Jadhav *et al.*
*Egypt J Neurol Psychiatry Neurosurg* (2024) 60:7
https://doi.org/10.1186/s41983-023-00775-8

The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

REVIEW

Open Access

# Targeting the molecular web of Alzheimer's disease: unveiling pathways for effective pharmacotherapy

Devika Jadhav[1], Nikita Saraswat[1*], Neeraj Vyawahare[1] and Devendra Shirode[1]

**Abstract**

**Introduction** Alzheimer's disease is a neurocognitive disorder that affects elderly people by slowly impaired cognition, dementia, and gets worse with age. It slowly impacts the quality of life. Clinically, it is distinguished by a transition from episodic memory to a gradual reduction in cognitive ability leading to cognitive dysfunction. Neurofibrillary tangles and amyloid plaques are unique structures that are thought to have a role in the pathogenesis of Alzheimer's disease. In this review, we focus our attention on the risk factors, pathophysiology, etiology, epidemiology, stages, diagnosis, treatment, mechanisms, pathways, ongoing clinical trials data and risks potentially associated with the development of Alzheimer's disease.

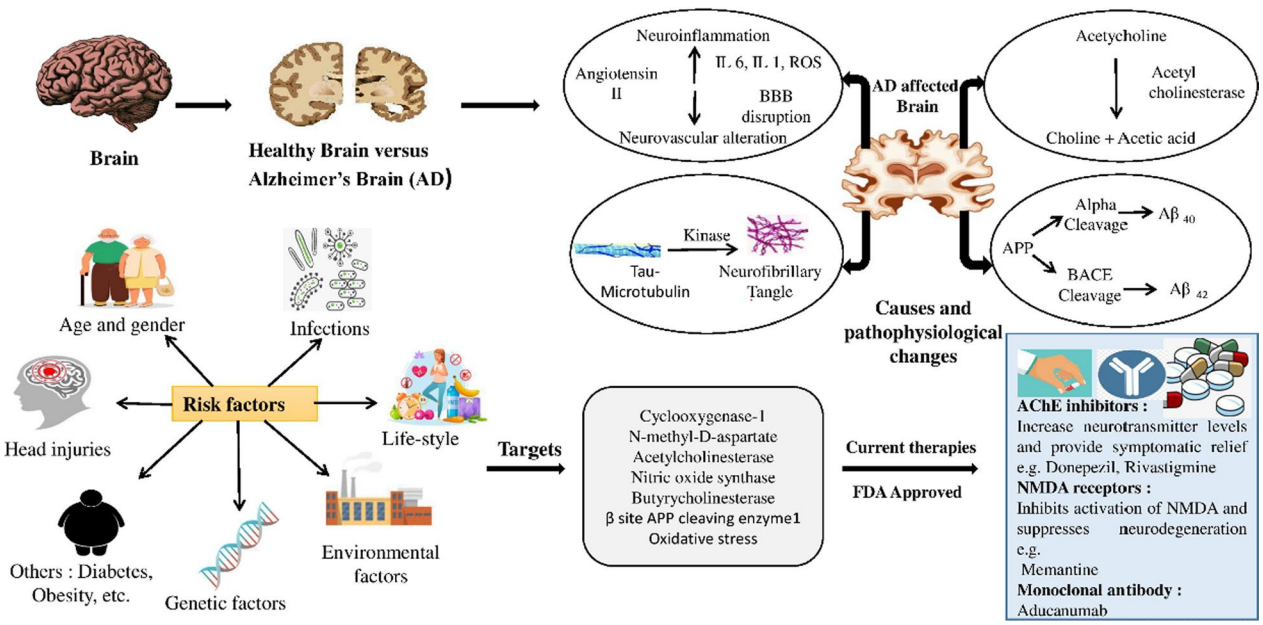
**Short summary** This review aims to extrapolate the information about Alzheimer's disease. Preliminary research was done by selecting reviews on PubMed, Elsevier, and Google open-access publications using the keywords like "Alzheimer, dementia, neurodegenerative, memory, amyloid β, mechanism of action, pathways".

**Conclusion** Here we show the discussion and interpretation of several signaling pathways in the pathogenesis of Alzheimer's disease such as amyloid β plaque cleavage, Metal ion hypothesis, amyloid β degradation, initiation of amyloidogenic and non-amyloidogenic pathway, oxidative stress hypothesis, Metabolic syndrome, insulin resistance and tau phosphorylation associated apolipoprotein- cholesterol, neurofibrillary tangles accumulation, and insulin resistance which are significant for better understanding of the disease initiation and progression. On studying the ongoing clinical trials, it was found that current drugs being tested are crenezumab, gantenerumab and sodium oligonucleotide.

**Keywords** Aducanumab, Alzheimer's disease, β-Amyloid, Cholinesterase inhibitors, Dementia, Cognitive dysfunction, Early-onset Alzheimer's disease, Inflammation, Late-onset Alzheimer's disease, N-Methyl-D-aspartate, Neurodegeneration, Neurofibrillary tangles, Memory, Neurocognitive disorders, Senile plaques, Tau proteins

*Correspondence:
Nikita Saraswat
nikita.saraswat07@gmail.com
Full list of author information is available at the end of the article

**Graphical Abstract**




## Introduction

Alzheimer's disease (AD) was initially identified by Dr. Alois Alzheimer, a German physician, in 1906. A female patient named Auguste D who was in her 50s and had AD appeared to be suffering from a mental condition. However, an autopsy carried out after her death in 1906 exposed large deposits, now better-known as nerve inflammation plaques, surrounding and around her brain's nerve cells. She also had behavioral signs such as hallucinations, delusions, paranoia, psychosocial impairment, and a gradual decline of memory and language. Neurofibrillary tangles (NFTs), or twisted fibers strands, were present inside the cells. The condition was first discovered by Dr. Alois Alzheimer's, and AD is named in his honor [1, 2].

AD is a neurological condition in which age is the most frequent risk factor for AD, and it is defined by a gradual overall loss in cognitive function. Dementia is a more comprehensive term encompassing conditions caused by illnesses or brain injuries that negatively affect memory, thought, and behavior. These modifications disrupt our daily lives. The condition progresses after brain cells begin to die and the brain begins to function more slowly. If it is found sooner, it is usually referred to as early-onset AD. There are medications that can halt the course of AD because there is no known treatment for it [3].

Based on the amyloid cascade theory, a key component of AD is the buildup of the amyloid peptide (Aβ), which is created when the secretases and sequentially cleave the amyloid precursor protein (APP). When soluble Aβ experiences conformational modifications to a high level of -sheets, it becomes more prone to aggregate into polymeric forms, such as bigger insoluble fibrils and soluble oligomers. In the brains of AD patients, these fibrils eventually accumulate as extracellular amyloid plaques [4]. The breakdown of amyloid precursor proteins, oxidative stress, tubulin associated protein phosphorylation (tau), decreased energetics, mitochondrial dysfunction, inflammatory processes, disruption of membrane lipids, and disruption of neurotransmitter pathways are just a few of the biochemical changes that make up the pathology of AD. AD is also significantly influenced by metabolic dysfunction, and the bulk of these clinical characteristics are directly connected to metabolic abnormalities [5]. Understanding how aging naturally occurs and what might go wrong to cause atypical illnesses like dementia are essential to understanding the complexities of dementia. While it is possible to distinguish between biological, social, and psychological ideas of aging, there is typically a large overlap and interaction between them [6].

Even modest changes to an individual's personal appearance are normal part of aging, as are some alterations to higher mental capacities, or "cognitive" activities [7]. Memory is, furthermore, either as a result

of incorrect information being received or sometimes as a result of the information no longer being able to be adequately stored [8]. The impact of aging on memory, in particular episodic memory, is frequently one of the first cognitive skills that others become aware of and can bring great anguish to the individual as well as to family, close friends, and professional relationships. Decline in memory performance is a characteristic feature of dementia, but is also be a sign of other dysfunctions that should always be taken into account. For instance, physical changes like arthritis may restrict motion, which in turn may lead to a decline in assessment [9]. It is not unexpected that there are still no accurate and trustworthy biomarkers for early illness diagnosis. Metabolite changes in the main areas of the brain as the cortex and hippocampus are useful in the early detection of AD [10].

Drugs such as galantamine, rivastigmine, donepezil till now, have been used for treating AD but have only proved to treat symptomatic. Nowadays, monoclonal antibodies are proving to be beneficial in AD treatment. Given the complicated etiology of AD, it is currently thought that medications that target various molecular pathways and disease-modifying therapies may be able to provide more effective treatments. Aducanumab is an amyloid-beta-directed monoclonal antibody while Leqembi is the first fully approved drug to slow down AD. For moderate phases of AD and mild cognitive impairment (MCI), aducanumab has FDA approval. It should not be given to those with mild, moderate, or severe stages of Alzheimer's disease (AD), as well as those with vascular dementia and Lewy body dementia [11].

Despite the fact that oxidative stress and inflammation have a significant role in cognitive impairment, a-amyloid plaque (Aβ) deposition and neurofibrillary tangles (NFTs) of hyperphosphorylated tau are the pathology of AD. Aβ is still a crucial diagnostic indicator that separates AD from other dementia's. The overproduction or impaired clearance of Aβ that results in an excessive Aβ buildup is referred to as amyloidogenesis. It is proposed that APP, which may be controlled by both amyloid and non-amyloid pathways, is the sole source from which Aβ is produced [12].

There are certain neuropharmacological adjuvants that affect brain plasticity processes involved in fear memory as well as neurochemical synaptic transmission. The regulation of these neurobiological systems influences human fear extinction learning is addressed by innovative neuropharmacological treatments that target the glutamatergic, noradrenergic, and endocannabinoid systems. Through the stability and control of receptor concentration, N-methyl-D-aspartate (NMDA) agonist delivery and manipulation of the endocannabinoid system by fatty acid amide hydrolase (FAAH) inhibition might enhance extinction learning. The long-term extinction processes are hampered by increased noradrenaline levels, which dynamically influence fear learning. These pharmaceutical therapies may provide brand-new, precise treatments and preventative measures for diseases based on fear and anxiety [13]. The N-methyl-D-aspartate receptor is vital for synaptic transmission and synaptic plasticity, which are considered to underlie learning and memory. These processes are crucial for the growth and function of the nervous system as well as for the prevention of neurotoxicity [14].

The excessive synthesis or poor clearance of Aβ that causes a buildup of excessive Aβ is known as amyloidogenesis [15]. Beta-side amyloid precursor protein cleaving enzyme (BACE1) is more active and has a greater protein level in brain tissue associated with AD, which is closely connected to the pathophysiology of AD. BACE1 links the significant molecular alterations with amyloidogenesis, which helps to explain how DEAD-box helicase 17 (DDX17) promotes amyloidogenesis. The strong relationship between DDX17 and amyloidogenesis suggests a possibility that DDX17 might be a novel AD therapeutic target [16]. The neurodegenerative pathology of Alzheimer's disease (AD) has recently begun to place more emphasis on the inflammatory process [17]. Several studies have linked dementia with depression, although they have not yet identified the mechanism through which they are related. While some studies identify depression as a prodrome of dementia, others see it as a risk factor for dementia. The inflammatory process is one of the events that happens frequently in dementia and depression [18]. A variety of neurodegenerative illnesses, including Alzheimer's disease (AD), have been linked to calcium signaling abnormalities, which is crucial for neuronal function [19]. According to a study, alterations in the calcium signaling of hippocampus neurons in the AD mice model occurred before the development of amyloid plaques or other symptoms of the disease [20]. Energy equilibrium in the face of constantly shifting external factors depends on mitochondria. AD impacts a number of processes including bio genesis and turnover, fission/fusion, trafficking, and bioenergetics that are critical to healthy mitochondrial function [21]. The stimulation of the tryptophan–kynurenine (Trp–KYN) metabolic pathway, which observably aids in the emergence of pathological illnesses such as neurological and mental disorders, has been related to stress and inflammation. Some studies also state the roles played by mitochondria and the Trp–KYN system, their interactions and their involvement in preclinical and clinical research on serious neurological and psychiatric diseases [22].

One of the competing mechanisms of tryptophan metabolism is the kynurenine pathway, which produces compounds that may contribute to disease and relate to AD pathogenesis [23]. Quinolinic acid is an NMDA receptor agonist, and elevated levels in cerebrospinal fluid (CSF) have been linked to mood disorders along with elevated levels of inflammatory cytokines. According to certain research, increased quinolinic acid has also been shown in neurodegenerative disorders such as AD, Parkinson's disease (PD), amyotrophic lateral sclerosis, and cognitive impairment associated with Human Immunodeficiency Viruses (HIV) [24].

AD is now recognized as a neurodegenerative condition with a protracted course that begins silently decades before symptoms appear and progresses slowly and steadily until it impairs a person's cognitive function. AD is more common in senior citizens [25]. Additionally, regional temperatures, environmental variables, even dietary and drinking patterns, may cause AD [26].

Various changes and alterations have been seen to be occurring in the parts of the brain as the ventricles are enlarged, shrinkage of cerebral cortex, hippocampus, formation of the NFTs and Aβ plaques. Figure 1 represents all the changes occurred in the Alzheimer's brain as that of the normal brain. Changes in hippocampal area of brain, cerebral cortex, ventricles as well as changes occurred in the neurons [27].

We have presented the mechanisms of action and pathophysiology of AD review, which examines the advancements achieved in this field over the past ten years. Numerous cellular and molecular processes that affect the prognosis of AD are reviewed. In light of this, we will also discuss the types of memory associated with AD. The essential diagnosis and treatments have also been covered, along with information on ongoing clinical studies. The frequency and incidence of progressive dementia are rising as the population's share of older people grows as well. Numerous studies are being conducted to identify the risk factors, biomarkers, and pathological mechanisms that could help to distinguish between typical aging symptoms, MCI, and dementia because there are many unanswered questions regarding the etiology and pathology of dementia [28].

## Material and methods

### Search engine

The data collected for reviewing was by studying the published work from PubMed, Elsevier, Science direct,

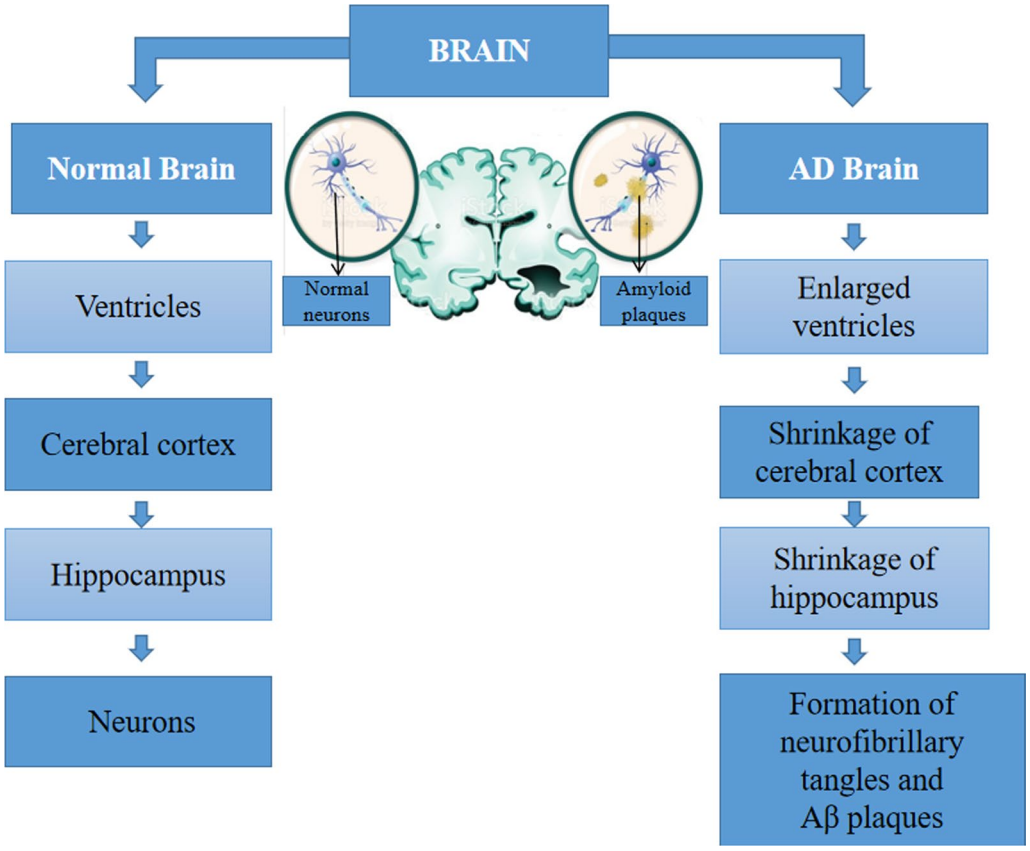



**Fig. 1** Changes occur in Alzheimer's brain compared to the normal brain [28]

Medline and Google open access publications by searching keywords such as Aducanumab; Alzheimer's disease; β-Amyloid; Cholinesterase inhibitors; Dementia; Cognitive dysfunction; Early Onset Alzheimer's Disease; Late Onset Alzheimer's Disease; N-Methyl-D-Aspartate; Neurodegeneration; Neurofibrillary tangles; Memory; Neurocognitive disorders; Senile plaques; tau Proteins.

### Exclusionary criteria

No-English and incomplete articles were rejected. Even the repetitive studies were ignored. We tried to include the latest researches thereby excluding very old literature so as to make the review updated. Articles lacking informative and scientific explanations were not considered for this review.

### Data abstraction and analysis

We have searched the published research, reports, reviews, global health data, epidemiological data on AD. We have filtered out the significant information in accordance to our paper title and complied it in our work from the research work conducted from year 2018 to 2023. Review data include symptoms, causes, risk factors, pathophysiology, epidemiology, diagnosis, treatment and ongoing clinical trial data with respect to prognosis of AD.

### Alzheimer's disease and its effect on memory: memory functioning recognition

The primary 5A symptoms of AD are amnesia, apraxia, agnosia, aphasia, and anomia. Short-term and long-term memory are affected in AD. A familiar phone number may be remembered from day-to-day live basis and year to year due to long-term memory but is affected in people suffering from AD [29, 30]. Semantic and episodic memory is also lost or majorly affected in AD patients like deficits in performing regular tasks [31]. Declarative and procedural memory is also proven to be affected during the course of AD thus routines and skills are impaired [32].

### Symptoms of Alzheimer's memory based on long and short-term time duration

#### *Memory functioning recognition*

*Short-term and long-term memory* The primary 5A symptoms of AD are amnesia, apraxia, agnosia, aphasia, and anomia. The method that enables one to dial a new phone number while keeping it in mind, providing one is not diverted, is elaborated upon in the idea of working memory [33]. A familiar phone number may be remembered from day-to-day live basis and year to year due to long-term memory [34]. Some pilot studies following the music feedback physical training may also enhance short-term memory [35]. A strong correlation between short- and long-term memory functions that, remarkably, remained constant across the age range. With healthy aging, both short-term and long-term memory deteriorate [36].

Semantic and episodic memory: It appears that various kinds of information are stored in different ways. There has come to be accepted to be a difference between procedural and declarative memories, in contrast to the earlier distinction between episodic and semantic memories. Episodic memories are for specific experiences, whereas semantic memories are truths that are not based on any context. An example of episodic memory is recalling what I had for breakfast; a semantic memory is recalling that the word "breakfast" refers to a morning meal [37].

Declarative and procedural memory: This category—which stands for the memory of facts—can contain both episodic and semantic memories. Procedure memory is used for routines and skills and can involve certain sensory inputs. Driving an automobile is an example of memory for procedures. Understanding how the engine functions is crucial. In general, older individuals are just as capable of learning as younger ones, but it will take them longer to accomplish due to the slower rate at which they 'digest' and interpret information. This speed loss can occasionally become obvious and noticeable and may appear following sadness. If memory has visibly changed and is still changing, along with another cognitive impairment, this may be a symptom of a dementing process [38].

### Etiology—old age, Down syndrome, genetics, environmental and lifestyle associated factors which elevate the risk of onset and progression of AD-lvl2

The death of neurons causes AD, a neurological disorder that develops gradually. Usually, it starts in the hippocampus nucleus entorhinal cortex. Genetics has a role in both early-onset and late-onset AD. Numerous risk elements have been connected to AD. Old age is the most common risk factor associated with AD. Traumatic brain injury, depression, heart, and blood vessel illness, the advanced age of parents, smoking, the ancestry of dementia, high homocysteine levels are all risk factors for AD [39]. Higher education, female estrogen use, anti-inflammatory drugs, pastimes like a balanced diet, frequently received cardiovascular activity, reading, or playing an instrument are all shown to lower the incidence of AD. When it was compared to the overall population, those who have 2 or more siblings with late-onset Alzheimer disease (LOAD have a threefold increased chance of developing the disease [40].

#### *Age*

Old age is the primary risk factor for the evolution of AD. The probability of contracting the illness raises every five years after you become 65.

#### *Down syndrome*

Down syndrome (DS) is a sort of accelerated aging, and those who have it are far more likely to develop vascular and neurological diseases that are linked to aging [41]. Individuals with Down syndrome are more prone to developing AD. The main cause is aggregation of Amyloid plaques over time due to the potential that some people may develop AD as an outcome of the genetic defect that causes Down syndrome [42].

#### *Genetics*

A large percentage of AD patients are sporadic late-onset instances. However, AD seems to have the highest amount of heredity (70%) among human complex disorders. Familial different kinds of autosomal dominant inheritance account for roughly 0.1% of instances with an onset before the age of 65. This kind of sickness is referred to as juvenile onset familial AD. Even though AD is rare, only a tiny percentage of people develop it before the age of 65. Because of mutations in these three genes amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2), AD has been linked to their development. Habitual and environmental factors may also leads to Herpes simplex virus (HSV), Human Herpervirus (HHV), hypothalamic pituitary adrenocortical (HPA) due to stress and Sleep deprivation (SD) along with cerebral amyloid angiopathy (CAA) due to lifestyle changes. Apolipoprotein E (ApoE) glycoprotein that is abundantly expressed in some microglia, the liver, and the brain. For the creation of myelin and healthy brain activities, it performs as a ligand for receptor-mediated endocytosis in lipoprotein particles that transmit cholesterol. Three isoforms of the ApoE gene, Alleles of Apolipoprotein E, Apolipoprotein E2 (Apo E2), Apolipoprotein E3 (Apo E3) and Apolipoprotein E4 (Apo E4) can be found on chromosome 19. As a result of single-nucleotide polymorphisms (SNPs) alter the coding sequence. When compared to Apo E3 and Apo E4 alleles, which are linked to a lower risk and a protective impact, severally, early-onset Alzheimer's disease (EOAD) and late-onset Alzheimer's disease (LOAD), the ApoE4 allele is a significant risk factor. Cerebral amyloid angiopathy (CAA), which is recognized as a hallmark for AD, is caused by Apo E4 and plays a significant role in the deposition of the Aβ senile plaque additionally, it has been demonstrated that Apo E4 contributed to the development of AD by causing vascular injury in the brain [43]. The pathological processing of the tau protein and the amyloid beta (Aβ) peptide, as well as synaptic and mitochondrial dysfunctions, neurovascular changes, oxidative stress, and neuroinflammation, among other neuropathological events involved in LOAD, have all been linked to multiple genes [44].Recent research on the molecular causes of AD has revealed that amyloid buildup not only causes tau hyperphosphorylation and immune response but also sets off a chain of additional mechanisms that increase stress in the brain, such as an impairment in blood flow to the brain or an increase in neuronal hyperactivity [45].

Age, gender, genetics, infectious, lifestyle and environmental factors lead to progressive generation of AD. The risk factors which lead to the development of AD are represented in Fig. 2 as follows [46].

### AD epidemiology states 71% rise in patients of dementia by year 2050

Alzheimer's illness affects the elderly after the age of 65. Globally, there may be 24 million people who have dementia, and by the year 2050, that figure is predicted to have multiplied four times. The United States (US) healthcare system is estimated to lose $172 billion a year because of AD. The anticipated amount of persons aged 65 and over with AD dementia comes from updated research using the current data starting with 2023 population projections from US Census Bureau and Chicago Health and Aging Project (CHAP), a population-based chronic study of the health status of the elderly. After the age of 65, the prevalence of AD climbs every five years. Currently, 60% of dementia patients reside in low-income or middle-income nations, but by 2050 this number will increase to 71%. Less than 1% per year before the age of 65 to 6% per year beyond the age of 85 are the apparent age-specific incidence increases. The prevalence rates rise from 10 to 40% at the age of 65, and they quickly approach 40% at age 85. Particularly beyond the age of 85, women are somewhat more likely than males to get AD. AD affects more than 6 million Americans of all ages. In 2023, AD will affect an estimated 6.7 million Americans aged 65 or older. 73 percent of them are 75 years of age or older. About one in nine people aged 65 and older (10.7%) have AD. The two types of AD include familial and sporadic, as well as early-onset which is before age 65 and late-onset that is beyond age 65. AD appears to affect 5.5% to 9% of the general population every 6 months [47]. Every 10 years, the disease's ratio doubles. About half of adults aged 85 and older had AD at this time. Around the world, up to 75% of people with dementia are undiagnosed. People who have cognitive deficiencies are commonly recognized clinical criteria for AD, but who show a noticeable drop from preceding levels of cognitive function and have trouble acquiring

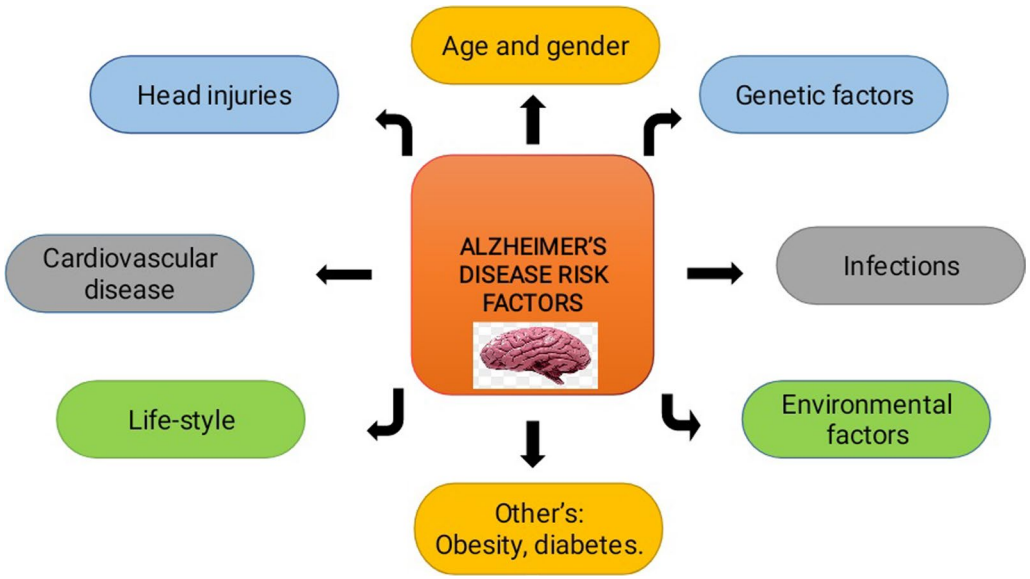



**Fig. 2** Risk factors associated with development of Alzheimer's disease including factors as age and gender related, genetic factors, infectious and environmental, cardiovascular and other disease related factors as obesity and diabetes [46]

new information may have mild cognitive impairment. Recent studies indicate that 40% of these communities will develop AD within three years. SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona Virus 2) positive individuals may have long-term effects from the virus infection, including dementia and neurological illness. SARS-CoV-2 infection and the likelihood of developing Alzheimer's disease may be related, according to several theories that assess potential disease-causing pathways [48].

### Pathophysiology of the AD

An accumulation of aberrant neurotic Neurofibrillary tangles and plaques is a characteristic of AD. Plaques are sphere microscopic lesions that have a developing axonal end along with extracellular amyloid beta-peptide core. Microglia cells are known as the immune cells of the Central Nervous System (CNS) and are crucial in inflammatory and infectious brain conditions. Most instances of familial early-onset AD are triggered by mutations in the PSEN1 and PSEN2 genes. Microglia have both a short-term and long-term ability to affect neuronal activity in the mature brain, and they can react to changes in sensory activity. The integrity of synaptic function appears to be specifically under the control of microglia. The transmembrane protein known as an APP is responsible for producing the beta-amyloid peptide. The proteases alpha, beta, and gamma-secretases cleave the beta-amyloid peptide from the APP. Alpha and beta-secretase often shreds APP, and the resultant tiny fragments have little impact on neurons. The fact that triggering receptors expressed on myeloid cells 2 (TREM2) which is triggering receptor expressed on myeloid cells-2, considerably increases the risk of developing AD indicates the role that microglia play in the progression of the condition. The TREM2 gene is activated by a subset of myeloid cells, comprising dendritic cells, granulates, and tissue-specific macrophages including osteoclasts, Kupffer cells, and alveolar macrophages. Beta and then gamma-secretases sequentially cleave the 42 amino acid peptides to generate them. An increase in beta-amyloid 42 induces amyloid aggregation, which harms neurons. Beta-amyloid 42 promotes the development of aggregated fibrillary amyloid protein in contrast to usual APP breakdown. The key neuropathological features of the AD brain include neurofibrillary tangles, neuropathic plaques, and neuronal loss. Modulating how APP and secretases are phosphorylated and how this impacts how APP and Aβ pathology function and are processed [49].

Transmembrane protein 21 (TMP21) is a 219 amino acid protein that has a mature peptide with 188 amino acids and a signal peptide with 31 amino acids. The newly synthesized TMP21 gets instructed by the signal peptide to translocate into the Endoplasmic reticulum (ER), where it is cleaved and the mature TMP21 is produced. Age-matched controls and both familial and sporadic AD patients' brains had considerably lower levels of TMP21, which is consistent with a prior study that found that knocking down TMP21 boosts the expression of Aβ. TMP21 plays a central role in neurite plaque formation. TMP21 plays an important

role in neurite plaque formation and in the mechanisms underlying neurofilament formation, synaptic disruption, and neuronal loss [50]. On chromosome 21, one of the locations connected to familial AD, is where the APP gene is found [51]. In AD, meningeal, cerebral, and grey matter arteries are encircled by amyloid buildup. Military structures resembling plaques are created by the combination of several grey matter deposits. However, despite having dementia, some individuals with the disease had amyloid plaques on their brain scans, and others did not. Tau protein in neurons generates fibrillary intracytoplasmic clumps called neurofibrillary tangles (NFTs) [52]. Tau protein's major role is to keep axonal microtubules stable. All neuronal axons involve microtubules, which are required for intracellular trafficking. Tau protein holds the assembly of microtubules together. Hyperphosphorylation of tau, which results in the production of beta-amyloid plaques, occurs in AD as a result of extracellular beta-amyloid aggregation and tau aggregates. The aggregation of tau proteins is reciprocally related with hippocampal atrophy, cognitive decline, and brain atrophy. In the neuropathology of AD, the temporofrontal cortex undergoes neuronal loss and atrophy, which causes inflammation, the development of amyloid plaques, an abnormally formed protein fragments, and a tangled network of fibers. Monocyte and macrophages numbers rise in the cerebral cortex as a result, and the immune cells microglia in the parenchyma are activated [53].

Figure 3 represents the progressive development of AD initiated by mutations in APP (amyloid precursor protein) cleaved by secretase enzymes leading towards mutation and increased production of APP and thus this accumulation was neurotoxin induced AD [54].

Tau clusters are twisted into pairs of helical filaments termed neurofibrillary tangles. Prior to traveling to other areas of the cerebral cortex, they first develop in the hippocampus. Tau-aggregates are deposited in the neurons. The Barak staging, developed by Barak and Barak and based on the topographic staging of plaques and tangles into 6 phases, is one of the neuropathological criteria used by the National Institute of Aging and the Reagan Institute to diagnose AD. Tangles have a higher association with AD than plaques do. Another sign of AD is the granulovacuolar degeneration of hippocampus pyramidal cells brought on by amyloid angiopathy. Cognitive impairment is more closely associated with a decrease in the density of presynaptic boutons from pyramidal neurons in laminae III and IV than it is with a rise in plaque density. Additionally, it has been demonstrated that the Meyer nucleus basalis has lost neurons, causing low levels of acetylcholine. The amount of vasculature's involvement in AD's neurodegenerative process is unknown. Dementia risk is four times higher after subcortical infarcts. Cerebrovascular disease exacerbates dementia's severity and rate of development even further [55]. Recent research found that atrophy clusters and tau clusters have different clinical correlations. Clusters of atrophy and tau were somewhat linked [56].

### Secretase enzymes (α, β and γ) and their roles in normal physiology and pathology of AD

It has long been believed that the APP processing pathway contains a putative-secretase-secretase, a protein that has the potential to cleave APP inside the avoid. The

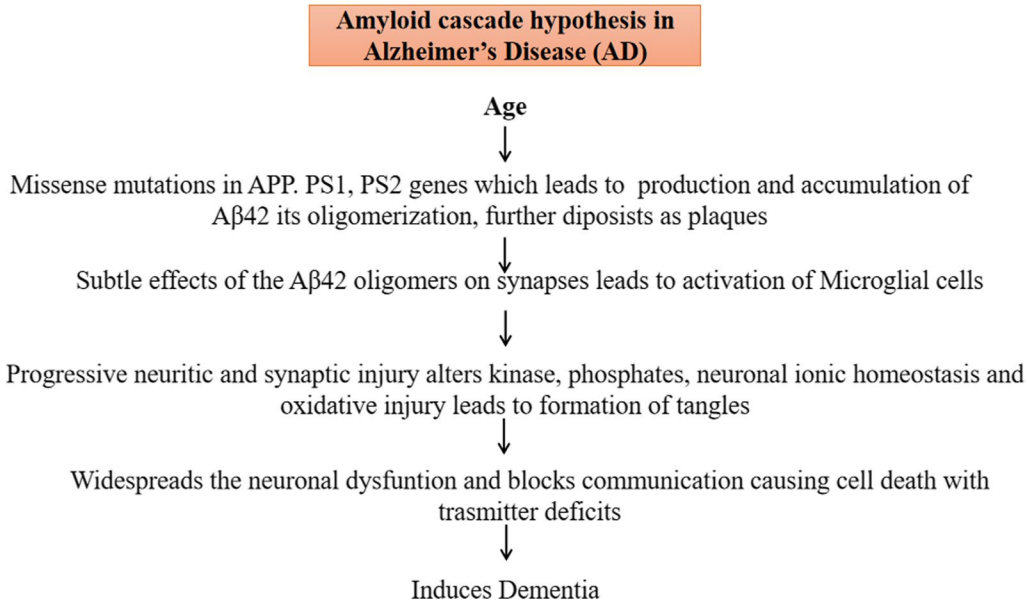



**Fig. 3** Pathophysiology of amyloid cascade hypothesis in Alzheimer's disease [54]

most important -secretase in neurons from a physiological standpoint is likely A disintegrin and metalloprotease (ADAM10). This substance was recognized as a metalloprotease that are present on the Golgi complex and the cell layer. At residue L688, which is located in the center of the Aβ gap, the secretase cleaves the APP. Total Aβ cannot be delivered by cleavage by secretase, for this reason. In a process known as "ectodomain shedding", it releases the APP (sAPP) solvent outside of cells in one step. It is believed that this ectodomain has neuroprotective qualities. The -secretase protein, BACE1, contend with secretase for cleavage of the APP. At the N-terminal of the Aβ space, BACE1 cleaves APP, and the subsequent secretase cleavage releases the Aβ isoforms. Although it was known that secretase was broadly distributed, it was most obvious in the pancreas and brain, particularly in neurons [57]. It was anticipated that it would be confined to endosomes, lysosomes, and the Golgi complex inside of cells, and that it would function best at an acidic pH. In any case, AD patients do not always have dynamic secretase. Instep it shows up to be creating Aβ amid the typical cell digestion system. In this way, the activation of secretase and the generation of Aβ are not the only causes of advertisement, but rather a change in the amount of APP that secretase produces. Presenilin, nicastrin (NCT), anterior pharynx-defective 1 (APH-1), and presenilin enhancer 2(PEN-2) are potential elements of the protein complex known as secretase. Following the secretase cleavage, it splits the APP portion to produce Aβ. However, it turned out that secretase could cleave a considerably wider range of substrates than was previously thought possible. Clinical investigations of secretase inhibitors have stated serious adverse effects and the requirement for beneficial cognitive effects. Since secretase cleaves a variety of essential substrates other than APP, this is often expected [58].

### Amyloid beta fragments responsible for the pathological conditions in AD

AD patients have insoluble peptides known as amyloid beta due to the digestion of APP by alpha- and gamma-secretases, leading to amyloid beta plaques and cell degeneration. APP product is Aβ and is present in the brain for signal transduction. High Aβ levels in the brain cause senile plaque and cognitive problems in AD patients. APP is a protein with three domains [59]. APP is digested by alpha, beta, and gamma-secretases to produce Aβ peptides like Aβ42 and Aβ40. Studies on Aβ focus on its role in cognitive decline and Alzheimer's, while APP promotes neurite outgrowth and strengthens synapses by regulating calcium release. In AD brains, neuroinflammation contributes to neurodegeneration through Aβ-induced inflammatory responses causing synaptic dysfunction and neuronal death. The main

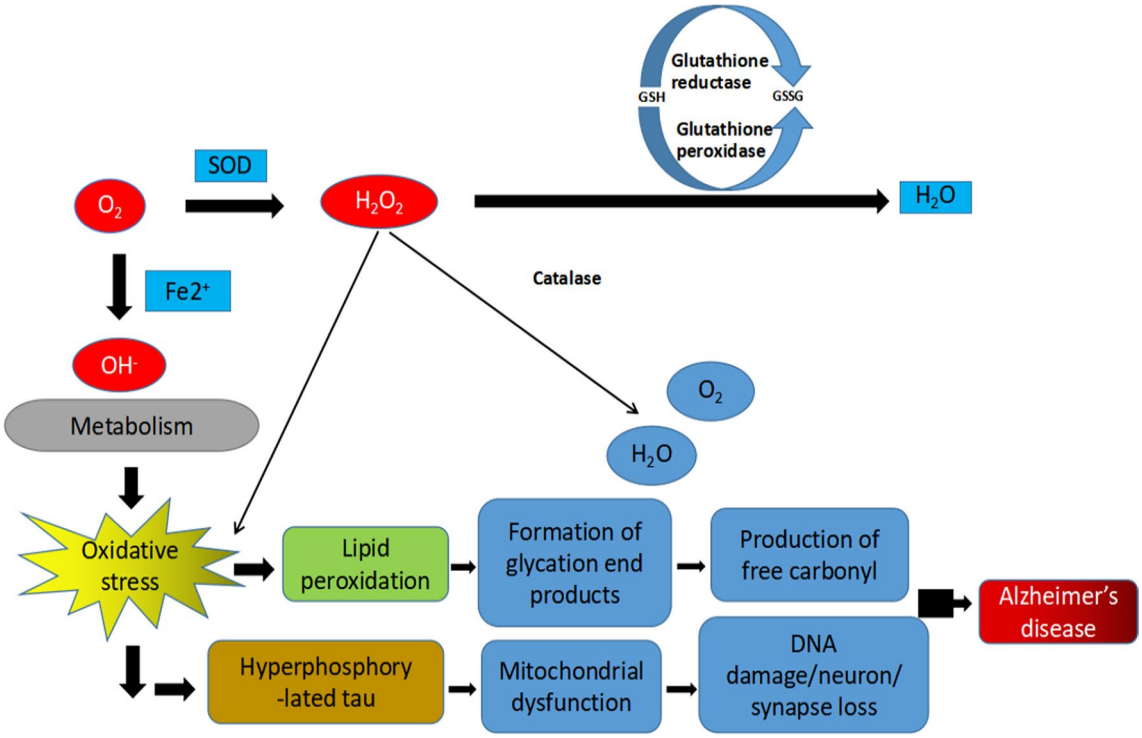



**Fig. 4** Oxidative stress in Alzheimer's disease (AD). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) cause various cellular changes as mitochondrial dysfunction, DNA damage leading neurodegeneration along with metal ion hypothesis [68]

contributors to neuroinflammation in AD brains are microglial cells, brain astrocytes, cytokines, chemokines, acute-phase proteins, acetylcholine receptors (AChRs), peroxisome proliferator activated receptors (PPARs), and alternate complement pathways. An imbalance in anti-inflammatory and proinflammatory signals leads to neuroinflammation [60].

## Molecular and cellular pathways associated with pathogenesis of Alzheimer's disease

### *Non-amyloidogenic and amyloidogenic pathways in AD*

βA 1–42 and βA 1–40 peptide monomers are produced by APP in the amyloidogenic pathway and assemble into the characteristic amyloid plaques of AD. β-Secretase (BACE) uses the APP protein as a substrate for enzymatic cleavage, producing soluble amyloid precursor proteins (sAPPs) and the C99 fragment in the membrane. The secretase, which is a complex of presenilin 1 or 2 and nicastrin, then cleaves the C99 fragment. The activity of the amyloidogenic pathway and the membrane damage induced by the peptide Aβ1-42 are increased in regions associated with lipid. In the non-amyloidogenic pathway, alpha-secretase cleavage occurs in the Aβ region, the C83 peptide is cleaved by γ-secretase, and then the amyloid beta fragment of the peptide is formed, which prevents the formation of Aβ [61]. By restoring nuclear factor erythroid-derived 2-like 2 (Nrf2) and lowering inducible nitric oxide synthase (iNOS) levels, treatment with -tocopherol was also able to minimize oxidative stress, as shown by immunocytochemistry [62].

### *Hyperphosphorylated tau protein*

Alois Alzheimer first described the intra-neuronal lesions known as neurofibrillary tangles (NFT) in the beginning of the nineteenth century. The paired helical filaments (PHFs) of hyperphosphorylated tubulin associated protein (TAU) are the primary component of NFTs. At least 25 aberrant phosphorylation sites that are a sign of neuronal degeneration in AD have been identified [63]. The formation of NFT is promoted by aberrant phosphorylation of tubulin associated protein (TAU) on serine/threonine residues close to the tubulin binding domain, which encourages dissociation of the TAU-tubulin complex and TAU reassembly into paired helical filaments (PHFs). Tubulin associated protein (TAU) is crucial for the upkeep of neuronal stability and homeostasis, therefore its hyper phosphorylation triggers a path of events that results in neuronal death [64].

### *Amyloid β cascade/hypothesis*

Senile plaques (SP), which are caused by the accumulation of amyloid beta (Aβ), are one of the particular characteristics of AD. The enzyme secretase converts the precursor protein of amyloid (APP) into

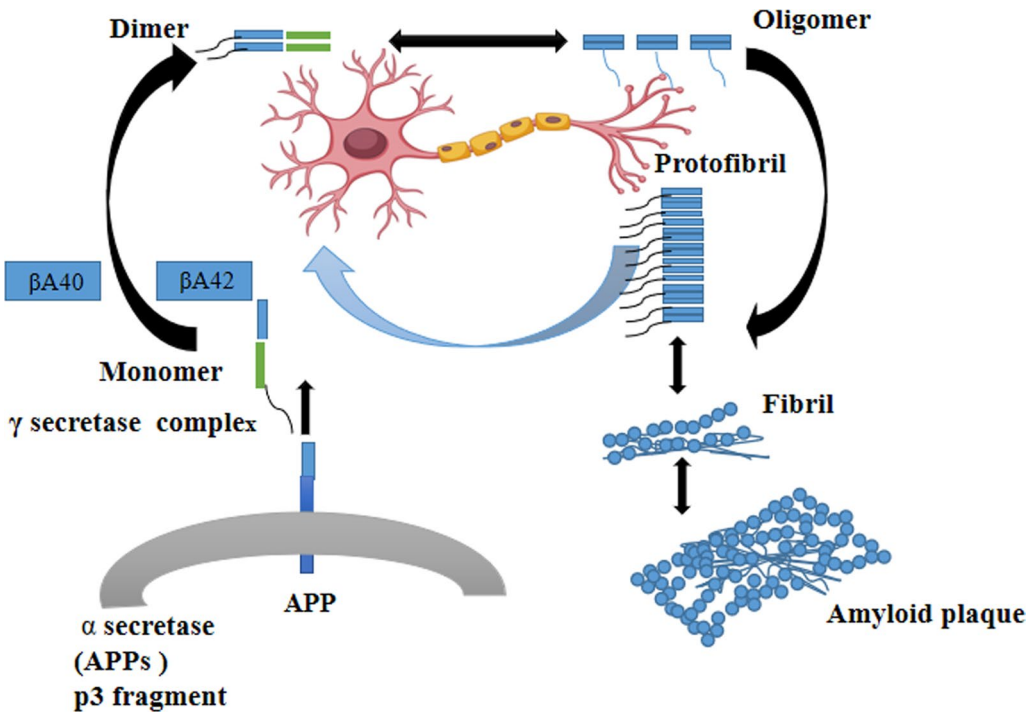



**Fig. 5** The amyloid-β pathway in Alzheimer's disease with initiation of APP and differentiation between non-amyloidogenic and amyloidogenic pathways [74]

soluble little peptides known as Aβ [65]. Protofibrils, fibrils, and plaques are three distinct types of dangerous oligomers that develop from an imbalance between -amyloid (Aβ) constitution and separation, depending on the degree of oligomerization. Although the precise reason for Aβ creation is still a mystery, its sequence, concentration, and stabilizing conditions all have a big impact. One of the key pathogenic features of AD is the development of senile plaques (SP), which are origination by the accumulation of amyloid beta [66].

#### *Oxidative stress hypothesis in AD*

Humans form reactive oxygen species (ROS) and reactive nitrogen species (RNS) in both normal and diseased processes. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) serve complementary roles in cellular signaling pathways and engage in hazardous activities that can harm cellular components, such as cell membranes, lipids, proteins, and deoxyribonucleic acid (DNA). The brain requires 20% more oxygen than other mitochondrial respiratory tissues due to its high oxygen demand. To oxidative stress, it is especially susceptible. Neuron is the basic structural and functional unit of the brain. It is mostly composed of polyunsaturated fatty acids. Lower levels of glutathione in neurons, which can work with reactive oxygen species (ROS) to cause molecular apoptosis and lipid peroxidation [67]. Figure 4 below represents the schematic representation of cellular damages and changes caused due to reactive oxygen species (ROS) as oxidative stress leading towards inflammation, mitochondrial dysfunction, neurodegeneration [68].

#### *Metal ion hypothesis*

The pathogenesis and procession of diseases, such as cancer and neurological disorders, is affected by metal homeostasis. Numerous of these substances are used in clinical research. The well-known modulators of transition metal homeostasis include the ionosphere and metal chelators [69]. Other drugs can potentially target the homeostasis of transition metals in addition to those that bind to metals. According to recent discoveries, the chemical equilibrium of redox transition metals, especially iron (Fe), copper (Cu), and other trace metals is shifting. The amount in the brain is seen to be higher in AD. Numerous neurological illnesses are impacted by copper (Cu), manganese (Mn), aluminum (AI), and zinc (Zc) [70].

#### *Metabolic syndrome associated with the AD pathway*

There are several molecular events linked to metabolic syndrome that contribute to the evolution of AD in the brain. Deregulated lipid metabolism, advanced glycation end products, oxidative stress, dysfunctional inflammatory response, and signaling systems could all have a role in Amyloid-aggregation and Tau neurofibrillation. The hyperphosphorylation of Tau and the aggregation of A can occur from this activation. AD is brought on by neurofibrillation, which causes synapse loss and brain cell death [71, 72].

#### *Cholinergic hypothesis*

The apolipoprotein E (APOE) genotype influences how well Ach inhibitors (AChEIs) work in people with AD. The primary risk factor for AD is the apolipoprotein E (APOE) genotype, and AchEI therapies constitute the cornerstone of therapy. Reduced cholinergic receptor binding in certain brain regions is related to neuropsychiatric symptoms in mild-to-severe AD. In elderly, healthy individuals, slower processing may be associated with reduced receptor binding. In vivo, cholinergic receptor binding may be a target for biological therapies and may be connected to other significant alterations in the brain connected with aging and AD. A significant failure of cholinergic neurons generated in the medial forebrain nuclei, together with a concomitant drop in acetylcholine-mediated neurotransmission, are linked to clinical deterioration. The symptomatic therapy for AD for more than 20 years has been donepezil and other medicines that tend to normalize cholinergic transmitter levels [73]. Figure 5 below shows that Aβ is found in several different intermediate aggregation states with secretases and dimers, trimers, soluble oligomers, and protofibrils all represent amyloidogenic processes that lead fibrils to build up in plaques, which are frequently thought of as an AD neuropathological signature [74].

#### *Insulin resistance*

Hyperinsulinemia and reduced serine/threonine protein kinase (Akt) activation are effects of insulin resistance. Glycogen synthase kinase 3 (GSK-3) is activated as serine/threonine protein kinase (Akt) activity decreases. Insulin resistance pulls insulin-degrading enzyme (IDE) away from Aβ. The atmosphere of hyperglycemia causes oxidative stress and ages. These promote an impairment in Aβ clearance and a rise in neural fibrillation, which causes neurodegeneration [75]. Insulin is able to freely cross the blood–brain barrier (BBB) [76].

#### *Mitochondrial cascade hypothesis*

Mitochondria are multifunctional, active eukaryotic organelles. They serve as the main location for oxidative phosphorylation, which produces adenosine triphosphate (ATP). They contribute to calcium signaling, maintain calcium homeostasis in control, and modulate intrinsic apoptosis. The reduction of mitochondrial function

**Table 1** Stages in progression of Alzheimer's disease [89]

| No. | Stages | Observations |
|---|---|---|
| 1 | No impairment | Appears normal<br>Stays mentally and physically active<br>No treatment is necessary |
| 2 | Very mild decline | Will begin to experience forgetfulness<br>No treatment necessary |
| 3 | Mild decline | Will begin to notice change and decline in function<br>AD can now be diagnosed |
| 4 | Moderate decline | Thinking and reasoning become more obvious and new issues appear<br>Clear signs and symptoms of AD are seen |
| 5 | Moderately severe decline | May experience significant confusion and become agitated<br>Begins to require help with normal day-to-day activities |
| 6 | Severe decline | May begin to wander<br>Requires assistance and/or reminders with many of the activities of daily life<br>Requires constant supervision |
| 7 | Very severe decline | Loss of the ability to respond to the environment or communicate<br>Loss of movement and communication<br>Disease complications may result in death |

*AD*, Alzheimer's disease

with age is commonly acknowledged. In AD patients blood cells, brain fibroblasts and fibroblasts cell lines as well as in cell line expressing mutant APP or treated with Aβ, mitochondrial dysfunction has been reported. All of these developments gave rise to the "mitochondrial cascade hypothesis" which states the mitochondrial baseline function and endurance are determined by inheritance. Many mitochondrial enzyme activities are drastically reduced in AD, which leads to errors in electron transport and encourages the synthesis of Reactive oxygen and nitrogen species (RONS). Additionally, a reduction in mitochondrial-mediated autophagy may enhance the deposition of Aβ. An overproduction and deposition of Aβ can result from early oxidative stress and mitochondrial function deficits [77].

#### *Calcium hypothesis in AD*

According to several studies, intracellular calcium homeostasis is altered in AD, which has been associated with abnormal synaptic plasticity, hyperphosphorylation of tau protein, amyloid β (Aβ) protein deposition, and apoptosis, all of which are involved in the onset and progression of AD. Additionally, several based on pathways relating to calcium homeostasis and AD have had success in treating AD [78]. In order to offer a theoretical foundation for further research on AD and the creation of new treatment medications, this study thoroughly examines the connection underlying calcium homeostasis and the pathogenesis of AD. In AD brains, there are changes in the RNA expression of genes that regulate calcium. In the early stages of AD, alterations in calcium homeostasis take place along with variations in calcium-dependent proteases. The four routes listed below can be used to categorize how calcium affects the development of AD: increased intracellular calcium concentrations result in the deposition of Aβ; large calcium influx damages the neuronal structure and hinders tau's ability to bind to microtubules, eventually leading to neurofibrillary tangles; intracellular calcium overload causes abnormal tau phosphorylation and interferes with synaptic plasticity in the brain; and calcium homeostasis disorder contributes to abnormal synaptic plasticity in the brain [79–81].

*Presenilin hypothesis in AD* The calcium hypothesis of AD implies that genetic abnormalities producing flavin adenine dinucleotide (FAD) also lead to dysregulation of neuronal calcium (Ca2+) processing and may contribute to AD pathogenesis. Presenilin protein mutations are to blame for the bulk of FAD instances. Presenilins serve as the secretase's catalytic subunit in the production of the Aβ peptide [82–84] Unrelated to -secretase activity, we recently learned that presenilins serve as low-conductance, passive endoplasmic reticulum (ER) calcium (Ca2+) leak channels. Further research revealed that certain presenilin FAD mutations enable the ER to become overloaded with Ca2+ and lose its ability to operate as a Ca2+leak. The results obtained offered a plausible justification for the aberrant Ca2+signaling seen in FAD cells with presenilin mutations [85].

### Staging of Alzheimer's disease on memory

#### *Preclinical or presymptomatic*

Individuals are asymptomatic at this point, but there is undeniable laboratory evidence. Finding the biomarkers

can assist in making a diagnosis of AD at this stage. Although they are a biomarker for AD, low amyloid and elevated tau proteins in CSF are not. According to a different analysis, the progression to mild cognitive impairment (MCI) can be predicted by a figure of different factors, including the presence of apolipoprotein E4 (ApoE4), paired with the score that links instant recall test and the digits symbol substitution test, as well as indicators of the right hippocampus area on MRI and the thickness and volume of the right entorhinal cortex [86].

#### *Mild cognitive impairment (MCI)*

Patients in this stage exhibit either memory impairment or impairment in non-memory areas, like executive function or language function. These individuals continue to engage in independent jobs, social interactions, and function. 10% of patients with mild cognitive impairment (MCI) develop dementia each year [87].

#### *Dementia*

Patients in this stage have severe memory damage. Anomia, paraphasia errors, a decline in impulsive verbal output, and a propensity for evasion to avoid forgotten words are only just a few examples of language changes. Constructional apraxia and wandering in one's familiar surroundings are symptoms of visuospatial impairment. Delusions will occur in 20–40% of patients. Although patients also have auditory olfactory hallucinations, visual hallucinations are more frequent. Nearly 50% of patients engage in disruptive behaviors. Patients also experience sleeplessness and lose their regular circadian sleep–wake pattern. These patients have greater rates of traffic crashes [88].

Various stages are seen to be occurring in the progression of AD, as Table 1 represents no impairment and its observation similarly very mild decline, mild decline, moderate decline, moderately severed decline, severe decline and very severe decline [89].

#### *AD progression related to genetic basis*

Autosomal dominant inheritance induces AD, which has a penetrance of about 100%. The APP gene on chromosome 21, presenilin 1 (PSEN1) on chromosome 14, and presenilin 2 (PSEN2) on chromosome 1 have all been linked to the autosomal dominant type of the disease [90]. Beta-amyloid peptide creation and clumping may increase as a result of APP mutations. Because PSEN1 and PSEN2 mutations inhibit gamma-secretase processing, beta-amyloid builds up. The majority of situations of early-onset AD and 5% to 10% of all cases are inception by these three genes [91]. Another genetic risk factor for AD is apolipoprotein E, a lipid metabolism regulator with a preference for beta-amyloid protein. Greater sporadic and familial types of AD that manifest after the age of 65 have been connected to the APOE isoform e4 gene, which is located on chromosome 19 [92]. One apolipoprotein e4 (APOE4) allele does not always cause AD, but about 50% of individuals with one allele and 90% of individuals with two alleles get AD. Every APOE4 allele also delays the disease's start. Possessing the APOE e4 allele is an important risk factor for AD. Both familial and sporadic cases of AD include variations in the gene encoding the sortieing receptor, sortilin 1 (SORT1), which is necessary for moving APP from the cell surface to the Golgi–endoplasmic reticulum complex [93].

#### *Diagnosis*

Primary care physicians (PCPs) (family doctors, internal medicine doctors, and general practitioners), as well as diagnosing aging is a specialty practiced by geriatricians, neurologists, geriatric psychiatrists, and neuropsychologists. AD and other forms of dementia. According to studies, PCPs typically provide the initial dementia diagnosis [94, 95]. One study found that 85% of people were first diagnosed with and were then diagnosed with the help of non-specialist physicians and the remaining 15% by a specialist [96]. Of those, 44% were by neurologists and 34% by psychiatrists and 22% were by geriatricians [97]. By 2050, there will be three times as many people with Alzheimer's as there are today, predicts recent research. According to an investigation from the Institute for Health Metrics and Evaluation (IHME) that was written about in *The Lancet*, 153 million individuals globally will have Alzheimer's disease by the year 2050 [98]. Nearly 40% of PCPs claimed they would never, "only occasionally, or never" feel comfortable diagnosing AD on their own [99].

#### *Differential diagnosis*

The diagnosis includes differential therapy such as pseudodementia, vascular dementia, Lewy body dementia and frontotemporal lobar degeneration are some of the differential diagnoses of Alzheimer's dementia. When testing for AD, it is also important to exclude other conditions such as memory loss linked to old age, drug usage, vitamin B12 shortfall, dialysis patients, issues with the thyroid, and polypharmacy [100].

#### *Lewy body dementia (LBD)*

LBD affects 15% of patients with dementia on average. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), it can be defined as a neurocognitive disorder/senile dementia with Lewy bodies [101] The histological abnormalities noticed in these

people are cortical Lewy bodies. Lewy body counts are associated with dementia severity [102]. These masses are eosinophilic circular intracytoplasmic inclusions with a free fibril on top and a dense eosinophilic center point. The core is composed of protein clumps comprising synuclein and ubiquitin. Rapid eye movement (REM) sleep behavior patterns disorder and severe anti-psychotic sensitivity are suggestive clinical features of Lewy body dementia patients, who also exhibit main clinical features such as fluctuating cognition, visible hallucinations, and one or more Parkinson's symptoms that appear after the occurrence of cognitive loss) and suggestive biomarkers (poor uptake of iodine-123-meta-iodobenzylguanidine) (123-MIBG), decreased dopamine transporter uptake in the basal ganglia on single photon emission computed tomography (SPECT) or positron emission tomography (PET), and rapid eye movement (REM) sleep without atonia on polysomnography (PSG) [103–106]. A probable diagnosis is given when a patient exhibits two core symptoms, one suggestive trait, and one or more core symptoms. A likely diagnosis is given if the patient only displays one core characteristic or one or more implicated traits [107].

#### *Frontotemporal dementia (FTD)*

Frontotemporal dementia (FTD) is a diverse neurological condition that manifests as specific abnormalities in behavior, language, and motor function [108]. Even though it is sometimes thought of as an uncommon condition, FTD—which has an estimated lifetime risk of 1 in 742—is perhaps the most prevalent kind of dementia seen by persons under the age of 60 [109]. Patients experience behavior and personal abnormalities before dementia develops slowly over time, with or without language impairment. Pick disease is a former name for FTD settled on the histological finding of intra-neuronal view called "Pick bodies". The two categories of FTD are language variations and behavioral variants [110–112]. For a behavioral variations to be diagnosed, three of the symptoms listed above loss of compassion, disinhibition, apathy, stereotyped or compulsive actions, hyperorality, and a decrease in social psychological feature and executive functioning must be present [113]. The language skills of the language variety is declining [114].

#### *Dialysis dementia*

Chronic dialysis has a neurological side effect called "dialysis dementia". Dialysis itself, metabolic problems, vascular reasons or both could be to blame. It was once attributed to aluminum toxicity, but because substitutes for substances containing aluminum are now widely used, this is no longer the case. The precise mechanism is still a mystery [115].

#### *Brain magnetic resonance imaging (MRI) analysis*

Studies on machine learning that used neuroimaging data for the creation of diagnostic tools significantly assisted automated brain MRI segmentation and categorization. Most of them produce and extract characteristics from MRI data by hand. These manually developed features are inserted into support vector machines and logistic regression models for additional analysis. These multi-step, complex patterns, human specialists are absolutely necessary. Furthermore, datasets from neuroimaging investigations frequently have a small number (n) of samples. Neuroimaging datasets often only feature a few hundred photos, in contrast to the millions of images seen in image classification datasets used for object recognition and classification (such as the Image Net database). But in order to create strong neural networks, a sizable dataset is necessary [116].

#### *Treatment/management*

Until now, there was no cure for AD, but only symptomatic treatment is available. The objectives of treatment are to reduce behavioral problems (such as depression, psychosis, agitation, and sleeplessness) and to improve cognition.

#### *Psychosocial support*

Patients with AD can function better when their environment is altered, their families are supported, and other medical comorbidities are prevented. A patient's surroundings need to be adjusted in order to keep AD

**Table 2** Below table contains some drugs used in the management of Alzheimer's disease (AD) [123]

| Drug name | Dosage | Side effects |
|---|---|---|
| Donepezil (Aricept) | 5–10 mg PO qHs | Nausea, vomiting, diarrhea |
| Tacrine | 20–40 mg PO qid | Nausea, vomiting, muscle cramps, hepatotoxicity |
| Galantamine (Remini) | 8–12 mg PO bid | Nausea, fatigue, diarrhea |
| Rivastigmine (Exelon) | 2–6 mg PO bid | Nausea, vomiting, diarrhea, lowered blood pressure, loss of appetite |
| Aducanumab | 1 mg/kg IV infusion for 4 Weeks | Allergic reactions—skin rash, swelling of face, lips and tongue<br>Diarrhea |

PO, oral route of administration; qHs, once a day at bedtime; qid, four times a day; bid, twice a day; IV, intravenous

patients in their homes for as long as feasible. Written daily reminders might be useful for carrying out everyday tasks. It is crucial to maintain a healthy diet, regular exercise, and good hygiene. Since patient are susceptible to depression, anxiety disorders, and insomnia, family support is crucial [117].

#### *Pharmacotherapy in cognitive disturbance treatment*

Drugs including antipsychotics, antidepressants, and hypnotics are utilized to treat behavioral issues and cognitive enhancers to treat cognitive loss and are some of the current medication choices available to doctors treating AD. Two medication classes cholinesterase inhibitors and partial N-methyl D-aspartate (NMDA) antagonists have been approved for the treatment of AD [118].

#### *Anti-amyloid antibodies in AD*

The only anti-amyloid monoclonal antibody currently allowed for the treatment of AD is aducanumab, and the FDA's (US Food and Drug Administration) clearance was based on evidence from the FDA. Aducanumab was the first medicine to demonstrate that eliminating beta-amyloid from the brain, one of the signs of AD, slowed the decline in cognition and function in people with early Alzheimer's. Aducanumab is intended to target and eliminate certain forms of beta-amyloid that build up from plaques and may cause the death of cells and tissue loss in regions of the brain crucial for memory, cognition, learning, and behavior. Aducanumab is a monoclonal immunoglobulin G1 (IgG1) antibody that binds to the amino acids 3, 7, and 18 of amyloid-. The amyloid residues Phe4, His6, Glu3, and Arg5 are mainly accountable for the interaction between the amyloid- and the aducanumab Fab region. The quantity of beta-amyloid plaques the brain continues to manufacture is reduced with aducanumab. Additionally, getting rid of it could make other brain functions run more effectively [119].

#### *Cholinesterase inhibitors*

Acetylcholine is a neurotransmitter that interacts with nerve cells and is essential for memory, learning, and other cognitive functions. Acetylcholine is produced more in the body as an outcome of cholinesterase inhibitors [120]. Donepezil, rivastigmine, and galantamine are the three drugs in this class that have FDA clearance for the treatment of AD. Donepezil is effective at treating AD at all stages. Treatment for MCI and dementia stages is permitted with galantamine [121] and rivastigmine. Galantamine and donepezil are acetyl cholinesterase inhibitors that work quickly and repetitively. Rivastigmine inhibits butyryl cholinesterase and acetyl cholinesterase slowly and irreversibly. Donepezil has been recommended above all others because of its once-daily dose. A once-daily extended-release capsule of galantamine or a twice-daily pill is also an option. Unless there is severe liver disease or end-stage renal illness, it cannot be utilized. Rivastigmine is available orally and topically. Cholinesterase inhibitors' most common gastrointestinal adverse reactions include nausea, vomiting, and diarrhea. The prevalence of sleep issues increases when donepezil is used. Due to the fact that these medications increase vagal tone, which can cause bradycardia, cardiac conduction errors, and syncope for people with severe cardiac conduction abnormalities, they should not be administered [122]. Different medications used to treat the conditions are listed below in Table 2 [123].

#### *Estrogen replacement therapy*

There is a lot of research showing how estrogen affects development of the brain, regeneration of neurons, their survival, and plasticity. It seems to work in the brain via improving transcription and mediating nongenomic occurrences. Men, on the other hand, have an inbuilt demand of estrogen due to the brain's ability to aromatize testosterone, whereas postmenopausal women suffer a sudden fall in estrogen production that raises their chance of developing AD. There is growing proof that estrogen replacement therapy (ERT) may help postmenopausal women delay the onset of AD by enhancing psychological features and lowering the chance of developing both AD and cognitive impairment. Currently, a class of drugs called selective estrogen-receptor modulators is being researched for AD. Raloxifene, raloxifene, tamoxifen, and tibolone) function as estrogen agonists in some tissues and antagonists in different tissues [124].

#### *Anti-inflammatory medications in AD*

Some retrospective epidemiological investigations have provided evidence in favor of the idea that anti-inflammatory medication can decrease AD progression [44]. Non-steroidal anti-inflammatory drugs (NSAIDS) prospective double-blind clinical trials in AD are quite rare. Non-randomized studies using NSAIDS such as indomethacin, ibuprofen, diclofenac, naproxen, steroids as prednisone at low dose and other anti-inflammatory drugs (hydroxychloroquine, colchicine) shown encouraging outcome in controlling the progression of the illness [125].

#### *Antioxidant agents*

Vitamin E and selegiline are antioxidants. According to current views, AD may be caused by an increase in

**Table 3** Ongoing phase 3 trials on anti-amyloid and non-anti-amyloid therapy in AD by year 2023 [129]

| Agent | Mechanism of action | Target type and therapeutic purpose | Clinical Trials gov identifier | Start date | Status of estimated primary completion date |
|---|---|---|---|---|---|
| Crenezumab | Monoclonal antibody directed at oligomers | Remove amyloid | NCT02670083 | Dec 2013 | March 2022 |
| Gantenerumab | Monoclonal antibody | Remove amyloid | NCT02051608<br>NCT01224106 | Nov 2010 | Nov 2022 Active<br>Not recruiting |
| GV-971(sodium oligomannate) | Aβ aggregation inhibitor | Amyloid-related | NCT02293915 | Oct 2022 | Oct 2026 |
| AXS-05 (dextromethorphan and bupropion) | Sigma-1 receptor agonist, NMDA receptor antagonist and dopamine-nor epinephrine reuptake inhibitor | Neurotransmitter based; BPSD (agitation) | NCT0494755<br>NCT05557409 | June 2021<br>Sept 2022 | June 2023<br>June 2025<br>Recruiting |
| Aducanumab | Selectively binding amyloid aggregates in both the oligomeric and fibrillary states rather than amyloid monomers | Remove amyloid | NCT04241068<br>NCT05310071 | Mar 2022<br>June 2022 | Oct 2023<br>Dec 2025<br>Ongoing |
| AGB101 (Levetiracetam) | SV2A Modulator, CA3 area downregulation | Synaptic plasticity, neuroprotection | NCT03486938 | Dec 2022 | Dec 2025 |
| Donepezil | Acetylcholinesterase inhibitor, adipokine modulation | Neurotransmitter receptor | NCT04661280<br>NCT05592678 | Feb 2022<br>Feb 2023 | Aug 2024<br>Feb 2027 |
| E2814 | Anti -tau monoclonal antibody | Tau | NCT01760005<br>NCT05269394 | Dec 2012<br>Dec 2021 | Oct 2027<br>Jul 2017 |
| Lecanemab | Anti-amyloid monoclonal antibody directed at amyloid protofibrils and amyloid plaques | Aβ | NCT01760005<br>NCT03887455<br>NCT04468659<br>NCT05269394 | Dec 2012<br>Mar 2019<br>Jul 2020<br>Dec 2021 | Oct 2027<br>Sept 2027<br>Oct 2027<br>Jul 2027 |
| Solanezumab | Anti-amyloid monoclonal antibody directed at amyloid monomers | Aβ | NCT01760005<br>NCT02008357 | Dec 2012<br>Feb 2014 | Oct 2027<br>Dec 2022 |

NCT, National Clinical Trial; GV-971, sodium oligomannate; AXS-05, dextromethorphan and bupropion; NMDA, N-methyl-D-aspartate; BPSD, behavioral and psychological symptoms of dementia, AGB101, low dose preparation of levetiracetam; SV2A, synaptic vesicle glycoprotein 2A; CA3, Cornu ammonis; E2814, high affinity antibody targeting microtubule binding repeat domain of tau; Tau, tubulin associated unit; Aβ, amyloid beta

free-radical production, which would have a direct harmful effect. The presence of catecholamines and relatively low concentration of antioxidant enzymes in the brain may make it susceptible to the harmful effects of oxidative stress which includes parameters such as superoxide dismutase (SOD), catalase (CAT), glutathione per-oxidase (GSH). AD has also been linked to an increase in free-radical production [126].

#### *Partial N-methyl D-aspartate (NMDA) memantine*

The partial NMDA antagonist memantine inhibits NMDA receptors and reduces intracellular calcium accumulation. It has been approved to treat mild-to-severe AD by the FDA. Common side effects include nausea, vomiting, headaches, and body pains. When used with cholinesterase inhibitors, it is beneficial. When AD is in the middle to late stages, controlling anxiety, hopelessness, and psychosis is essential. Due to their anticholinergic effects, tricyclic antidepressants should be avoided. Only when the patient or caretaker has reached their crisis point should anti-psychotic be administered for acute agitation. However, the minor advantages should be looked at against the slight risk of stroke and death. In particular, controlling behavioral issues benefits from environmental and behavioral methods. Maintaining a familiar like atmosphere, keeping personal comfort in check, giving security objects, refocusing attention, eliminating doorknobs, and avoiding confrontation are all applied in this method that can be quite effective in managing behavioral disorders. Mild sleep problems can be lessened to lessen the load on caretakers by getting view to sunlight and engaging in daytime exercise. The treatment's anticipated advantages are not great. If there are no discernible benefits or unacceptably severe adverse effects, treatment should be discontinued or changed. It has been demonstrated that regular aerobic exercise can halt the progression of AD [127].

#### *Plasma exchange with albumin 1 immunoglobulin*

Before blood cells are put back into the bloodstream, a method called plasma exchange separates the plasma from them. The AMBAR (Alzheimer's Management By Albumin Replacement) trial is intended to investigate if

Pulmonary Embolism (PE) with infusion of human albumin coupled with Intravenous immune globulin (IVIG) can stop or postpone progression of the cognitive and functional impairment in individuals with mild-to-severe AD. Clinical effectiveness is assessed using both the Alzheimer Disease Assessment Scale—Cognitive Subscale (ADAS-Cog) and Alzheimer Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL) scores as co-primary outcomes. The AMBAR study examines plasma exchange with therapeutic albumin replacement as a novel strategy with immediate clinical applicability for the treatment of Alzheimer's disease [128].

#### *Clinical trials of new drugs for Alzheimer's disease*

Clinical trials are still being conducted, and researchers have created and are currently putting to the test a wide range of potential treatments with various targets, such as anti-amyloid and anti-tau, neurotransmitter modification, anti-neuroinflammation and neuro protection, cognitive improvement, and treatments that relieve behavioral symptoms and psychological symptoms [129]. The following Table 3 represents the data of the current state of ongoing clinical trials for anti-amyloid and non-anti-amyloid therapy in AD as per clinical trials.gov.

Crenezumab in the CREAD (A Study of Crenezumab Versus Placebo to Evaluate the Efficaciousness and Safety in the Participants With Symptomatic to Mild AD) trials, which are intended to treat prodromal to mild AD, crenezumab is being tested [130]. A human recombining monoclonal IgG1 antibody called gantenerumab binds to the protein Aβ's amino-terminal and central regions. Gantenerumab exhibits a higher affinity for Aβ oligomers and fibrils compared to Aβ monomers [131]. The amyloid-binding agent GV-971 (sodium oligo-mannurarate) can further destabilize and impede aggregation before enhancing Aβ clearance [132]. Additionally, GV-971 can alter gut Aβ microbiota and reduce neuroinflammation brought on by dysbiosis [133]. By suppressing the expression of ADP-ribosylation factor 1, coconut oil prevents the secretion and aggregation of Aβ and limits the development of APP [134]. Dextromethorphan (DMP) and bupropion are used together as the medication AXS-05. DMP acts as an antagonist of the NMDA receptor, an agonist for the sigma-1 receptor, a modulator of the glutamate receptor, and an inhibitor of the NE and serotonin transporters [135]. Recently, food and drug administration has a new drug treatment for early Alzheimer's as a drug named Leqembi. Studies on the medication, which is given as an intravenous infusion every two weeks, indicate that it is more promising than the limited of alternative treatments that are now available. However, a number of experts on the disease argued that the medical data did not clearly show if Leqembi may decrease cognitive deterioration to the point where patients would notice it. Even a recent report of findings from a significant 18-month clinical trial, which was co-authored by scientists from the main manufacturer of the drug and published in the New England Journal of Medicine, stated that "longer trials are warranted to determine the efficacy and safety of Leqembi in early AD"[136].

## Discussion

This review focuses on all insights related to progression, risk factors, mutations, genetics, precursors, mechanisms, pathways, diagnosis, pharmacotherapy and treatments of AD. The cognitive decline refers to the occurrence of dementia. Secretase enzymes such as (α, β and γ) play a leading role in the progression of AD by APP [137]. The dysregulation of TMP21, a selective modulator of secretase, impairs the processing of APP. Dementia is a general term used to describe a loss of memory function that is intense enough to make daily tasks difficult. Treatment of AD is still symptomatic and the prognosis of the disease does not change. Cholinesterase enzyme inhibitors like galantamine, donepezil, and rivastigmine and NMDA antagonists like memantine boost basic cognitive process and alertness, but the progression remains unchanged. Numerous studies indicate that altering lifestyle choices, including nutrition and exercise, can enhance brain function and lessen AD without the need for medical treatment, and this strategy is now recommended as the initial treatment for all AD patients. In recent years, research has concentrated on finding ways to combat pathological signs of AD such as Aβ and p-tau. Future treatments, such as disease-modifying therapy, may halt the course of AD by focusing on the route. A number of medications, including Interlukin-17 (IL-17) solanezumab, bapineuzumab, avagacestat, and tarenflurbil, have entered clinical trials, although they have not yet shown clinically significant efficacy. With a gradual beginning and progressive deterioration, AD is a neurological disorder that impairs a range of behavioral and cognitive skills, including memory, understanding, language, attention, reasoning, and judgement [138].

As the condition progresses, the symptoms of Alzheimer's alter. Based on the severity AD is classified into preclinical or presymptomatic, mild, and dementia-stage classes. These stages are distinct from how AD is classified in the DSM-5. The earliest and most common presenting symptom is episodic short-term memory loss with relatively preserved long-term memory, and even in most people without it, it may be generated. Short-term memory issues lead to issues with multitasking and

abstract cognition, which are then preceded by issues with problem-solving, judgment, executive functioning, lack of motivation, and disorganization. In its early phases, executive functioning impairment can range from modest to severe. The following two are visuospatial skill deficits and language dysfunction. It is also normal to encounter mental symptoms including apathy, social withdrawal, inhibition, agitation, psychosis. Late in the course of the illness, symptoms such olfactory dysfunction, dyspraxia, sleep problems, extra pyramidal efferent signs like dystonia, catharsis, and Parkinsonism manifest. Amyloid (Aβ) plaque extracellular aggregates and hyperphosphorylated protein-based intracellular deposits have been found in the cortical and limbic areas of the human brain. Pathogenesis has been connected to neurofibrillary tangles. Its features include memory loss and progressive neurocognitive impairment. Several signaling pathways in the pathology of AD such as amyloid β plaque cleavage, metal ion hypothesis, amyloid β degradation, initiation of amyloidogenic and non-amyloidogenic pathway, oxidative stress hypothesis, metabolic syndrome, insulin resistance and tau phosphorylation associated, apolipoprotein (APOE)-cholesterol, neurofibrillary tangles (NFTs) accumulation and Insulin resistance prove to be beneficial in order to find the definite target for treatment of AD. The aberrant processing of APP by -secretes and -secretases results in the constitution of the monomers Aβ 40 and Aβ 42. Senile plaques are created when these monomers oligomerize and agglomerate [139].

Furthermore, elevated A-peptide concentrations in the central nervous system initiate microglial invasion during disease development. Drugs such as donepezil, galantamine, rivastigmine, and memantine are currently available treatments for AD, and they only provide symptomatic relief [140].

Polypharmacology is the most efficient technique to influence several physiological pathways in a pertinent manner and without unfavorable side effects, nevertheless, as AD is multifactorial in nature and involves so many physiological channels. The present accessibility of many pharmacoinformatics tools, the use of artificial intelligence and networks to conduct extensive analysis, and the availability of constructs like pharmacophores to guide this process are some key components for the growth of the ensuing decades. The issue moving forward will be to effectively use the many tools and technologies available for drug design in order to keep making progress in this discipline. Finding medications that could alter the course of the condition has therefore been a top goal. The major focus has been on amyloid-targeting treatments for approximately 30 years. Recently, however, phase III studies for long-awaited drugs have been unable to show any therapeutic outcomes. Researchers are now concentrating their attention on medications that target the tau protein since tau protein appears to be more linked with the severity of cognitive decline than amyloid. Immunotherapies represent the majority of anti-tau drugs now undergoing clinical trials, and these studies are still in their early phases. Phase II has been achieved for one Anti-tau vaccine (AADvac1) and four anti-tau monoclonal antibodies such as gosuranemab, tilavonemab, semorinemab, and zagotenemab. In this work, we evaluate potential disease-modifying drugs tested in clinical trials and present updated information on drugs now undergoing clinical review [141].

Aducanumab (Aduhelm) was approved by the Food and Drug Administration (FDA) for the treatment of a few instances of A.D. The medication was taken into account in patients with early-stage AD, including those who had mild cognitive impairment from AD. The lecanemab clinical study demonstrated decreased amyloid markers in early Alzheimer's infection and moderately lessened declines in cognitive and function tests. The Food and Drug Administration (FDA) has authorized the monoclonal antibody aducanumab, which works by specifically targeting (Aβ) oligomers and fibrils. It has been shown to diminish Aβ accumulation and halt the course of cognitive impairment. It was also said to have an impact on the second characteristic of AD, lowering the phospho-Tau level measured in cerebrospinal fluid (CSF) [142].

Immunotherapies represent the majority of anti-tau drugs now undergoing clinical trials, and these studies are still in their early phases. Phase II has been achieved for one anti-tau vaccine (AADvac1) and four anti-tau monoclonal antibodies such as gosuranemab, tilavonemab, semorinemab, and zagotenemab. In this work, we evaluate potential disease-modifying drugs tested in clinical trials and present updated information on drugs now undergoing clinical review. Immunotherapies have been at the forefront of these efforts in recent years. In a nutshell, immunotherapies employ the patient's immune system to treat an illness; typical immunotherapies for AD involve monoclonal antibodies or vaccinations. Due to its neurotoxicity, the majority of these therapies target Aβ synthesis and deposition, however treatments specifically targeting tau protein are also being investigated. There is always a need for the study and development of new safe and effective therapies because of the wide variation in the efficacy and safety of these treatments [143].

Research on the improvement of cognitive and functional abilities in Alzheimer's disease patients treated with plasma exchange + albumin replacement is confirmed, it will open up a promising new field for developing treatment approaches for this fatal condition [144].

Recent clinical trial findings indicate that apathy symptoms may improve after treatment with drugs like methylphenidate, which may play a crucial role in conjunction with developing non-pharmacological therapeutic approaches. Various drugs are used in the treatment of AD such as galantamine, rivastigmine, donepezil along with recently FDA approved drugs as Aducanumab and Lecanemab. Because both aducanumab and lecanemab will be FDA approved medications in 2023, although aducanumab is preferred over lecanemab because of adverse effects. Till now, no cure has been found, but treatment with Aducanumab is effective. This monoclonal antibody IgG1 is the newest AD treatment [145].

Sex differences should be considered while researching the pathophysiology of AD since the prevalence of the disease differs between men and women and may indicate the necessity for various therapy modalities [146]. Combination pharmacotherapy may also produce advantages for AD treatment. Medicines that, when combined, provide synergistic or additive effects yet are ineffective when taken alone [147].

The timetable for recruitment and failures in recruitment, difficulty in forecasting success based on earlier research for particular medications, and total expenditures for such large-scale clinical trials are some of the ongoing difficulties noted. A better indicator of successful clinical trials can be developed with more collaboration between researchers, corporate and governmental financing, and screening of at-risk groups [148].

The two main neuropathological signs of AD that have been studied are Tau (tangles) aggregation and Aβ-plaque development. This review offers useful information on current developments in the molecular pathways linked to Aβ- and tau, as well as glial dysfunction in AD [149]. Risk factors linked to the pathophysiology of AD have also been explored and generalized. Age is considered as the most prominent risk factor in the prognosis of AD [150]. Progression of various pathways are associated with AD development but the most common pathways are oxidative stress related pathways leading to mitochondrial dysfunction and amyloid beta pathways [151].

Biomarkers can be used as CSF or imaging depending on cost, availability, and patient preference, in particularly difficult cases where the diagnosis is ambiguous and both patient and clinician want to determine the etiology of cognitive impairment to modify the plan of care (counseling and prescription of cholinesterase inhibitors and/or memantine).To better understand the complexities of this diverse illness and increase diagnostic precision, the study suggests investigating new biomarkers outside of the amyloid and tau pathology [152].

It is necessary to understand the molecular etiology of AD and its connections in order to develop appropriate therapeutic methods for the treatment of AD in cases when current pharmacological treatments cannot stop its development and progression.

## Conclusion

Among all the risk factors, age is the major cause of AD development. The pathogenesis behind AD progression is mainly based on the accumulation of amyloid (Aβ) plaques and neurofibrillary tangles, which result from the accumulation of hyperphosphorylated beta-protein which indicated the cognitive dysfunction.

Prime receptor for triggering AD is TREM 2 which is unregulated on microglia and is surrounded by amyloid plaques. Genetic mutations of APP, PSEN1 and PSEN2 are key reasons for AD development.

The current state of ongoing clinical trials states that treatment of aducanumab has so far proven beneficial. According to the evidences discussed in their paper, it is far from ensured that inhibiting the secretase enzymes involved in the processing of APP, such as α, β, and γ will result in the game-changing therapeutic success for treating AD.

Thus, there is a need to conduct research studies in order to reduce the development of AD. We must look into accurate and molecular diagnostics, as well as genetic profiles that will reveal the anticipated course of disease and serve as the foundation for choosing preventative measures.

We conclude by offering an outlook on a future with personalized medicine for AD, in which patients and care partners are empowered and more actively involved in the management of their health and disease and in which customized combinations of lifestyle interventions and disease-modifying treatment are provided as needed to target AD pathology to stop or delay the onset of dementia.

**Abbreviations**

| | |
|---|---|
| AADvaC1 | Anti-tau vaccine |
| Aβ | Amyloid beta |
| Aβ | Amyloid beta 42 substrate |
| AChEIs | Acetylcholine inhibitors |
| AChRs | Acetylcholine receptors |
| AD | Alzheimer's disease |
| ADAM10 | A Disintegrin and metalloprotease |
| ADAS-Cog | Alzheimer's disease Assessment Scale Cognitive Subscale |
| ADCS-ADL | Alzheimer's disease Cooperative Study-Activities of Daily Living Scale |
| Al | Aluminum |
| Akt | Serine/threonine protein kinase |
| AMBAR | Alzheimer's management by albumin replacement |

| | |
|---|---|
| APH1 | Anterior pharynx defective 1 |
| APP | Amyloid precursor protein |
| APOP | Apolipoprotein |
| ApoE | Apolipoprotein E |
| Apo E2 | Allele of apolipoprotein E2 |
| Apo E3 | Allele of apolipoprotein E3 |
| Apo E4 | Allele of apolipoprotein E4 |
| ATP | Adenosine triphosphate |
| AXS-05 | Dextromethorphan and Bupropion |
| AGB 101 | Low dose preparation of levetiracetam |
| BACE1 | β Site-amyloid converting enzyme 1 |
| BBB | Blood brain barrier |
| bid | Twice a day |
| BPSD | Behavioral psychological symptoms of dementia |
| CAA | Cerebral amyloid angiopathy |
| $Ca2^+$ | Calcium |
| CA3 | Cornu ammonis |
| CAT | Catalase |
| CHAP | Chicago Health and Aging Project |
| CNS | Central Nervous System |
| CREAD | A study of crenezumab versus placebo to evaluate the efficacy and safety in participants with prodromal to mild Alzheimer's disease |
| CSF | Cerebrospinal fluid |
| CTPSG | Centralized telemetry processing system |
| CT | Computed tomography |
| Cu | Copper |
| DDX17 | DEAD-Box Helicase 17 |
| DMP | Dextromethorphan |
| DNA | Deoxyribonucleic acid |
| DS | Down syndrome |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders |
| EOAD | Early-onset Alzheimer's disease |
| ER | Endoplasmic reticulum |
| ERT | Estrogen replacement therapy |
| E2814 | High affinity antibody targeting microtubule binding repeat domain of tau |
| FAAH | Fatty acid amide hydrolase |
| FAD | Flavin adenine dinucleotide |
| FDA | Food and Drug Administration |
| Fe | Iron |
| $Fe2^+$ | Iron compound |
| FTD | Frontotemporal dementia |
| Gov | Government |
| GSH | Reduced glutathione |
| GSSG | Glutathione disulfide |
| GSK-3 | Glycogen synthase kinase 3 |
| GV-971 | Sodium oligomannate |
| HHV | Human herpes virus |
| HIV | Human immunodeficiency viruses |
| HSV | Herpes simplex virus |
| HPA | Hypothalamus pituitary adrenocortical |
| $H_2O$ | Water |
| $H_2O_2$ | Hydrogen peroxide |
| IDE | Insulin degrading enzyme |
| INOS | Inducible nitric oxide synthase |
| IV | Intravenous |
| IVIG | Intravenous immunoglobulin |
| IHME | Institute of Health Metrics and Evaluation |
| IgG1 | Immunoglobulin G |
| IL-17 | Interleukin 17 |
| KYN | Kynurenine |
| LOAD | Late-onset Alzheimer's disease |
| LBD | Lewy body dementia |
| MCI | Mild cognitive impairment |
| Mn | Manganese |
| MRI | Magnetic resonance imaging |
| NCT | National Clinical Trial |
| NCT | Nicastrin |
| NFTs | Neurofibrillary tangles |
| NMDA | N-Methyl-D-aspartate memantine |
| Nrf2 | Nuclear factor erythroid-derived 2-like 2 |
| NSAIDs | Non-steroidal Anti-inflammatory Drugs |
| OH | Hydrogen ion |
| $O_2$ | Oxygen gas |
| PCP | Primary care physician |
| PD | Parkinson's disease |
| PO | Oral route of administration |
| PCPs | Primary care physician |
| PE | Pulmonary embolism |
| PEN-2 | Presenilin enhancer 2 |
| PET | Positron emission tomography |
| PHFs | Paired helical filaments |
| PO | Oral route of administration |
| PSG | Polysomnography |
| PS1 | Presenilin 1 |
| PS2 | Presenilin 2 |
| PSEN 1 | Presenilin-1 |
| PPARs | Peroxisome proliferator activated receptor |
| qHs | Once a day at bedtime |
| qid | Four times a day |
| REM | Rapid eye movement |
| ROS | Reactive oxygen species |
| RNSx | Reactive nitrogen species |
| RONS | Reactive oxygen and nitrogen species |
| SARS-COV-2 | Severe Acute Respiratory Syndrome Coronavirus 2 |
| SApps | Soluble amyloid precursor protein |
| SD | Sleep deprivation |
| SNPs | Single-nucleotide polymorphisms |
| SOD | Superoxide dismutases |
| SORT 1 | Sortilin 1 |
| SP | Senile plaques |
| SPECT | Single photon emission computerized tomography |
| SV2A | Synaptic vesicle glycoprotein 2A |
| Tau | Tubulin associated unit |
| TMP21 | Transmembrane protein 21 |
| TRP | Tryptophan |
| Trp–KYN | Tryptophan–kynurenine |
| TREM 2 | Triggering receptor expressed on myeloid cells |
| US | United States |
| Zn | Zinc |

**Acknowledgements**
We are thankful for entire Pharmacology Department at DYPCOP, Akurdi for successful completion of work.

**Author contributions**
DJ contributed to the drafting of the paper, hypothesis, epidemiology and risk factors with scientific contributions. NS contributed in the interpretation of molecular mechanisms. NV contributed in treatment and management of AD. DS contributed in the clinical trials and its interpretation.

**Funding**
No funding sources were present.

**Availability of data and materials**
Cited reviews can be seen from https://pubmed.ncbi.nlm.nih.gov/.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

**Author details**
[1]Pharmacology Department, Dr. D.Y Patil College of Pharmacy, Akurdi, D.Y Patil Educational Complex, Sector Pradhikaran, Nigdi, Pune 411044, Maharashtra, India.

Received: 20 May 2023 Accepted: 13 December 2023
Published online: 11 January 2024

**References**

1. Moller HJ, Graeber MB. The case described by Alois Alzheimer in 1911. Historical and conceptual perspectives based on the clinical record and neurohistological sections. Eur Arch Psychiatry Clin Neurosci. 1998;248(3):111–22.
2. Hippius H, Neundorfer G. The discovery of Alzheimer's disease. Dialogues Clin Neurosci. 2003;5(1):101–8.
3. Cummings J, Lee G, Zhong K, Fonseca J, Taghva K. Alzheimer's disease drug development pipeline: 2021. Alzheimers Dement (N Y). 2021;7(1): e12179.
4. Frozza RL, Lourenco MV, De Felice FG. Challenges for Alzheimer's disease therapy: insights from novel mechanisms beyond memory defects. Front Neurosci. 2018;12: 334515.
5. Poddar MK, Banerjee S, Chakraborty A, Dutta D. Metabolic disorder in Alzheimer's disease. Metab Brain Dis. 2021;36:781–813.
6. Beata BK, Wojciech J, Johannes K, Piotr L, Barbara M. Alzheimer's disease-biochemical and psychological background for diagnosis and treatment. Int J Mol Sci. 2023;24:1059.
7. Vik-Mo AO, Bencze J, Ballard C, Hortobagyi T, Aarsland D. Advanced cerebral amyloid angiopathy and small vessel disease are associated with psychosis in Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2019;90:728–30.
8. Moussa-Pacha NM, Abdin SM, Omar HA, Alniss H, Al-Tel TH. BACE1 inhibitors: current status and future directions in treating Alzheimer's disease. Med Res Rev. 2020;40:339–84.
9. Bernstein A, Rogers KM, Possin KL, Steele NZR, Ritchie CS, Kramer JH, Geschwind M, Higgins JJ, Wohlgemuth J, Pesano R, Miller BL, Rankin KP, et al. Dementia assessment and management in primary care settings: a survey of current provider practices in the United States. BMC Health Serv Res. 2019;19:919.
10. Rahim F, Khalafi M, Davoodi M, Shirbandi K. Metabolite changes in the posterior cingulate cortex could be a signature for early detection of Alzheimer's disease: A systematic review and meta-analysis study based on 1H-NMR. Egypt J Neurol Psychiatry Neurosurg. 2023;59:1–14.
11. Hazegh FD, Kargar A, Noroozian M. Aducanumab: an uprising hope with vague horizons. Egyptian J Neurol Psychiatry Neurosurg. 2023;59:1–6.
12. Pfundstein G, Nikonenko AG, Sytnyk V. Amyloid precursor protein (APP) and amyloid β (Aβ) interact with cell adhesion molecules: Implications in Alzheimer's disease and normal physiology. Front Cell Dev Biol. 2022;10: 969547.
13. Battaglia S, Di Fazio C, Vicario CM, Avenanti A. Neuropharmacological modulation of N-methyl-D-aspartate, noradrenaline and endocannabinoid receptors in fear extinction learning: synaptic transmission and plasticity. Int J Mol Sci. 2023;24:5926.
14. Liu J, Chang L, Song Y, Li H, Wu Y. The role of NMDA receptors in Alzheimer's disease. Front Neurosci. 2019;13:43.
15. Kayed R. Infectious etiology and amyloidosis in Alzheimer's disease: the puzzle continues. J Biol Chem. 2021;297: 100936.
16. Liu Y, Zhou G, Song L, Wen Q, Xie S, Chen L, Wang L, Xie X, Chen X, Pu Y, Chen G, et al. DEAD-Box helicase 17 promotes amyloidogenesis by regulating BACE1 translation. Brain Sci. 2023;13:745.
17. Kinney JW, Bemiller SM, Murtishaw AS, Leisgang AM, Salazar AM, Lamb BT, et al. Inflammation as a central mechanism in Alzheimer's disease. Alzheimers Dement (N Y). 2018;4:575–90.
18. Gonzalez C, Pilar MD. Aging, depression and dementia: the inflammatory process. Adv Clin Exper Med. 2022;31:469–73.
19. Ryan KC, Ashkavand Z, Norman KR. The role of mitochondrial calcium homeostasis in Alzheimer's and related diseases. Int J Mol Sci. 2020;21:9153.
20. Skobeleva K, Shalygin A, Mikhaylova E, Guzhova I, Ryazantseva M, Kaznacheyeva E, et al. The STIM1/2-regulated calcium homeostasis is impaired in hippocampal neurons of the 5xFAD mouse model of Alzheimer's disease. Int J Mol Sci. 2022;23:14810.
21. Agrawal I, Jha S. Mitochondrial dysfunction and Alzheimer's disease: role of microglia. Front Aging Neurosci. 2020;12:252.
22. Tanaka M, Szabo A, Spekker E, Polyak H, Toth F, Vecsei L, et al. Mitochondrial impairment: a common motif in neuropsychiatric presentation? The link to the Tryptophan–Kynurenine metabolic system. Cells. 2022;11:2607.
23. Fernandes BS, Inam ME, Enduru N, Quevedo J, Zhao Z. The kynurenine pathway in Alzheimer's disease: a meta-analysis of central and peripheral levels. Braz J Psychiatry. 2023;45:286–97.
24. Hestad K, Alexander J, Rootwelt H, Aaseth JO. The role of tryptophan dysmetabolism and quinolinic acid in depressive and neurodegenerative diseases. Biomolecules. 2022;12:998.
25. Lloret A, Esteve D, Lloret MA, Cervera-Ferri A, Lopez B, Nepomuceno M, Monllor P, et al. When does Alzheimer's disease really start? The role of biomarkers. Int J Mol Sci. 2019;20:5536.
26. Bayraktar Y, Isik E, Isik I, Ozyilmaz A, Toprak M, Kahraman Guloglu F, Aydin S, et al. Analyzing of Alzheimer's disease based on biomedical and socio-economic approach using molecular communication, artificial neural network, and random forest models. Sustainability. 2022;14:7901.
27. Lee J, Kim HJ. Normal aging induces changes in the brain and neurodegeneration progress: review of the structural, biochemical, metabolic, cellular, and molecular changes. Front Aging Neurosci. 2022;14: 931536.
28. Kouter K, Nikolac Perkovic M, Nedic Erjavec G, Milos T, Tudor L, Uzun S, Mimica N, Pivac N, Videtic Paska A, et al. Difference in methylation and expression of brain-derived neurotrophic factor in Alzheimer's disease and mild cognitive impairment. Biomedicines. 2023;11:235.
29. Norton DJ, Parra MA, Sperling RA, Baena A, Guzman-Velez E, Jin DS, Andrea N, Khang J, Schultz A, Rentz DM, Pardilla-Delgado E, Fuller J, Johnson K, Reiman EM, Lopera F, Quiroz YT, et al. Visual short-term memory relates to tau and amyloid burdens in preclinical autosomal dominant Alzheimer's disease. Alzheimers Res Ther. 2020;12:99.
30. Jahn H. Memory loss in Alzheimer's disease. Dialogues Clin Neurosci. 2013;15:445–54.
31. Joyal M, Groleau C, Bouchard C, Wilson MA, Fecteau S. Semantic processing in healthy aging and Alzheimer's disease: a systematic review of the N400 differences. Brain Sci. 2020;10:770.
32. De Wit L, Marsiske M, O'Shea D, Kessels RPC, Kurasz AM, DeFeis B, Schaefer N, Smith GE, et al. Procedural learning in individuals with amnestic mild cognitive impairment and Alzheimer's dementia: a systematic review and meta-analysis. Neuropsychol Rev. 2021;31:103–14.
33. Laghrissi F, Douzi S, Douzi K, Hssina B. Intrusion detection systems using long short-term memory (LSTM). J Big Data. 2021;8:1–16.
34. Guzman VE, Jaimes S, Aguirre-Acevedo DC, Norton DJ, Papp KV, Amariglio R, Rentz D, Baena A, Henao E, Tirado V, Muñoz C, Giraldo M, Sperling RA, Lopera F, Quiroz YT, et al. A three-factor structure of cognitive functioning among unimpaired carriers and non-carriers of autosomal-dominant Alzheimer's disease. J Alzheimers Dis. 2018;65:107–15.
35. Strong JV, Arnold M, Schneider L, Perschl J, Villringer A, Fritz TH, et al. Enhanced short-term memory function in older adults with dementia following music-feedback physical training: a pilot study. Brain Sci. 2022;12:1260.
36. Cepukaityte G, Thom JL, Kallmayer M, Nobre AC, Zokaei N. The relationship between short- and long-term memory is preserved across the age range. Brain Sci. 2023;13(1):106.
37. Teng E, Manser PT, Shah M, Pickthorn K, Hu N, Djakovic S, Swendsen H, Blendstrup M, Faccin G, Ostrowitzki S, Sink KM, et al. The use of episodic memory tests for screening in clinical trials for early Alzheimer's Disease: a comparison of the free and cued selective reminding test (FCSRT) and the repeatable battery for the assessment of neuropsychological status (RBANS). J Prev Alzheimers Dis. 2023;10(1):41–9.
38. Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, Cummings J, van der Flier WM, et al. Alzheimer's disease. Lancet. 2021;397:1577–90.
39. Silva MVF, Loures CMG, Alves LCV, de Souza LC, Borges KBG, Carvalho MDG, et al. Alzheimer's disease: risk factors and potentially protective measures. J Biomed Sci. 2019;26:33.

40. Kaloni D, Negi A. A review on Alzheimer's disease. Int J Neurodegener Dis. 2019;2:010.
41. Alldred MJ, Martini AC, Patterson D, Hendrix J, Granholm AC. Aging with Down syndrome-where are we now and where are we going? J Clin Med. 2021;10:4687.
42. Rodrigues M, Nunes J, Figueiredo S, Martins de Campos A, Geraldo AF, et al. Neuroimaging assessment in Down syndrome: a pictorial review. Insights Imaging. 2019;10:52.
43. Bellenguez C, Grenier-Boley B, Lambert JC. Genetics of Alzheimer's disease: where we are, and where we are going. Curr Opin Neurobiol. 2020;61:40–8.
44. Andrade GJ, Santiago BA, Jeronimo AP, Vargas RI, Cadena SAR, Sanchez GC, Pozo-Molina G, Mendez CCF, Cardenas AMD, Diaz CS, Pacheco HM, Luna MJ, Soto RLO, et al. Alzheimer's disease: an updated overview of its genetics. Int J Mol Sci. 2023;24:3754.
45. Ibanez L, Cruchaga C, Fernández MV. Advances in genetic and molecular understanding of Alzheimer's disease. Genes (Basel). 2021;12:1247.
46. Armstrong RA. Risk factors for Alzheimer's disease. Folia Neuropathol. 2019;57:87–105.
47. Association A. Alzheimer's disease facts and figures. Alzheimer Dement. 2023;16:391–460.
48. Abate G, Memo M, Uberti D. Impact of COVID-19 on Alzheimer's disease risk: viewpoint for research action. Healthcare (Basel). 2020;8:286.
49. Zhang T, Chen D, Lee TH. Phosphorylation signaling in APP processing in Alzheimer's disease. Int J Mol Sci. 2019;21:209.
50. Qiu K, Zhang X, Wang S, Li C, Wang X, Li X, Wu Y, et al. TMP21 in Alzheimer's disease: molecular mechanisms and a potential target. Front Cell Neurosci. 2019;13:328.
51. Lee MH, Siddoway B, Kaeser GE, Segota I, Rivera R, Romanow WJ, Liu CS, Park C, Kennedy G, Long T, Chun J, et al. Publisher correction: somatic APP gene recombination in Alzheimer's disease and normal neurons. Nature. 2019;566:E6.
52. DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. Mol Neurodegener. 2019;14:32.
53. Takeda K, Uda A, Mitsubori M, Nagashima S, Iwasaki H, Ito N, Shiiba I, Ishido S, Matsuoka M, Inatome R, Yanagi S, et al. Mitochondrial ubiquitin ligase alleviates Alzheimer's disease pathology via blocking the toxic amyloid-β oligomer generation. Commun Biol. 2021;4:192.
54. Nakamura M, Li Y, Choi BR, Matas-Rico E, Troncoso J, Takahashi C, Sockanathan S, et al. GDE2-RECK controls ADAM10 α-secretase-mediated cleavage of amyloid precursor protein. Sci Transl Med. 2021;13:6178.
55. Ju Y, Tam KY. Pathological mechanisms and therapeutic strategies for Alzheimer's disease. Neural Regen Res. 2022;17:543–9.
56. Toledo JB, Liu H, Grothe MJ, Rashid T, Launer L, Shaw LM, Snoussi H, Heckbert S, Weiner M, Trojanwoski JQ, Seshadri S, Habes M, et al. for the Alzheimer's disease neuroimaging initiative. Disentangling tau and brain atrophy cluster heterogeneity across the Alzheimer's disease continuum. Alzheimers Dement (N Y). 2022;8: e12305.
57. Akasaka MK, Manya H. The role of APP O-glycosylation in Alzheimer's disease. Biomolecules. 2020;10:1569.
58. Dai MH, Zheng H, Zeng LD, Zhang Y. The genes associated with early-onset Alzheimer's disease. Oncotarget. 2017;9:15132–43.
59. Lazarev VF, Dutysheva EA, Kanunikov IE, Guzhova IV, Margulis BA. Protein interactome of amyloid-β as a therapeutic target. Pharmaceuticals (Basel). 2023;16(2):312.
60. Rao CV, Asch AS, Carr DJJ, Yamada HY. "Amyloid-beta accumulation cycle" as a prevention and/or therapy target for Alzheimer's disease. Aging Cell. 2020;19: e13109.
61. Penke B, Bogar F, Fulop L. β-amyloid and the pathomechanisms of Alzheimer's disease: a comprehensive view. Molecules. 2017;22:1692.
62. Gugliandolo A, Chiricosta L, Silvestro S, Bramanti P, Mazzon E. α-Tocopherol modulates non-amyloidogenic pathway and autophagy in an in vitro model of Alzheimer's disease: a transcriptional study. Brain Sci. 2019;9:196.
63. Simic G, Babic Leko M, Wray S, Harrington C, Delalle I, Jovanov-Milošević N, Bažadona D, Buee L, De Silva R, Di Giovanni G, et al. Tau protein hyperphosphorylation and aggregation in Alzheimer's disease and other tauopathies, and possible neuroprotective strategies. Biomolecules. 2016;6:6.
64. Congdon EE, Sigurdsson EM. Tau-targeting therapies for Alzheimer disease. Nat Rev Neurol. 2018;14:399–415.
65. Kurkinen M, Fułek M, Fułek K, Beszłej JA, Kurpas D, Leszek J, et al. The amyloid cascade hypothesis in Alzheimer's disease: should we change our thinking? Biomolecules. 2023;13:453.
66. Wu T, Lin D, Cheng Y, Jiang S, Riaz MW, Fu N, Mou C, Ye M, Zheng Y, et al. Amyloid cascade hypothesis for the treatment of Alzheimer's disease: progress and challenges. Aging Dis. 2022;13:1745–58.
67. Buccellato FR, D'Anca M, Fenoglio C, Scarpini E, Galimberti D. Role of oxidative damage in Alzheimer's disease and neurodegeneration: from pathogenic mechanisms to biomarker discovery. Antioxidants (Basel). 2021;10:1353.
68. Simunkova M, Alwasel SH, Alhazza IM, Jomova K, Kollar V, Rusko M, Valko M, et al. Management of oxidative stress and other pathologies in Alzheimer's disease. Arch Toxicol. 2019;93:2491–513.
69. Babic Leko M, Langer Horvat L, Spanic Popovacki E, Zubcic K, Hof PR, Simic G, et al. Metals in Alzheimer's disease. Biomedicines. 2023;11:1161.
70. Wang L, Yin YL, Liu XZ, Shen P, Zheng YG, Lan XR, Lu CB, Wang JZ, et al. Current understanding of metal ions in the pathogenesis of Alzheimer's disease. Transl Neurodegener. 2020;9:10.
71. Marseglia A, Darin-Mattsson A, Skoog J, Rydén L, Hadarsson-Bodin T, Kern S, Rydberg Sterner T, Shang Y, Zettergren A, Westman E, Skoog I, et al. Metabolic syndrome is associated with poor cognition: a population-based study of 70-year-old adults without dementia. J Gerontol A Biol Sci Med Sci. 2021;76:2275–83.
72. Feng Y, Chen X, Zhang XD, Huang C. Metabolic pathway pairwise-based signature as a potential non-invasive diagnostic marker in Alzheimer's disease patients. Genes (Basel). 2023;14:1285.
73. Machado A, Ferreira D, Grothe MJ, Eyjolfsdottir H, Almqvist PM, Cavallin L, Lind G, Linderoth B, Seiger Å, Teipel S, Wahlberg LU, Wahlund LO, Westman E, Eriksdotter M, et al. Alzheimer's disease neuroimaging initiative. The cholinergic system in sub types of Alzheimer's disease: an in vivo longitudinal MRI study. Alzheimers Res Ther. 2020;12:51.
74. Penke B, Szucs M, Bogar F. Oligomerization and conformational change turn monomeric β-amyloid and tau proteins toxic: their role in Alzheimer's pathogenesis. Molecules. 2020;25:1659.
75. Nguyen TT, Ta QTH, Nguyen TTD, Le TT, Vo VG. Role of insulin resistance in the Alzheimer's disease progression. Neurochem Res. 2020;45:1481–91.
76. Sędzikowska A, Szablewski L. Insulin and insulin resistance in Alzheimer's disease. Int J Mol Sci. 2021;22:9987.
77. Lu MH, Zhao XY, Yao PP, Xu DE, Ma QH. The mitochondrion: a potential therapeutic target for Alzheimer's disease. Neurosci Bull. 2018;34:1127–30.
78. Baracaldo SD, AvendaNo LSS, Ariza SDF, Rodriguez GM, Calderon OCA, Gonzalez RRE, Nava MMO. Role of calcium modulation in the pathophysiology and treatment of Alzheimer's disease. Int J Mol Sci. 2023;24:9067.
79. Galla L, Redolfi N, Pozzan T, Pizzo P, Greotti E. Intracellular calcium dysregulation by the Alzheimer's disease-linked protein Presenilin 2. Int J Mol Sci. 2020;21:770.
80. Calvo RM, Kharitonova EK, Bacskai BJ. Therapeutic strategies to target calcium dysregulation in Alzheimer's disease. Cells. 2020;9:2513.
81. Ge M, Zhang J, Chen S, Huang Y, Chen W, He L, Zhang Y, et al. Role of calcium homeostasis in Alzheimer's disease. Neuropsychiatr Dis Treat. 2022;18:487–98.
82. Duncan RS, Song B, Koulen P. Presenilins as drug targets for Alzheimer's disease-recent insights from cell biology and electrophysiology as novel opportunities in drug development. Int J Mol Sci. 2018;19:1621.
83. Sarasija S, Norman KR. Role of presenilin in mitochondrial oxidative stress and neurodegeneration in *Caenorhabditis elegans*. Antioxidants (Basel). 2018;7:111.
84. Wolfe MS. Probing mechanisms and therapeutic potential of γ-secretase in Alzheimer's Disease. Molecules. 2021;26:388.
85. Bagaria J, Bagyinszky E, An SSA. Genetics, functions, and clinical impact of Presenilin-1 (PSEN1) gene. Int J Mol Sci. 2022;23:10970.
86. Mark RE, Brehmer Y. Preclinical Alzheimer's dementia: a useful concept or another dead end? Eur J Ageing. 2022;19:997–1004.
87. Patil V, Madgi M, Kiran A. Early prediction of Alzheimer's disease using conventional neural networks: a review. Early prediction of Alzheimer's disease using convolutional neural network: A review. Egyptian J Neurol Psychiatry Neurosurg. 2022;58:1–10.

88. Emmady PD, Schoo C, Tadi P. Major neurocognitive disorder (dementia). In: Emmady PD, editor. StatPearls. Treasure Island: StatPearls Publishing; 2023.
89. Bos I, van der Flier WM, Kern S, Ousset PJ, Maruff P, Skoog I, Verhey FRJ, Freund LY, Tsolaki M, Wallin ÅK, Olde RM, Soininen H, Spiru L, Zetterberg H, Blennow K, Scheltens P, Muniz-Terrera G, Visser PJ, et al. Alzheimer Disease Neuroimaging Initiative; AIBL Research Group; ICTUS/DSA study groups. Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. Alzheimers Dement. 2019;15:888–98.
90. Shim KH, Kang MJ, Bae H, Kim D, Park J, An SA, Jeong DE, et al. A possible pathogenic PSEN2 Gly56Ser mutation in a Korean patient with early-onset Alzheimer's disease. Int J Mol Sci. 2022;23:2967.
91. Chen SD, Lu JY, Li HQ, Yang YX, Jiang JH, Cui M, Zuo CT, Tan L, Dong Q, Yu JT, et al. Alzheimer's disease neuroimaging initiative. Staging tau pathology with tau PET in Alzheimer's disease: a longitudinal study. Transl Psychiatry. 2021;1:483.
92. Song C, Shi J, Zhang P, Zhang Y, Xu J, Zhao L, Zhang R, Wang H, Chen H, et al. Immunotherapy for Alzheimer's disease: targeting β-amyloid and beyond. Transl Neurodegener. 2022;11:18.
93. Zhou SL, Tan CC, Hou XH, Cao XP, Tan L, Yu JT, et al. TREM2 variants and neurodegenerative diseases: a systematic review and meta-analysis. J Alzheimers Dis. 2019;68:1171–84.
94. Porsteinsson AP, Isaacson RS, Knox S, Sabbagh MN, Rubino I. Diagnosis of early Alzheimer's disease: clinical practice in 2021. J Prev Alzheimers Dis. 2021;8:371–86.
95. Drabo EF, Barthold D, Joyce G, Ferido P, Chang Chui H, Zissimopoulos J, et al. Longitudinal analysis of dementia diagnosis and specialty care among racially diverse Medicare beneficiaries. Alzheimers Dement. 2019;15:1402–11.
96. Maity S, Farrell K, Navabpour S, Narayanan SN, Jarome TJ. Epigenetic mechanisms in memory and cognitive decline associated with aging and Alzheimer's disease. Int J Mol Sci. 2021;22:12280.
97. Barnes J, Bartlett JW, Wolk DA, van der Flier WM, Frost C, et al. Disease course varies according to age and symptom length in Alzheimer's disease. J Alzheimers Dis. 2018;64:631–42.
98. Agudelo BM, Giraldo RL, Rojas RME. Systematic and Comparative Analysis of the Burden of Alzheimer´s Disease and Other Dementias in Mexico. Results at the National and Subnational Levels. J Prev Alzheimers Dis. 2023;10:120–9.
99. Trejo-Lopez JA, Yachnis AT, Prokop S. Neuropathology of Alzheimer's disease. Neurotherapeutics. 2022;19:173–85.
100. Nguyen H, Clement M, Mansencal B, Coupe P. Interpretable differential diagnosis for Alzheimer's disease and Frontotemporal dementia. In: Wang L, Dou Q, Fletcher PT, Speidel S, Li S, editors. International Conference on Medical Image Computing and Computer Assisted Intervention. Cham: Springer; 2022.
101. Milan TA, Fernandez MM, Rodríguez OMC. Lewy body dementias: a coin with two sides? Behav Sci (Basel). 2021;11:94.
102. Capouch SD, Farlow MR, Brosch JR. A review of dementia with Lewy bodies' impact, diagnostic criteria and treatment. Neurol Ther. 2018;7:249–63.
103. Ferrando R, Damian A. Brain SPECT as a biomarker of neurodegeneration in dementia in the era of molecular imaging: still a valid option? Front Neurol. 2021;12: 629442.
104. Malkani RG, Wenger NS. REM sleep behavior disorder as a pathway to dementia: if, when, how, what, and why should physicians disclose the diagnosis and risk for dementia. Curr Sleep Med Rep. 2021;7:57–64.
105. Choudhary G, Bhambhvani P. Myocardial sympathetic innervation imaging with MIBG in dementia with Lewy bodies. J Nucl Cardiol. 2021;28:2164–6.
106. Kantarci K, Lowe VJ, Chen Q, Przybelski SA, Lesnick TG, Schwarz CG, Senjem ML, Gunter JL, Jack CR Jr, Graff-Radford J, Jones DT, Knopman DS, Graff-Radford N, Ferman TJ, Parisi JE, Dickson DW, Petersen RC, Boeve BF, Murray ME, et al. β-amyloid PET and neuropathology in dementia with Lewy bodies. Neurology. 2020;94(3):e282–91.
107. Etminani K, Soliman A, Davidsson A, Chang JR, Martínez-Sanchis B, Byttner S, Camacho V, Bauckneht M, Stegeran R, Ressner M, Agudelo-Cifuentes M, Chincarini A, Brendel M, Rominger A, Bruffaerts R, Vandenberghe R, Kramberger MG, Trost M, Nicastro N, Frisoni GB, Lemstra AW, van Berckel BNM, Pilotto A, Padovani A, Morbelli S, Aarsland D, Nobili F, Garibotto V, Ochoa-Figueroa M, et al. A 3D deep learning model to predict the diagnosis of dementia with Lewy bodies, Alzheimer's disease, and mild cognitive impairment using brain 18F-FDG PET. Eur J Nucl Med Mol Imaging. 2022;49:563–84.
108. Antonioni A, Raho EM, Lopriore P, Pace AP, Latino RR, Assogna M, Mancuso M, Gragnaniello D, Granieri E, Pugliatti M, et al. Frontotemporal dementia, where do we stand? A narrative review. Int J Mol Sci. 2023;24:11732.
109. Greaves CV, Rohrer JD. An update on genetic frontotemporal dementia. J Neurol. 2019;266:2075–86.
110. Huber N, Korhonen S, Hoffmann D, Leskelä S, Rostalski H, Remes AM, Honkakoski P, Solje E, Haapasalo A, et al. Deficient neurotransmitter systems and synaptic function in frontotemporal lobar degeneration-Insights into disease mechanisms and current therapeutic approaches. Mol Psychiatry. 2022;27:1300–9.
111. https://www.alz.org/alzheimers-dementia/what-is-dementia/types-of-dementia/frontotemporal-dementia. Accessed on 15 April 2023.
112. Yu Q, Mai Y, Ruan Y, Luo Y, Zhao L, Fang W, Cao Z, Li Y, Liao W, Xiao S, Mok VCT, Shi L, Liu J, et al. National Alzheimer's coordinating center, the Alzheimer's disease neuroimaging initiative; frontotemporal lobar degeneration neuroimaging initiative. An MRI-based strategy for differentiation of frontotemporal dementia and Alzheimer's disease. Alzheimers Res Ther. 2021;13:23.
113. Jenkins LM, Wang L, Rosen H, Weintraub S. A transdiagnostic review of neuroimaging studies of apathy and disinhibition in dementia. Brain. 2022;145:1886–905.
114. Williams E, McAuliffe M, Theys C. Language changes in Alzheimer's disease: a systematic review of verb processing. Brain Lang. 2021;223: 105041.
115. Bansal VK, Bansal S. Nervous system disorders in dialysis patients. Handb Clin Neurol. 2014;119:395–404.
116. AlSaeed D, Omar SF. Brain MRI analysis for Alzheimer's disease diagnosis using CNN-based feature extraction and machine learning. Sensors (Basel). 2022;22:2911.
117. Qiu D, Hu M, Yu Y, Tang B, Xiao S. Acceptability of psychosocial interventions for dementia caregivers: a systematic review. BMC Psychiatry. 2019;19:23.
118. Wang R, Reddy PH. Role of glutamate and NMDA receptors in Alzheimer's Disease. J Alzheimers Dis. 2017;57:1041–8.
119. Perneczky R, Jessen F, Grimmer T, Levin J, Flöel A, Peters O, Froelich L, et al. Anti-amyloid antibody therapies in Alzheimer's disease. Brain. 2023;146:842–9.
120. Alexander GC, Karlawish J. The problem of aducanumab for the treatment of Alzheimer disease. Ann Intern Med. 2021;174:1303–4.
121. Ray B, Maloney B, Sambamurti K, Karnati HK, Nelson PT, Greig NH, Lahiri DK, et al. Rivastigmine modifies the α-secretase pathway and potentially early Alzheimer's disease. Transl Psychiatry. 2020;10:47.
122. Kim JK, Park SU. Pharmacological aspects of galantamine for the treatment of Alzheimer's disease. EXCLI J. 2017;16:35–9.
123. Lang FM, Mo Y, Sabbagh M, Solomon P, Boada M, Jones RW, Frisoni GB, Grimmer T, Dubois B, Harnett M, Friedhoff SR, Coslett S, Cummings JL, et al. Intepirdine as adjunctive therapy to donepezil for mild-to-moderate Alzheimer's disease: a randomized, placebo-controlled, phase 3 clinical trial (MINDSET). Alzheimers Dement (N Y). 2021;7: e12136.
124. Song YJ, Li SR, Li XW, Chen X, Wei ZX, Liu QS, Cheng Y, et al. The effect of estrogen replacement therapy on Alzheimer's disease and Parkinson's disease in postmenopausal women: a meta-analysis. Front Neurosci. 2020;14:157.
125. Lourdes H, Poluyi E, Ikwuegbuenyi C, Morgan E, Imaguezegie G. Peripheral inflammation and neurodegeneration; a potential for therapeutic intervention in Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). Egypt J Neurosurg. 2022;37:1–9.
126. Browne D, McGuinness B, Woodside JV, McKay GJ. Vitamin E and Alzheimer's disease: what do we know so far? Clin Interv Aging. 2019;14:1303–17.
127. Kikuchi T. Is memantine effective as an NMDA-receptor antagonist in adjunctive therapy for Schizophrenia? Biomolecules. 2020;10:1134.
128. Boada M, Lopez O, Nunez L, Szczepiorkowski ZM, Torres M, Grifols C, Paez A, et al. Plasma exchange for Alzheimer's disease management by albumin replacement (AMBAR) trial: study design and progress. Alzheimers Dement (N Y). 2019;5:61–9.

129. Cummings J, Zhou Y, Lee G, Zhong K, Fonseca J, Cheng F, et al. Alzheimer's disease drug development pipeline: 2023. Alzheimers Dement (N Y). 2023;9: e12385.
130. Huang LK, Chao SP, Hu CJ. Clinical trials of new drugs for Alzheimer disease. J Biomed Sci. 2020;27:18.
131. Soderberg L, Johannesson M, Nygren P, Laudon H, Eriksson F, Osswald G, Möller C, Lannfelt L, et al. Lecanemab, Aducanumab, and Gantenerumab: binding profiles to different forms of amyloid-beta might explain efficacy and side effects in clinical trials for Alzheimer's disease. Neurotherapeutics. 2023;20:195–206.
132. Athar T, Al Balushi K, Khan SA. Recent advances on drug development and emerging therapeutic agents for Alzheimer's disease. Mol Biol Rep. 2021;48:5629–45.
133. Brandt NJ, Wheeler C, Courtin SO. Navigating disease-modifying treatments for Alzheimer's disease: focusing on medications in phase 3 clinical trials. J Gerontol Nurs. 2023;49:6–10.
134. Sandupama P, Munasinghe D, Jayasinghe M. Coconut oil as a therapeutic treatment for Alzheimer's disease: a review. J Future Foods. 2022;2:41–52.
135. Iosifescu DV, Jones A, O'Gorman C, Streicher C, Feliz S, Fava M, Tabuteau H, et al. Efficacy and safety of AXS-05 (Dextromethorphan-Bupropion) in patients with major depressive disorder: a phase 3 randomized clinical trial (GEMINI). J Clin Psychiatry. 2022;83:21m14345.
136. https://investors.biogen.com/news-releases/news-release-details/fda-approves-leqembitm-lecanemab-irmb-under-accelerated-approval. Accessed on 11 Jun 2023.
137. Zhang X, Wu Y, Cai F, Liu S, Bromley-Brits K, Xia K, Song W, et al. A novel Alzheimer-associated SNP in Tmp21 increases amyloidogenesis. Mol Neurobiol. 2018;55:1862–70.
138. Chi H, Chang HY, Sang TK. Neuronal cell death mechanisms in major neurodegenerative diseases. Int J Mol Sci. 2018;19:3082.
139. Honig LS, Vellas B, Woodward M, Boada M, Bullock R, Borrie M, Hager K, Andreasen N, Scarpini E, Liu-Seifert H, Case M, Dean RA, Hake A, Sundell K, Poole Hoffmann V, Carlson C, Khanna R, Mintun M, DeMattos R, Selzler KJ, Siemers E, et al. Trial of solanezumab for mild dementia due to Alzheimer's disease. N Engl J Med. 2018;378:321–30.
140. Wang X, Sun G, Feng T, Zhang J, Huang X, Wang T, Xie Z, Chu X, Yang J, Wang H, Chang S, Gong Y, Ruan L, Zhang G, Yan S, Lian W, Du C, Yang D, Zhang Q, Lin F, Liu J, Zhang H, Ge C, Xiao S, Ding J, Geng M, et al. Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. Cell Res. 2019;29:787–803.
141. Shokri-Kojori E, Wang GJ, Wiers CE, Demiral SB, Guo M, Kim SW, Lindgren E, Ramirez V, Zehra A, Freeman C, Miller G, Manza P, Srivastava T, De Santi S, Tomasi D, Benveniste H, Volkow ND, et al. β-Amyloid accumulation in the human brain after one night of sleep deprivation. Proc Natl Acad Sci USA. 2018;115:4483–8.
142. Van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, Kanekiyo M, Li D, Reyderman L, Cohen S, Froelich L, Katayama S, Sabbagh M, Vellas B, Watson D, Dhadda S, Irizarry M, Kramer LD, Iwatsubo T, et al. Lecanemab in early Alzheimer's disease. N Engl J Med. 2023;388:9–21.
143. Cummings J. Anti-Amyloid Monoclonal Antibodies are Transformative Treatments that Redefine Alzheimer's Disease Therapeutics. Drugs. 2023;83:569–76.
144. Costa M, Paez A. Emerging insights into the role of albumin with plasma exchange in Alzheimer's disease management. Transfus Apher Sci. 2021;60: 103164.
145. Wojtunik-Kulesza K, Rudkowska M, Orzel-Sajdlowska A. Aducanumab-hope or disappointment for Alzheimer's disease. Int J Mol Sci. 2023;24:4367.
146. Mielke MM. Sex and gender differences in Alzheimer's disease dementia. Psychiatr Times. 2018;35:14–7.
147. Knorz AL, Quante A. Alzheimer's disease: efficacy of mono- and combination therapy. A systematic review. J Geriatr Psychiatry Neurol. 2022;35:475–86.
148. Weller J, Budson A. Current understanding of Alzheimer's disease diagnosis and treatment. F1000Res. 2018;7:F1000.
149. Ratan Y, Rajput A, Maleysm S, Pareek A, Jain V, Pareek A, Kaur R, Singh G, et al. An insight into cellular and molecular mechanisms underlying the pathogenesis of neurodegeneration in Alzheimer's disease. Biomedicines. 2023;11:1398.
150. Zhao N, Ren Y, Yamazaki Y, Qiao W, Li F, Felton LM, Mahmoudiandehkordi S, Kueider-Paisley A, Sonoustoun B, Arnold M, Shue F, Zheng J, Attrebi ON, Martens YA, Li Z, Bastea L, Meneses AD, Chen K, Thompson JW, St John-Williams L, Tachibana M, Aikawa T, Oue H, Job L, Yamazaki A, Liu CC, Storm P, Asmann YW, Ertekin-Taner N, Kanekiyo T, Kaddurah-Daouk R, Bu G, et al. Alzheimer's risk factors age, APOE genotype, and sex drive distinct molecular pathways. Neuron. 2020;106:727-742.e6.
151. Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH, Villemagne VL, Aisen P, Vendruscolo M, Iwatsubo T, Masters CL, Cho M, Lannfelt L, Cummings JL, Vergallo A, et al. The amyloid-β pathway in Alzheimer's disease. Mol Psychiatry. 2021;26:5481–503.
152. Khoury R, Ghossoub E. Diagnostic biomarkers of Alzheimer's disease: a state-of-the-art review. Biomark Neuropsychiatry. 2019;1: 100005.


## Publisher's Note