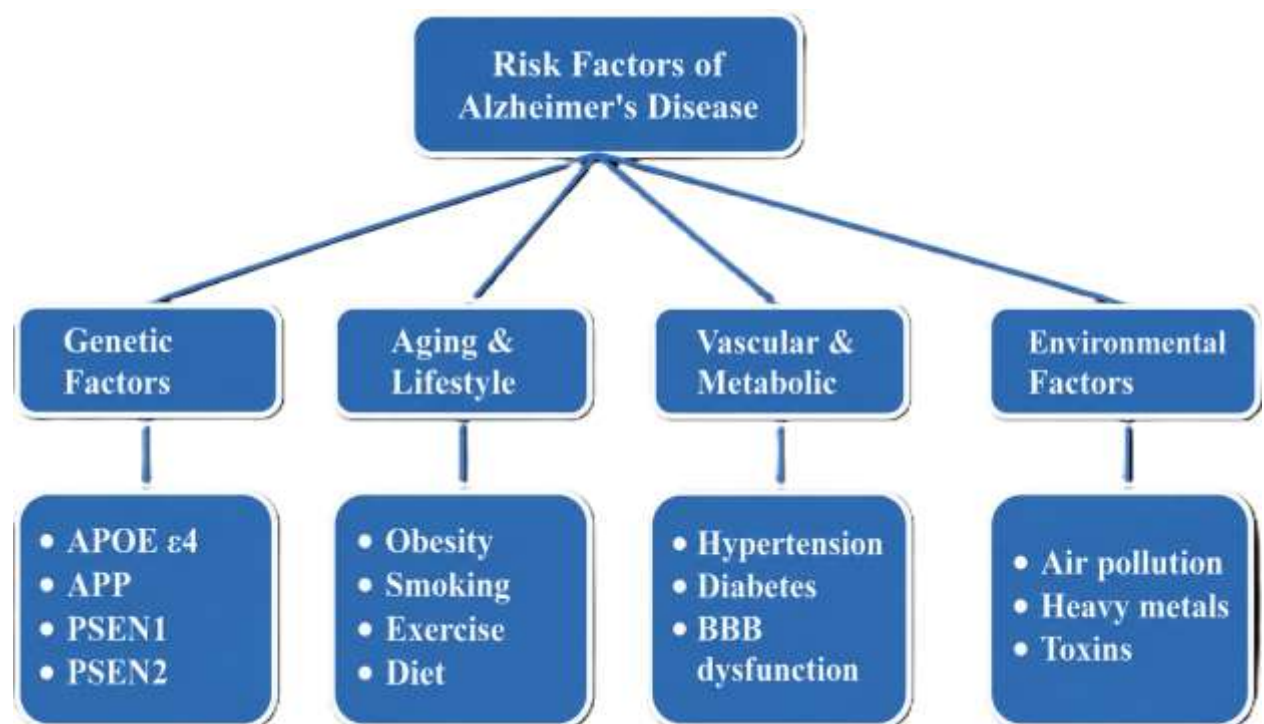


Figure 1. Risk factors associated with Alzheimer's disease

Early-Onset Alzheimer's Disease (EOAD)

EOAD differs from late-onset Alzheimer's disease (LOAD) by its strong genetic basis. Approximately 10–15% of familial EOAD cases follow an autosomal dominant inheritance pattern, and 35–60% of patients have an affected first-degree relative [26]. The major causative genes are APP, PSEN1, and PSEN2, which alter amyloid precursor protein processing and increase β -amyloid ($A\beta$) production, leading to

disease onset typically between 30 and 50 years of age [27,28]. Additional susceptibility genes, including SORLA, ABCA7, TREM2, PLD3, PSD2, TCIRG1, RIN3, RUFY1, GRN, MAPT, and C9ORF72, contribute to pathways involving lipid metabolism, immune regulation, and endolysosomal transport [29, 30]. Incorporating these variants into polygenic risk scores has improved EOAD risk prediction, with reported accuracies of 72.9–75.5% [31].

Late-Onset Alzheimer's Disease (LOAD)

Genetic Risk Factors: Unlike EOAD, LOAD is not caused by a single dominant mutation but results from the combined effects of multiple genetic variants. The APOE ϵ 4 allele is the strongest genetic risk factor; carrying one allele increases AD risk, whereas two alleles confer a greater risk, although many carriers never develop the disease [32]. Genome-wide association studies (GWAS) have also identified susceptibility genes including CLU, CR1, PICALM, BIN1, CD2AP, PLD3, and TREM2, which contribute to immune regulation, lipid metabolism, and amyloid clearance but are not independently causative [33, 34].

Environmental and Lifestyle Risk Factors in Alzheimer's disease

Environmental and lifestyle factors significantly influence Alzheimer's disease risk. According to the Scaffolding Theory of Aging and Cognition (STAC), compensatory brain mechanisms may help preserve cognitive function despite age-related brain changes [35]. Increased brain activation in cognitively healthy older adults may reduce AD susceptibility [36]. Environmental exposures, including air pollution, heavy metals, occupational toxins, and trace elements, have been associated with increased AD risk [37]. Although aluminum exposure and obesity have been proposed as contributing factors, their roles remain controversial [38–41].

Non-Genetic Risk Factors

Early-Onset Alzheimer's Disease: Although EOAD is predominantly genetic, traumatic brain injury and other environmental factors may accelerate neurodegeneration, particularly in individuals carrying pathogenic mutations [42–44].

Late-Onset Alzheimer's Disease: Several modifiable cardiovascular and lifestyle factors increase the risk of LOAD.

Hypertension: Chronic hypertension contributes to cerebrovascular damage and increases the risk of Alzheimer's disease by promoting vascular pathology [45].

Diabetes Mellitus: Type 2 diabetes mellitus increases LOAD risk through insulin resistance, impaired glucose metabolism, and neuronal dysfunction [46].

Smoking: Smoking promotes oxidative stress and chronic inflammation, accelerating neurodegeneration and increasing Alzheimer's disease risk [47].

Additional Contributing Factors

Epigenetic Factors: Epigenetic regulation plays an important role in Alzheimer's disease. Non-coding RNAs, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs, and piRNAs, regulate gene expression, chromatin remodeling, mRNA stability, and other cellular processes involved in AD pathogenesis [48].

MicroRNAs as Emerging Biomarkers: MicroRNAs and lncRNAs are promising biomarkers for Alzheimer's disease diagnosis and progression. Increased expression of miR-455-3p enhances neuronal survival by reducing amyloid precursor protein (APP) expression, improving mitochondrial function, and promoting synaptic gene expression, highlighting its potential therapeutic and diagnostic value [49].

Classification of Alzheimer's disease

Alzheimer's disease is broadly classified according to the age at symptom onset into early-onset Alzheimer's disease (EOAD) and late-onset Alzheimer's disease (LOAD).

Early-Onset Alzheimer's Disease (EOAD): EOAD develops before 65 years of age and accounts for approximately 5–10% of AD cases. It is highly heritable (92–100%) and is commonly associated with mutations in APP, PSEN1, and PSEN2. Compared with LOAD, EOAD exhibits distinct clinical and biological characteristics, leading some researchers to consider it a separate AD subtype [50–53].

Late-Onset Alzheimer's Disease (LOAD): LOAD, occurring after 65 years of age, represents about 90–95% of AD cases. It typically begins with episodic memory impairment followed by progressive cognitive decline. Its heritability is estimated at 60–80%, and unlike EOAD, it rarely follows an autosomal dominant inheritance pattern [50].

Clinical Classification: The 2011 National Institute on Aging–Alzheimer's Association (NIA-AA) guidelines classify AD into preclinical Alzheimer's disease, mild cognitive impairment (MCI) due to AD, and Alzheimer's dementia [54–56]. The NIA-AA AT(N) framework further categorizes disease using biomarkers of amyloid deposition (A), tau pathology (T), and neurodegeneration (N) to improve biological diagnosis and disease staging [57].

Pathophysiology of Alzheimer's disease

Alzheimer's disease is a multifactorial neurodegenerative disorder characterized primarily by β -amyloid ($A\beta$) accumulation and tau hyperphosphorylation, which initiate neuronal dysfunction and progressive neurodegeneration [58–60]. The amyloid cascade hypothesis proposes that $A\beta$ accumulation triggers neuroinflammation, oxidative stress, synaptic dysfunction, tau pathology, and neuronal death [59, 61]. Pathological changes may begin 15–25 years before clinical symptoms appear, progressing from mild cognitive impairment to dementia [62–64]. The defining pathological hallmarks are extracellular $A\beta$ plaques, mainly composed of $A\beta_{42}$ and $A\beta_{40}$, and intracellular neurofibrillary tangles (NFTs) formed by hyperphosphorylated tau protein [65–67].

Amyloid- β ($A\beta$) Pathology

$A\beta$ Deposition and Plaque Formation: $A\beta$ deposition begins years before symptom onset. Impaired $A\beta$ production and clearance result in extracellular accumulation of $A\beta_{42}$ and $A\beta_{40}$, leading to amyloid plaque formation, a hallmark of Alzheimer's disease [68, 69].

Processing of APP and Secretase Activity: Amyloid precursor protein (APP) is processed by α -, β -, and γ -secretases. The amyloidogenic pathway involves BACE1

(β -secretase) and the γ -secretase complex, containing PSEN1 and PSEN2, producing aggregation-prone A β peptides, particularly A β 42 [70–72].

Genetic Factors Contributing to A β Accumulation: Mutations in APP, PSEN1, PSEN2, and the APOE ϵ 4 allele promote abnormal APP processing and increase A β accumulation. Excess A β also activates apoptotic pathways, further enhancing amyloid production [72–74].

Neurotoxicity of A β Peptides: Among A β isoforms, A β 42 is the most aggregation-prone and neurotoxic. It induces oxidative stress, calcium imbalance, synaptic dysfunction, and neuronal degeneration [75–77].

Neuroinflammation Induced by A β : Amyloid plaques activate microglia, triggering the release of inflammatory cytokines that promote chronic neuroinflammation, neuronal injury, and cell death [78].

Neurofibrillary Degeneration and Tau Pathology

Tau is a microtubule-associated protein essential for neuronal stability. In AD, abnormal activation of kinases including CDK5 and GSK-3 β causes tau hyperphosphorylation, resulting in microtubule disruption and formation of intracellular neurofibrillary tangles (NFTs) [79–82]. A β further enhances tau pathology through activation of CDK5, GSK-3 β , and impaired TREM2-mediated microglial clearance [83, 84]. Tau aggregation disrupts axonal transport, synaptic function, neurotrophic signaling, and neuronal survival, ultimately leading to cognitive decline and neurodegeneration [85, 86]. Consequently, therapeutic strategies targeting tau stabilization, kinase inhibition, and post-translational modifications are being actively investigated [87, 88].

Synaptic Dysfunction in Alzheimer's disease

Synaptic dysfunction is a major contributor to cognitive decline in Alzheimer's disease (AD). The combined effects of amyloid- β (A β) and tau pathology impair synaptic plasticity, leading to progressive synapse loss that strongly correlates with cognitive impairment [89, 90]. A β oligomers disrupt intracellular calcium homeostasis, causing proteasomal dysfunction and impaired synaptic signaling, whereas hyperphosphorylated tau interferes with axonal transport and synaptic protein function [91–93]. These abnormalities particularly affect glutamatergic and cholinergic neurotransmission. NMDA receptor dysfunction and disruption of the glutamate–glutamine cycle promote excitotoxicity, while cholinergic deficits reduce acetylcholine levels, impair blood–brain barrier (BBB) integrity, decrease A β clearance, and facilitate A β aggregation [94–96].

Oxidative Stress and Mitochondrial Dysfunctions in Alzheimer's disease

Oxidative stress is a central mechanism in AD pathogenesis. Excessive production of reactive oxygen species (ROS) combined with impaired antioxidant defenses damages neuronal lipids, proteins, and DNA, leading to neurodegeneration. Mitochondrial dysfunction further enhances oxidative stress by impairing energy metabolism and mitochondrial dynamics. ROS also promote abnormal APP processing, tau hyperphosphorylation, and A β aggregation, accelerating neuronal injury and disease progression [97, 98].

Impaired Autophagy and Protein Homeostasis

Autophagy maintains neuronal homeostasis by degrading damaged organelles and misfolded proteins. In AD, impaired autophagy disrupts protein homeostasis, resulting in the accumulation of A β peptides, hyperphosphorylated tau, and dysfunctional mitochondria. Defects in autophagic proteins, vesicle trafficking, and lysosomal function contribute to progressive neurodegeneration [99, 100].

Contribution of Peripheral Immune Cells to Neuroinflammation

Peripheral immune cells significantly contribute to AD-associated neuroinflammation. Neutrophils infiltrate the brain through the BBB, reduce cerebral blood flow, form neutrophil extracellular traps (NETs), and release inflammatory cytokines [101]. T lymphocytes regulate glial activation and neuroinflammatory responses [102]. B lymphocytes modulate immune signaling through cytokine and antibody production, while natural killer (NK) cells interact with microglia and amplify inflammatory responses, thereby promoting disease progression [103–107].

Blood–Brain Barrier Dysfunction in Alzheimer’s disease

Blood–brain barrier (BBB) dysfunction is a characteristic feature of Alzheimer's disease. Human autopsy studies have demonstrated capillary leakage, loss of tight junctions, degeneration of endothelial cells and pericytes, infiltration of plasma proteins, and red blood cell extravasation, indicating impaired BBB integrity [108]. Although aging alone can compromise the BBB, cognitive decline generally requires concurrent neuroinflammation [109]. BBB disruption is associated with Alzheimer's disease, vascular cognitive impairment, and dementia [110, 111]. Multiple factors, including APOE ϵ 4, inflammation, oxidative stress, reactive oxygen species (ROS), A β accumulation, gut dysbiosis, sex, and other comorbidities, contribute to BBB breakdown and disease progression [112–114].

Genetic Mechanisms Involved in Alzheimer’s disease

The APOE ϵ 4 allele is the strongest genetic risk factor for late-onset Alzheimer's disease (LOAD), conferring a dose-dependent increase in disease risk [115]. Apolipoprotein E, primarily produced by astrocytes, regulates lipid transport and cholesterol metabolism in the brain [116]. The APOE ϵ 4 isoform promotes AD through impaired A β clearance, enhanced amyloid deposition, abnormal lipid metabolism, tau hyperphosphorylation, and defective astrocyte- and microglia-mediated neuronal homeostasis [117–120]. APOE4-induced lipid dysregulation causes cholesterol accumulation, impaired fatty acid metabolism, and lipid droplet formation in microglia, creating a neurotoxic environment that accelerates neuronal degeneration [121–123].

Cholinergic and Glutamatergic Dysfunction in Alzheimer’s disease

Cholinergic and glutamatergic dysfunction are major contributors to cognitive decline in Alzheimer's disease [124,125]. Impaired signaling through ionotropic and metabotropic receptors disrupts neuronal communication, leading to deficits in learning and memory [126, 127]. Progressive degeneration of cholinergic neurons reduces acetylcholine availability, contributing to cognitive and behavioral

impairment [128–131]. Cholinergic dysfunction has also been associated with disruption of the default mode network, further aggravating cognitive deficits in AD [132].

Diagnosis of Alzheimer's disease

Early and accurate diagnosis of Alzheimer's disease is essential for timely intervention and disease management. Diagnosis combines clinical evaluation, cognitive testing, neuroimaging, and biomarker assessment to distinguish AD from other causes of cognitive impairment.

Clinical Assessment: Clinical assessment is the first step in diagnosing Alzheimer's disease and aims to exclude reversible causes of cognitive impairment, including depression, vitamin deficiencies, endocrine disorders, and electrolyte imbalances [133]. A detailed medical and family history should be obtained to identify genetic and environmental risk factors, particularly a history of dementia among first-degree relatives [134, 135]. Clinical evaluation also helps predict disease progression from mild cognitive impairment (MCI) to Alzheimer's dementia. Early impairment of episodic memory, especially reduced ability to learn and retain new information, is the most characteristic clinical feature. Assessment of episodic memory, together with executive function and attention, provides valuable information for predicting disease progression [136, 137] (Figure 2).

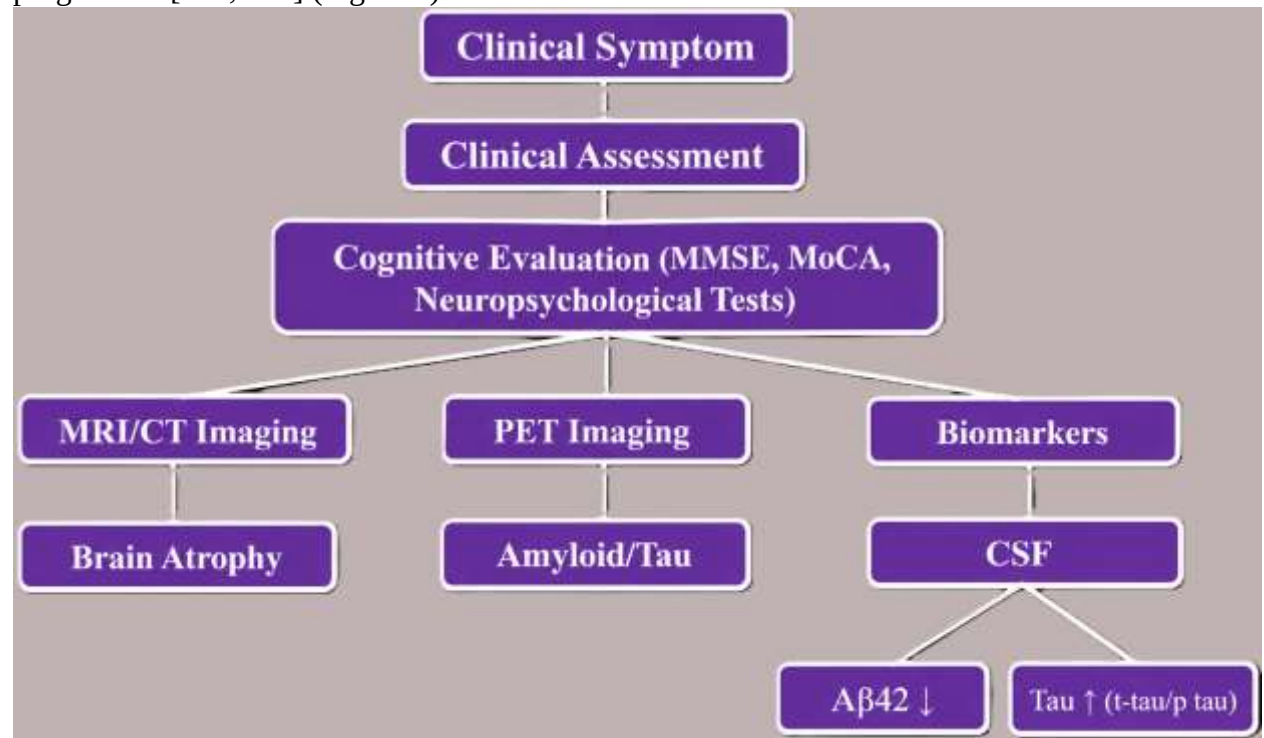


Figure 2: Diagnostic assessment pathway for Alzheimer's disease. The figure illustrates the major steps involved in AD diagnosis, including clinical evaluation, cognitive testing, neuroimaging, and biomarker analysis. MRI/CT identifies brain atrophy, PET detects amyloid and tau deposition, while CSF biomarkers show

decreased A β 42 and increased tau levels associated with AD pathology.

Cognitive Assessment: A two-step diagnostic approach is commonly used for Alzheimer's disease. The first stage involves cognitive screening by non-specialists to identify patients requiring specialist evaluation [138]. Cognitive function, behavior, and daily functioning are assessed using standardized clinical tests [139–150]. The Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) are the most widely used screening tools [139, 152]. While MMSE effectively assesses general cognitive impairment, it has limited sensitivity for executive dysfunction. In contrast, MoCA is more sensitive for detecting early Alzheimer's disease and mild cognitive impairment by evaluating memory, executive function, visuospatial ability, language, and orientation. Both assessments require approximately 10 minutes to complete [139, 152, 153].

Neuroimaging: Neuroimaging is essential for diagnosing Alzheimer's disease and monitoring disease progression by identifying structural and molecular brain changes [154–156]. MRI and CT detect cerebral atrophy and distinguish AD-related neurodegeneration from normal aging, with MRI providing greater sensitivity for early-stage disease [157–159]. Positron emission tomography (PET) enables visualization of amyloid plaques, neurofibrillary tangles, activated microglia, and astrocytes using specific radiotracers [160,161]. Amyloid PET tracers, including florbetapir, flutemetamol, florbetaben, and 11C-PIB, detect cortical A β deposition and improve the early diagnosis of Alzheimer's disease [160–162].

Plasma Biomarkers: Blood-based biomarkers have emerged as promising, minimally invasive tools for Alzheimer's disease diagnosis. Increased plasma levels of α 2-macroglobulin (α 2M), complement factor H (CFH), α 1-antitrypsin, and α 1-antichymotrypsin, together with reduced apolipoprotein A1, have been associated with AD pathology [163–169]. Plasma amyloid- β (A β), commonly measured by enzyme-linked immunosorbent assay (ELISA), remains the most extensively investigated biomarker, although findings have been inconsistent [170, 171]. Inflammatory and signaling proteins are also being explored for predicting disease progression in individuals with mild cognitive impairment [172].

Neuropsychiatric Evaluation: Neuropsychiatric assessment helps evaluate behavioral and psychological symptoms associated with Alzheimer's disease. The Geriatric Depression Scale (GDS) assesses depression and mood disturbances, whereas the Neuropsychiatric Inventory Questionnaire (NPI-Q) evaluates symptoms such as apathy, depression, irritability, agitation, and disinhibition [173]. Both instruments are reliable, easy to administer, and typically require only 5–10 minutes to complete [173, 174].

Cerebrospinal Fluid (CSF) Biomarkers: Cerebrospinal fluid (CSF), obtained by lumbar puncture, is a valuable source of biomarkers for Alzheimer's disease diagnosis [175]. The characteristic CSF profile includes decreased A β 42 and increased total tau (t-tau) and phosphorylated tau (p-tau), reflecting amyloid deposition and neuronal degeneration [176–179]. Although APP has been investigated as a diagnostic marker, its clinical utility remains inconsistent [177]. Measurement of t-tau and p-tau by ELISA provides high diagnostic accuracy, particularly when combined with reduced A β 42 levels [178, 179]. A β oligomers, detected in blood and CSF using highly sensitive methods such as oligomer-specific antibodies and nanoparticle-based assays,

represent additional promising biomarkers for early Alzheimer's disease diagnosis [180–182].

Urine Assessment as a Biomarker: Urine biomarkers offer a non-invasive alternative to CSF and plasma biomarker approaches. Levels of NTPs in urine have been widely studied as potential AD biomarkers [183,184]. Urine samples are easier to collect and more convenient compared to CSF or blood samples; therefore, they may be a promising tool for diagnosing AD [185].

Genetic Biomarkers: There are about 75 genetic risk loci that increase the susceptibility to Alzheimer's disease; the vast majority of cases belong to sporadic or late-onset form. Among all these genetic markers, the Apolipoprotein E (APOE) $\epsilon 4$ allele can be called the most significant one – it is the best studied genetic risk factor for AD. Over the past three decades, there have been thousands of scientific papers studying the role of APOE alleles in the development of AD [186]. APOE genotyping is an important tool for clinical research and therapeutic trials since it affects the assessment of disease risk, the prognosis and the treatment strategy. APOE genotypes affect patients' response to amyloid monoclonal antibodies, such as lecanemab, donanemab, and aducanumab. The discovery of the disease pathways associated with APOE4 has helped create drugs aimed at treating APOE-associated conditions [187, 188].

Therapeutic Approaches for Alzheimer's disease

The management of early-stage Alzheimer's disease involves both pharmacological and non-pharmacological approaches. Healthcare practitioners are expected to keep track of early-stage Alzheimer's patients' progress on a regular basis through follow-ups conducted every 6 to 12 months. More follow-ups can be organized when needed if symptoms become more severe.

Role of the Clinician after Diagnosis: In case of early-stage Alzheimer's disease diagnosis, the clinician has a critical role of discussing treatment options and management strategies, as well as providing support to patients, their families and caregivers. Patients and caregivers may also be referred to social service agencies and introduced to credible information sources, local research and clinical trial opportunities [189].

Non-Pharmacological Treatments: The use of non-pharmacological interventions like lifestyle modification, diet, and exercise in patients with early Alzheimer's disease may help maintain and possibly improve cognitive and functional capabilities. There are some dietary regimes that include green leafy vegetables, seafood, nuts, and berries which have proved to be helpful along with exercise and cognitive exercises that may improve cognitive functions in patients with early Alzheimer's disease. Those are safe, cheap, and improve the quality of life of people. However, compliance with those strategies needs to be monitored. Multimodal intervention like cognitive stimulation therapy may yield better results when added to pharmacological treatments [190, 191].

Pharmacological Treatments: There are several pharmacological drugs available for use in the treatment of mild to severe cases of Alzheimer's dementia disease. The common symptomatic drugs available include acetylcholinesterase inhibitors such as donepezil, rivastigmine, and galantamine. These drugs increase the levels of

acetylcholine by preventing its degradation. There is another drug named memantine which acts as NMDA antagonist and is used to treat moderate to severe cases of Alzheimer's dementia. Donepezil, rivastigmine, and galantamine offer benefits in cognition and performance of everyday life activities in patients of mild to moderate AD dementia [192-196] (Table 1).

Table 1. shows the current and emerging therapeutic agents for Alzheimer's disease, along with their molecular targets and reported therapeutic effects

Drug	Target	Effects	Reference
Intranasal insulin	Insulin receptor (IR) → Insulin receptor substrate (IRS) → AKT signaling pathway	Increases cerebral insulin levels; activates IRS/AKT signaling pathway; enhances neuroprotection, improves synaptic plasticity and cognitive function	197
GLP-1 receptor agonists (liraglutide/exenatide)	GLP-1 receptor (GLP-1R); PKA pathway; AMPK phosphorylation	Neuroregulatory and neuroprotective effects; GLP-1R activation; however, no substantial impact on A β , tau or short-term cognition in RCTs	198
Metformin	AMPK/mTOR/S6K/BACE1 signaling pathway	Improves insulin sensitivity; crosses BBB; improves cognition in experimental models; regulates AMPK/mTOR/S6K/BACE1 pathway; long-term use associated with vitamin B12 deficiency and increased AD risk	199
MitoQ	Mitochondria (mitochondrial ROS; lipid peroxidation)	Reduces ROS, decreases A β levels, reduces synaptic loss and astrogliosis, preserves cognitive function	200
SkQ1	Mitochondria (mitochondrial oxidative stress and	Improves mitochondrial function, reduces oxidative	201,202

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	mitochondrial function)	stress, inhibits progression of retinopathy; undergoing clinical evaluation for ocular disorders	
SS-31 (elamipretide)	Cardiolipin (CL) in the inner mitochondrial membrane	Promotes mitochondrial biogenesis, protects against A β -induced aggregation, preserves mitochondrial membrane integrity and respiratory activity; limited effect on BBB permeability and vascular remodeling	203,204
PGC-1 α	PGC-1 α regulated by SIRT1 and AMPK; TFAM	Regulates mitochondrial biogenesis, glucose transport, fatty acid oxidation and energy metabolism; reduced expression in AD	205
Exercise mimetics	AMPK and PGC-1 α signaling pathways	Activate AMPK/PGC-1 α pathways; reduce neuroinflammation and oxidative stress; promote neurogenesis, synaptic plasticity and neurotrophic factors; reduce A β plaques and tau tangles	206
NAD ⁺ boosters (NR, NMN, NAM)	NAD ⁺ metabolism; Sirtuin-mediated mitochondrial biogenesis	Restore cerebral NAD ⁺ ; improve learning and memory; enhance mitochondrial activity; reduce oxidative stress, neuroinflammation and apoptosis; improve cognition in animal models	207
Keto diet	Mitochondrial respiration; Complex I	Improves mitochondrial respiration; reduces	208

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Exogenous ketone esters	Mitochondrial Complex I; uncoupling proteins (UCPs)	ROS; improves rotarod performance; reduces glycolysis and increases ketone bodies Provide alternative brain fuel; β -hydroxybutyrate reduces ROS and improves electron transport chain efficiency	209
Medium chain triglycerides (MCTs)	Ketone body production (MCFAs)	Increase ketone body production; may improve cognitive clarity and performance in AD and MCI	210
Urolithin A	Mitophagy; autophagy; lysosomal-mitochondrial axis; Cathepsin Z (Ctsz)	Increases mitophagy; improves learning and memory; crosses BBB; induces autophagy and mitophagy; restores LTP and reduces A β plaque burden	211
Spermidine	Autophagy; mitochondrial structure and respiratory function	Stimulates autophagy; reduces oxidative stress; improves mitochondrial function; decreases neuroinflammation and soluble A β ; safe but no significant cognitive improvement in Phase 2b trial	212
Rapamycin (sirolimus)	mTOR (mechanistic target of rapamycin)	Enhances autophagic flux; reduces neuroinflammation and microglial activation; decreases A β plaque accumulation and tau phosphorylation; more effective in early AD	213
Caloric restriction (CR)	mTOR insulin pathway; signaling pathways	Reduces microglial activation; increases antioxidants, anti-apoptotic proteins and BDNF; enhances DNA	214

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Aducanumab	Amyloid- β plaques	(A β)	repair; inhibits mTOR; decreases A β plaques and tau phosphorylation A β removal via PET with amyloid tracer; effectively lowers amyloid PET ligand signals; approved for mild cognitive impairment due to AD and mild AD dementia; may cause ARIA-E and ARIA-H.	215,216
Donanemab	N-terminal pyroglutamate-modified A β proteins in amyloid plaques		Aids plaque removal through microglial-mediated phagocytosis; targets deposited plaque; significantly slowed cognitive decline and clinical progression in early symptomatic AD.	217,218
Gantenerumab	A β fibrils (N-terminal and central amino acids of A β)		Disassembles and degrades amyloid plaques by recruiting microglia and activating phagocytosis; preferentially binds aggregated A β .	219,220
Lecanemab (BAN2401)	Soluble aggregated A β (oligomers, protofibrils, insoluble fibrils)		Reduces brain amyloid; results in moderately less decline in cognition and function compared with placebo.	221,222
Remternetug (LY3372993)	Pyroglutamated A β aggregated in amyloid plaques		Investigational monoclonal antibody being evaluated for safety and efficacy in early symptomatic AD.	223
Solanezumab	Soluble A β		Did not significantly reduce decline in cognition or function; failed to slow cognitive	224,225

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		decline in preclinical AD.	
E2814	HVPGG peptide epitope in the microtubule-binding domain of tau	Binds extracellular tau; prevents cell-to-cell propagation of pathogenic tau; promotes clearance of tau aggregates by microglia.	226
Semaglutide	GLP-1 receptor (GLP-1RA)	Neuroprotective; targets glucose metabolism and insulin resistance; may restore brain metabolic function; associated with reduced dementia risk in people with type 2 diabetes.	227,228
Tertomotide (GV1001)	Human telomerase reverse transcriptase (hTERT) peptide	Anti-apoptotic and antioxidant effects through mitochondrial stabilization; blocks A β oligomer-induced toxicity; improves survival of neuronal cells; improved Severe Impairment Battery score in phase II study.	229,230
Donepezil	Acetylcholinesterase (AChE)	Stimulates cholinergic neurotransmission; attenuates symptoms and provides temporary relief from AD.	231
Galantamine	Acetylcholinesterase (AChE)	Stimulates cholinergic neurotransmission; attenuates symptoms and provides temporary relief from AD.	231
Rivastigmine	Acetylcholinesterase (AChE)	Stimulates cholinergic neurotransmission; attenuates symptoms and provides temporary relief from AD.	231
Tacrine	Acetylcholinesterase (AChE)	Stimulates cholinergic neurotransmission; retired due to	231

Memantine	NMDA receptor	hepatotoxicity. Acts as an NMDA receptor antagonist; attenuates symptoms and provides temporary relief from mild to severe AD.	232
Hydralazine	Nrf2 signaling pathway; autophagy; mitochondrial respiration	Anti-neurodegenerative efficacy based on its action on antioxidative stress mechanisms, such as activation of the Nrf2 signaling pathway, increase of mitochondria respiration capacity and adenosine triphosphate production, activation of autophagy, which facilitates intracellular aggregate clearance.	233

Emerging Disease-Modifying Therapies: The amyloid cascade hypothesis remains the primary framework for developing disease-modifying therapies for Alzheimer's disease. Although many anti-amyloid agents have failed in clinical trials, recent Phase III studies have shown encouraging outcomes. The CLARITY-AD trial demonstrated that lecanemab significantly slowed cognitive and functional decline, while the TRAILBLAZER-ALZ 2 trial showed similar benefits with donanemab [174]. Current therapeutic strategies target multiple pathogenic mechanisms, including amyloid- β accumulation, tau pathology, cholinergic and NMDA receptor dysfunction, mitochondrial impairment, oxidative stress, and glucose metabolism [234].

Current Treatment Strategies and Future Therapeutic Development: Current Alzheimer's disease management combines pharmacological and non-pharmacological interventions to preserve cognitive and functional abilities [234]. Existing medications provide modest improvements in cognition, behavior, and activities of daily living during the first 6–12 months of treatment but do not halt disease progression [235–237]. Advances in neuroimaging, blood and cerebrospinal fluid biomarkers, proteomics, and genomics are improving early diagnosis and supporting the development of personalized disease-modifying therapies [238]. The amyloid cascade hypothesis continues to guide therapeutic development. Recent Phase III trials demonstrated that targeted amyloid reduction with lecanemab (CLARITY-AD) and donanemab (TRAILBLAZER-ALZ 2) significantly slows cognitive and functional decline in patients with early symptomatic Alzheimer's disease, representing a major milestone in disease-modifying therapy [174, 238].

Conclusion

Alzheimer's disease (AD) is a complex, progressive, and multifactorial neurodegenerative disorder driven by the interaction of aging, genetic susceptibility, environmental exposures, vascular dysfunction, and molecular mechanisms. Although extracellular β -amyloid ($A\beta$) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau remain the defining pathological hallmarks of AD, increasing evidence indicates that neuroinflammation, mitochondrial dysfunction, oxidative stress, impaired autophagy, blood–brain barrier disruption, synaptic dysfunction, and metabolic abnormalities collectively contribute to disease onset and progression. These interconnected pathological processes highlight the heterogeneous nature of AD and emphasize the need for integrated therapeutic strategies rather than single-target interventions. Recent advances in biomarker discovery, neuroimaging, genomics, proteomics, and fluid-based diagnostics have significantly improved the early detection and biological characterization of Alzheimer's disease, enabling diagnosis during the preclinical and prodromal stages. The introduction of disease-modifying therapies targeting amyloid pathology, including lecanemab and donanemab, represents a major milestone in AD treatment by demonstrating modest but significant slowing of cognitive decline. However, these therapies do not fully prevent disease progression, emphasizing the need for treatments that simultaneously target multiple pathological pathways, including tau pathology, neuroinflammation, mitochondrial dysfunction, and synaptic impairment. Future progress in Alzheimer's disease management will depend on combining early diagnosis, personalized risk assessment, multimodal biomarkers, and precision medicine approaches with effective disease-modifying therapies. A deeper understanding of the biological heterogeneity and molecular mechanisms underlying AD will facilitate the development of individualized therapeutic strategies and preventive interventions. Continued multidisciplinary research integrating genetics, molecular neuroscience, immunology, and clinical medicine is essential to improve patient outcomes, reduce the global burden of dementia, and ultimately achieve more effective prevention and treatment of Alzheimer's disease.

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